An open-label, single-sequence study to evaluate the potential CYP 3A4 pharmacokinetic interaction of Darapladib (SB-480848) in healthy subjects

Synopsis:
Darapladib (SB-480848) is a novel, selective, orally active inhibitor of lipoprotein associated phospholipase A₂ (Lp-PLA₂) currently under clinical development by GlaxoSmithKline (GSK) as a potential anti-atherosclerosis agent for reduction of major adverse cardiovascular (CV) events in patient populations with chronic coronary heart disease and after an acute coronary syndrome.

This study will determine the effect of single and repeated administration of darapladib on the pharmacokinetics of a single oral dose of midazolam, a cytochrome P450 3A4 (CYP3A4) probe substrate. This study will investigate the inductive and inhibitory effect of darapladib on CYP3A4 metabolic pathway.

Subjects will receive a single oral dose of 5 mg midazolam on Day 1 no later than 30 days after screening. On Days 3-14, subjects will receive darapladib enteric-coated (EC) tablet 160mg once daily. On Days 3 and 14, subjects will also receive a single dose of 5 mg midazolam. At specified times throughout the study, blood samples will be drawn for pharmacokinetic analysis. Subjects will return for two follow-up visits: the first visit will occur 10 to 14 days after the last dose of darapladib and the second will occur 35 days (±7 days) after the last dose of darapladib.

Twenty-six healthy male and female subjects, aged 18-65 years will be recruited for this study. All subjects will undergo a medical/physical examination. If subjects successfully pass the pre-study safety assessments and fulfill all of the inclusion/exclusion criteria they will be eligible to enter the study.

Subject: Drug interaction, healthy volunteer, SB-480848, Lp-PLA2, darapladib, atherosclerosis, midazolam

Author(s): (CPSSO), (MPC), (CS), (CPMS), (GCSP), (MPC), (MPC)

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3 April 2013
Date
SPONSOR/MEDICAL MONITOR INFORMATION PAGE

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Regulatory Agency Identifying Number(s): US IND # 62,846
INVESTIGATOR PROTOCOL AGREEMENT PAGE

I confirm agreement to conduct the study in compliance with the protocol.
I acknowledge that I am responsible for overall study conduct. 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.

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LIST OF ABBREVIATIONS

ADME Absorption Distribution Metabolism and Excretion
AE Adverse Event
AH acetylhydrolase
ALT Alanine aminotransferase (SGPT)
AST Aspartate aminotransferase (SGOT)
AUC Area under concentration-time curve
AUC(0-∞) Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-τ) Area under the concentration-time curve over the dosing interval
β-HcG Beta-Human Chorionic Gonadotropin
BMI Body mass index
BP Blood pressure
BUN Blood urea nitrogen
Cmax Maximum observed concentration
CO₂ Carbon dioxide
°C Degree Celsius
CPK Creatine phosphokinase
CPMS Clinical Pharmacokinetics Modelling and Simulation
CRF Case Report Form
CS Clinical Statistics
Cτ Trough concentration
CVw Within-Subject Coefficient of Variation
CV Cardiovascular
CYP Cytochrome P450
DMPK Drug Metabolism and Pharmacokinetics
DNA Deoxyribonucleic acid
EC Enteric coated
ECmFB Enteric-Coated micronized Free-Base
ECG Electrocardiogram
EU European Union
°F Degree Fahrenheit
4-FBCl 4-fluorobenzyl chloride
FDA Food and Drug Administration
FEV Forced Expiratory Volume
FSH Follicle Stimulation Hormone
GCP Good Clinical Practice
GCSP Global Clinical Safety and Pharmacovigilance
GGT Gamma glutamyltransferase
GLP Good Laboratory Practice
GSK GlaxoSmithKline
HBsAg Hepatitis B surface antigen
hCG Human chorionic gonadotropin
HIV Human Immunodeficiency Virus
h/hr Hour(s)
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>HLA-B</td>
<td>Human Leukocyte Antigen B</td>
</tr>
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<td>HPLC</td>
<td>High-Performance Liquid Chromatography</td>
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<tr>
<td>HR</td>
<td>Heart Rate</td>
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<tr>
<td>IB</td>
<td>Investigator Brochure</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>IDMC</td>
<td>Independent Data Safety and Monitoring Committee</td>
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<td>IDSCL</td>
<td>Integrated Data Standards Library</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>IP</td>
<td>Investigational Product</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
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<tr>
<td>IUS</td>
<td>Intrauterine System</td>
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<tr>
<td>Kg</td>
<td>Kilogram</td>
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<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>Lipoprotein-associated phospholipase A2</td>
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<tr>
<td>LSLV</td>
<td>Last subject last visit</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>Mg</td>
<td>Milligrams</td>
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<tr>
<td>mL</td>
<td>Milliliter</td>
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<tr>
<td>Msec</td>
<td>Millisecond</td>
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<tr>
<td>MSDS</td>
<td>Material Safety Data Sheet</td>
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<tr>
<td>NOAEL</td>
<td>No Adverse Effect Level</td>
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<td>PAF</td>
<td>Platelet activating factor</td>
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<tr>
<td>PEF</td>
<td>Peak Expiratory Flow</td>
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<tr>
<td>PGx</td>
<td>Pharmacogenetics</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PI</td>
<td>Prescribing Information</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT duration corrected for heart rate by Fridericia’s formula</td>
</tr>
<tr>
<td>RAP</td>
<td>Reporting and Analysis Plan</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event(s)</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic-oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SPM</td>
<td>Study Procedures Manual</td>
</tr>
<tr>
<td>T1/2</td>
<td>Terminal phase half-life</td>
</tr>
<tr>
<td>τ</td>
<td>Dosing interval</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time of occurrence of Cmax</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
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1. INTRODUCTION

1.1. Study Rationale

This study will determine the effect of single and repeat administration of darapladib on the pharmacokinetics of a single oral dose of midazolam, a cytochrome P450 3A4 (CYP3A4) probe substrate.

A single oral dose of midazolam is well established as a sensitive CYP3A probe substrate with >93% of the dose metabolized by CYP3A. The 2012 draft FDA guidance for Industry Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations suggests the use of midazolam as the preferred probe substrate for evaluating inhibitory potential of a NCE on CYP3A pathway. The use of orally administered midazolam allows for the development of a classification system for CYP3A inhibitors that may be applied more widely to pharmacokinetic drug-drug interactions mediated through CYP3A.

In vitro inhibition screening data for darapladib indicated that the IC50 value for CYP3A4 was 8 uM using lovastatin as the substrate. A clinical pharmacology study was conducted evaluating the potential for drug interaction between darapladib and atorvastatin and showed that repeat dosing of 40 mg darapladib did not affect the exposure of atorvastatin in healthy volunteers. While atorvastatin is a commonly prescribed medication in atherosclerosis patients and the above study provided data allowing concomitant administration of the darapladib and atorvastatin in clinical trials, atorvastatin is also known to be a substrate for multiple metabolic pathways and transporters (e.g., CYP3A4, OATP1B1 and BCRP). The lack of drug interaction between atorvastatin and darapladib, while meaningful clinically, does not definitively answer the question of CYP3A4 inhibition by darapladib. This study using midazolam as the recommended probe substrate for CYP3A will answer this specific question.

Lastly, in an early repeat ascending dose healthy volunteer study (SB-480848/002), PK data indicated that darapladib exhibits time-dependent PK. The observed accumulation following repeat dosing (ranged from 30% to 60%) was less than predicted from single dose data (ranged from 130% to 200%), indicating that steady state exposure cannot be predicted from single dose data [GlaxoSmithKline Document Number PM2003/00003/00 SB-480848/002 Clinical Study Report 2006]. This observation has since been replicated in studies SB-480848/015 (ADME) and LPL112498. While the mechanism of this time-dependency in pharmacokinetics of darapladib is unclear, induction of its own metabolic pathway, i.e., CYP3A4, is a plausible hypothesis. By using a preferred probe substrate of CYP3A, this study may provide insight into the induction potential of darapladib on
CYP3A4. To that end, exposure of midazolam following co-administration with single
dose darapladib will be compared to that following co-administration with multiple doses
of darapladib.

1.2. Brief Background

Darapladib is a novel, selective, orally active inhibitor of lipoprotein associated
phospholipase A\textsubscript{2} (Lp-PLA\textsubscript{2}) currently under clinical development by GlaxoSmithKline
(GSK) as a potential anti-atherosclerosis agent for reduction of major adverse
cardiovascular (CV) events in patient populations with chronic coronary heart disease
and after an acute coronary syndrome.

Darapladib is also being developed for treatment of macular edema in diabetic patients to
prevent the progression of vision loss. Pre-clinical observations suggest that inhibition of
Lp-PLA\textsubscript{2} may reduce diabetes-induced central nervous system vascular permeability,
including the retina. A phase II, double masked (subjects and investigators), randomised,
placebo controlled study to investigate darapladib administered for 3 months to subjects
with diabetic macular edema was completed in February 2013.

Darapladib has been well tolerated in a clinical program of 34 studies (some placebo
controlled). To date, 27 phase I studies have been completed with 647 healthy subjects,
34 subjects with asthma, and 12 subjects with hepatic impairment exposed to at least one
dose of darapladib. In five completed Phase II studies to support the development of
darapladib in atherosclerosis, 1133 patients have received darapladib EC tablets 160mg
once daily for 12 weeks or longer. Ongoing Phase III trials in cardiovascular disease
include over 28,000 patients randomized 1:1 to darapladib or placebo. Data from the
Phase III studies remain blinded until completion.

Darapladib has been well tolerated to date with dysgeusia, diarrhea and odor of feces,
skin and urine as the most frequently reported adverse events. Additional safety
information can be found in the current IB [GlaxoSmithKline Document Number
RM2003/00513/06 Darapladib Investigator’s Brochure, Version 09].
2. **OBJECTIVE(S) AND ENDPOINT(S)**

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<td>To examine the effects of repeat oral dosing of darapladib (160mg EC tablet QD) on the pharmacokinetic parameters of a single oral dose of midazolam (5 mg)</td>
<td>AUC(0-∞) and Cmax (Days 1 and 14) for midazolam</td>
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<td><strong>Secondary</strong></td>
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<td>To examine the effects of single oral dose of darapladib (160mg EC tablet QD) as compared to multiple oral doses of darapladib on the single oral dose of midazolam (5 mg)</td>
<td>AUC(0-∞), Cmax, tmax and t1/2 (Days 3 and 14) for midazolam</td>
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<td>To assess the safety and tolerability of repeated oral doses of darapladib (160mg EC tablet QD) in combination with midazolam (5mg QD)</td>
<td>Clinical safety data from adverse event reporting, 12-Lead ECG, vital signs, oxygen saturation/pulse oximetry and safety laboratory tests.</td>
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<tr>
<td>To examine the effects of repeat oral dosing of darapladib (160mg EC tablet QD) on the other pharmacokinetic parameters of a single oral dose of midazolam (5mg QD)</td>
<td>Tmax and t1/2 (Days 1 and 14) for midazolam</td>
</tr>
<tr>
<td>To examine the effects of single oral dose of darapladib (160mg EC tablet QD) on the other pharmacokinetic parameters of a single oral dose of midazolam (5mg QD)</td>
<td>AUC(0-∞), Cmax, tmax and t1/2 (Days 1 and 3) for midazolam</td>
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3. **STUDY DESIGN**

3.1. **Study Schematic**

![Study Schematic Diagram]

3.2. **Study Design Detail**

This will be an open-label, single sequence study conducted in healthy subjects. Each subject will receive a single oral dose of midazolam 5 mg on Day 1. Starting on Day 3, subjects will receive darapladib EC tablet 160mg QD for 12 days. On Days 3 and 14, subjects will also receive midazolam 5 mg QD.
Subjects will be required to return to the unit 10-14 days following the last dosing of study drug for a clinic visit for assessments and then will return again at 35 ±7 days following the last dose of study drug for the final follow-up visit of the study. The duration of each subject's participation in the study from screening to follow-up will be approximately 12 weeks.

3.3. Discussion of Study Design

3.3.1. Dose Rationale

The proposed dose of darapladib in this study is a 160 mg enteric-coated micronized free-base tablet (ECmFB). This is the dose and the formulation used in the ongoing Phase III program for atherosclerosis as well as the Phase II study for diabetic macular edema.

In previous clinical pharmacology studies, single and repeat doses of up to 480mg of enteric-coated, micronized, free-base tablets of darapladib have been administered to healthy volunteers. In these studies, the various doses were well tolerated at mean exposure values up to 997ng.h/mL. Exposures at the clinical dose of 160mg EC tablet are approximately 2.9-fold and 7-fold less than the no adverse effect level (NOAEL) exposures observed in rats (NOAEL = 15mg/kg/day) and dogs (NOAEL = 10mg/kg/day), respectively, in the toxicology studies. At higher doses in rats and dogs, there were effects on body weight and gastro-intestinal disturbance and/or irritancy; exposures at the clinical dose are approximately 17-fold and 15-fold less than these effect doses in rats and dogs, respectively. In addition, in rats there was phospholipid accumulation at exposures 6-fold greater than those at the clinical dose.

The proposed dose of midazolam in this study is 5 mg single oral dose. The dose of midazolam used clinically is 0.07 to 0.1 mg/kg for sedation and 0.15 to 0.3 mg/kg for induction of anaesthesia (Dundee et al., 1984). With a typical body weight of 70 kg adult healthy volunteer, the clinical dose of midazolam ranges from 4.9 mg to 21 mg. Although a low dose of 2 mg has previously been shown to be a sensitive and reproducible probe to phenotype CYP3A activity, a slightly higher dose (5 mg) may be necessary to ensure drug concentrations do not fall below the lower level of quantification of the assay given the possibility of induction of midazolam clearance by darapladib. A single oral dose of 15 mg midazolam has been safely administered to healthy volunteers in drug interaction studies (Backman et al., 1994).

3.4. Risk Management

3.4.1. 4-Fluorobenzyl chloride (4-FBCl)

4-fluorobenzyl chloride (4-FBCl), a potential acid degradant of darapladib, is a weak genotoxin in-vitro [GlaxoSmithKline Document Number RM2003/00513/06 Darapladib Investigator’s Brochure, Version 09]. Based on preclinical data, the level of containment provided by enteric coating, and the low maximum potential exposure in the rare case where the enteric coat might fail, it is concluded that there is minimal genotoxic risk associated with the potential trace levels of 4-FBCl that might result from oral administration of darapladib.
In addition, subjects will be instructed that darapladib tablets must be swallowed whole and not chewed, to maintain the integrity of the enteric coat. Further, subjects will be instructed to take the tablets after eating a meal in order to raise the pH of the stomach and provide additional protection in the rare event that drug is released in the stomach.

For additional information, refer to the IB [GlaxoSmithKline Document Number RM2003/00513/06 Darapladib Investigator’s Brochure, Version 09]. Investigators will be instructed to ensure that patients understand and comply with dosing instructions.

### 3.4.2. Theoretical Concern Regarding Platelet Activating Factor (PAF) Accumulation with Lp-PLA₂ Inhibitors

#### Theoretical concern of bronchospasm with Lp-PLA₂ inhibition

All of the side effects of darapladib may not be known. Based upon mechanism of action, inhibition of Lp-PLA₂ may contribute to platelet activating factor (PAF) accumulation, which could contribute to bronchospasm.

A specific study to evaluate the effect of darapladib in patients with asthma (LPL107629) showed no statistically or clinically significant effect of darapladib on FEV₁ (forced expiratory volume in 1 second) following single day (day 1) and repeat oral doses (day 21), and no statistically significant treatment effect observed on PC₂₀ (provocative concentration of methacholine causing a 20% fall in FEV₁) at trough day 21. However, as a precautionary measure, subjects with history of severe asthma that is poorly-controlled by pharmacotherapy are excluded from clinical trials with darapladib. For additional information refer to the IB [GlaxoSmithKline Document Number RM2003/00513/06 Darapladib Investigator’s Brochure, Version 09].

#### Theoretical concern of increasing severity of anaphylaxis with Lp-PLA₂ inhibition

A study suggested that PAF is positively correlated and PAF-acetylhydrolase (AH) (PAF-AH, another name for Lp-PLA₂) is inversely correlated with anaphylaxis severity [Vadas, 2008]. A separate retrospective analysis showed that PAF-AH levels were significantly lower in patients with fatal peanut anaphylaxis than those with mild allergic reactions to peanuts and subjects in the control group. However, the exact association between PAF-AH level and the risk of increasing severity of anaphylaxis is unknown.

As a precautionary measure, subjects with history of anaphylaxis (refer to Appendix 3) or severe allergy (e.g., due to food, medications, or latex) as defined by the summary report of the second symposium on the definition and management of anaphylaxis [Sampson, 2006] are excluded from clinical studies with darapladib.

Events of anaphylaxis and severe allergy in this patient population will continue to be monitored by the sponsor. For additional information refer to the IB [GlaxoSmithKline Document Number RM2003/00513/06 Darapladib Investigator’s Brochure, Version 09].
3.4.3. **Ongoing Rat and Mouse, 2-Year (“Lifetime”) Carcinogenicity Studies**

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. 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. Specifically, drug exposure levels where these tumors were observed were 25-times greater in the male mice and 6.5-times greater in the male rats compared to drug exposures in humans at the clinical daily dose of 160mg being tested in clinical trials. Tumors were not increased at a lower dose of darapladib in the rodent studies where the blood levels were 7-times (mice) and 4-times (rats) higher than the blood levels of darapladib in humans at the 160mg dose.

The relevance to humans of these rodent jejunal tumors is unknown; however, it is noted that:

- The incidences of jejunal tumors were less than 10% and only reached statistical significance in mice at the highest dose, indicating a weak signal.
- There is no pattern to suggest accelerated tumor latency.
- There was minimal evidence of tumor multiplicity within an animal.
- Darapladib was tested for and did not show evidence of genetic toxicity (DNA damage, mutations).

The Independent Data Safety and Monitoring Committee (IDMC) for the Phase III studies has reviewed the findings from the ongoing 2-year oral carcinogenicity studies in rodents and the updated safety information from the ongoing Phase III Program in June 2012. This was followed by repeated reviews at the regularly scheduled intervals with all recommendations to date being that the trial continue without modification: on August 25, 2012 (full Committee review), December 2012 (review by Committee chair), and most recently on March 9, 2013 (full Committee review).

The exposure to darapladib in this study is 12 days, and therefore, in addition to the aforementioned reasons, the risk of carcinogenicity is considered minimal.

For additional information refer to the Investigator’s Brochure [GlaxoSmithKline Document Number RM2003/00513/06 Darapladib Investigator’s Brochure, Version 09].

### 4. STUDY POPULATION

#### 4.1. Number of Subjects

Approximately 26 subjects will be enrolled such that approximately 20 subjects complete dosing and critical assessments.
If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor in consultation with the investigator.

### 4.2. Eligibility Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for darapladib and the midazolam PI.

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

#### 4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female aged between 18 and 65 years of age inclusive, at the time of signing the informed consent.
2. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and ECG.
3. A subject with an ALT, AST, alkaline phosphatase or bilirubin laboratory result outside the reference range may be included only if both the Investigator and the GSK Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
4. BMI within the range 19-37 kg/m² (inclusive).
5. A female subject is eligible to participate if she is of:
   - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy [for this definition, “documented” refers to the outcome of the investigator's/designee’s 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]; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/ml and estradiol < 40 pg/ml (<147 pmol/L) is confirmatory].
   - Child-bearing potential and is abstinent or agrees to use one of the contraception methods listed in Section 4.3.1 for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until the final follow-up visit.
   - Child-bearing potential and has only same-sex partners, when this is her preferred and usual lifestyle.
6. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form

7. Single QTcF < 450 msec

### 4.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

#### 4.2.2.1. Criteria Based Upon Medical Histories

1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

2. History of regular alcohol consumption within 6 months of the study defined as:
   - an average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.

3. History of sensitivity to heparin or heparin-induced thrombocytopenia.

4. History of sensitivity to any of the study medications, including midazolam and flumazenil, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.

5. Any contraindications for midazolam or flumazenil administration.

6. Any condition that, in the opinion of the investigator, presents undue risk from the study medications, including midazolam and flumazenil, or procedures.

7. Requiring the use of oral or injectable strong CYP3A4 inhibitors or use of other CYP3A4 inhibitor/inducers within 14 days prior to dosing (refer to Section 5.11.2).

8. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions (refer to Appendix 3: Clinical criteria for diagnosing anaphylaxis [Sampson, 2006] or severe allergic response.

#### 4.2.2.2. Criteria Based Upon Diagnostic Assessments

9. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening

10. A positive pre-study drug/alcohol screen.

11. A positive test for HIV antibody.

12. Pregnant females as determined by positive hCG test at screening or prior to dosing.
4.2.2.3. Other Criteria

13. Where participation in the study would result in donation of blood or blood products in excess of 500mL within a 56 day period.

14. Lactating females.

15. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

16. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

17. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John’s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

18. Unwillingness or inability to follow the procedures outlines in the protocol.

19. Subject is mentally or legally incapacitated.

20. Consumption of grapefruit or grapefruit juice within 7 days prior to the first dose of study medication.

4.3. Lifestyle And/or Dietary Restrictions

4.3.1. Contraception Requirements

4.3.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Female subjects of childbearing potential with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Contraceptive Methods with a Failure Rate of < 1%

- Non-hormonal intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label.
- **Documented** male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s 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.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).

**NOTE:** These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

4.3.2. Meals and Dietary Restrictions

- Subjects should fast for a minimum of 8 hours and abstain from alcohol use for 24 hours prior to any blood draws for safety laboratory testing.
- Subjects will abstain from ingesting alcohol and caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final blood sample in the study.
- Because darapladib is primarily metabolized by CYP3A4 and >8oz daily of grapefruit juice may be a strong inhibitor of CYP3A4 [Bjornsson, 2003], subjects will be instructed to refrain from consumption of grapefruit juice (refer to Section 4.2.2 Exclusion Criteria) for at least 7 days prior to the first dose of study medication.
- Water may be consumed ad libitum beginning 2 hours after dosing; soft drinks without caffeine or fruit juices (except grapefruit) may be consumed ad libitum beginning 4 hours after dosing.
- Meals will be provided during the in-patient periods. A standard breakfast will be served approximately 1 hour before dosing of darapladib. Lunch and dinner will be served approximately 6 and 10 hours after dosing respectively. An evening snack will be permitted up to 2200 hours.

4.3.3. Tobacco

- Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit.
4.3.4. **Activity**

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

4.4. **Screen and Baseline Failures**

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

4.5. **Withdrawal Criteria and Procedures**

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons.

Refer to Section 5.3 for dose adjustment/stopping criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.3.1 for details.

If a subject is withdrawn from the study, the following should be performed if appropriate and feasible: clinical safety labs and AE assessment.

4.6. **Subject Completion**

A completed subject is one who has completed all phases of the study including the final follow-up visit.

The end of the study is defined as the last subject’s last visit.
5. STUDY TREATMENT

5.1. Investigational Product and Other Study Treatment

<table>
<thead>
<tr>
<th>Study Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product name:</strong></td>
<td>Darapladib (SB-480848)</td>
</tr>
<tr>
<td><strong>Formulation description:</strong></td>
<td>Enteric coated, free base (micronized) tablet</td>
</tr>
<tr>
<td><strong>Dosage form:</strong></td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Unit dose strength(s)/Dosage level(s):</strong></td>
<td>160mg</td>
</tr>
<tr>
<td><strong>Route/Administration/Duration:</strong></td>
<td>Oral/repeat dose/12 days</td>
</tr>
<tr>
<td><strong>Dosing instructions:</strong></td>
<td>Take with food. Swallow whole, do not chew.</td>
</tr>
<tr>
<td><strong>Physical description:</strong></td>
<td>White round tablets</td>
</tr>
<tr>
<td><strong>Manufacturer/source of procurement:</strong></td>
<td>GSK</td>
</tr>
<tr>
<td><strong>Method for individualizing dosage:</strong></td>
<td>One 160mg tablet taken once a day</td>
</tr>
</tbody>
</table>

5.2. Treatment Assignment

All subjects will be assigned to the same sequence in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

<table>
<thead>
<tr>
<th>Period</th>
<th>Regimen A</th>
<th>Midazolam 5mg for 1 day (Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 2</td>
<td>Regimen B</td>
<td>Darapladib EC tablet 160mg + Midazolam 5mg for 1 day (Day 3)</td>
</tr>
<tr>
<td>Period 3</td>
<td>Regimen C</td>
<td>Darapladib EC tablet 160mg for 10 days (Days 4-13)</td>
</tr>
<tr>
<td>Period 4</td>
<td>Regimen D</td>
<td>Darapladib EC tablet 160mg + Midazolam 5mg for 1 day (Day 14)</td>
</tr>
</tbody>
</table>
5.3. **Subject Specific Dose Adjustment/Stopping Criteria**

5.3.1. **Liver Chemistry Stopping Criteria**

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Study treatment will be stopped for a subject if the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN

NOTE: Refer to Appendix 1 for details of the required assessments if a subject meets the above criteria.

5.3.2. **QTc Withdrawal Criteria**

The only planned ECG measures in this study are at the screening visit and follow-up 1 visit (see Time and Events table). However in the case of an unscheduled ECG, a subject that meets the criteria below will be withdrawn from the study.

The QT correction formula (e.g., QTcF) used to determine discontinuation should be the same one used throughout the study.

- QTcF > 500 msec, or
- Change from baseline: QTcF >60 msec

If a subject has underlying bundle branch block the following withdrawal criteria should be used instead:

<table>
<thead>
<tr>
<th>Baseline QTc value (with underlying bundle branch)</th>
<th>QTc withdrawal criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;450 msec</td>
<td>&gt;500 msec</td>
</tr>
<tr>
<td>450-480 msec</td>
<td>&gt;530 msec</td>
</tr>
</tbody>
</table>

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of at least 5 minutes and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.4. **Blinding**

This will be an open-label study.
5.5. Packaging and Labeling

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

5.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff. Study treatment is to be stored at 0°C - 30°C (32-86°F). Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount supplied and/or administered to and/or returned by subjects. The required accountability unit for this study will be tablet. Discrepancies are to be reconciled or resolved. The GSK monitor conducts and documents final drug accountability and reconciliation of all study provided medication and is responsible for ensuring that all used and unused study medication is accounted for and returned to GSK.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

5.7. Assessment of Compliance

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each subject’s mouth to ensure that the study treatment was ingested.
5.8. Treatment of Study Treatment Overdose

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

There is no specific antidote for an overdose of darapladib; however, the Lp-PLA$_2$ inhibition is reversible and plasma levels of Lp-PLA$_2$ activity should return to baseline within several days upon discontinuation or dosing. Supportive care should be provided as appropriate.

5.9. Precautions for Midazolam Administration

Study personnel will take every precaution to assure the subject’s safety (i.e., respiratory and cardiac monitoring, resuscitative drugs and equipment will be available) following administration of midazolam.

Midazolam may cause problems with coordination and the ability to think. Study personnel will instruct subjects not to drive, use machines, or do anything else that could be dangerous until the effects of midazolam have worn off.

Midazolam has been associated with severe respiratory depression and arrest, especially when administered with an opioid analgesic or when administered to rapidly in parental formulations. Midazolam should be administered only in a hospital or ambulatory care setting that has respiratory and cardiac monitoring and resuscitative drugs and equipment available. If respiratory depression should occur, key supportive measures include:

- Support ventilation (maintain a patent airway and administer oxygen as needed).
- Support circulation as needed (establish intravenous access and administer intravenous fluids as needed).
- Flumazenil is recommended for intravenous use only.
- Flumazenil is compatible with 5% dextrose in water, lactated Ringer’s and normal saline solutions.
- The recommended initial dose of flumazenil is 0.2mg (2mL) intravenously over 15 seconds.

If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further flumazenil dose of 0.2mg (2mL) can be injected and repeated at 60-second intervals, when necessary, for a maximum total dose of 1mg (10mL) (initial dose + four additional doses) [Rogers, 2002].

5.10. Treatment After the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.
5.11. Concomitant Medications and Non-Drug Therapies

5.11.1. Permitted Medications

Acetaminophen, at doses of $\leq 2$ grams/day, is permitted for occasional use any time during the study. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

5.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer)) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

Because darapladib is primarily metabolized by CYP3A4, strong oral or injectable CYP3A4 inhibitor(s) are prohibited (refer to Section 4.2.2 Exclusion Criteria). A CYP3A4 inhibitor is classified as being strong if the in vivo effect on the plasma AUC of orally administered midazolam is increased by $\geq 5$ fold [Bjornsson, 2003].

Examples of strong CYP3A4 inhibitors include, but are not limited to, those listed below.

- The following antiretrovirals: amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, telaprevir
- The following macrolide antibiotics: clarithromycin, telithromycin, troleandomycin
- The following antifungals: ketoconazole, itraconazole, posaconazole, voriconazole
- Other: conivaptan, nefazadone
- Grapefruit juice

Except for IP administered for this study, no investigational drugs are permitted from study entry through completion of the final follow-up visit.
6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 6.1. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

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

The timing and number of planned study assessments, including safety and pharmacokinetic assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be approved and documented by GSK, but this will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
### 6.1. Time and Events Table

<table>
<thead>
<tr>
<th>Study Assessments</th>
<th>Screening</th>
<th>Study Days</th>
<th>Follow-up 1 (10-14 days post last dose)</th>
<th>Follow-up 2 (35± 7 days post last dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window (relative to Day 1)</td>
<td>-30 to -2 days</td>
<td>-1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15</td>
<td>24 to 28 days</td>
<td>42 to 56 days</td>
</tr>
<tr>
<td>Admission to Unit</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Informed Consent</td>
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<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Verify Eligibility</td>
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<tr>
<td>Demographics</td>
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<td>X</td>
</tr>
<tr>
<td>BMI</td>
<td>X</td>
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</tr>
<tr>
<td>Treatment Assignment</td>
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</tr>
<tr>
<td>Midazolam 5mg Dosing</td>
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<tr>
<td>Darapladib 160mg dosing</td>
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<tr>
<td>Meal Served</td>
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<td>X</td>
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<tr>
<td>Discharge</td>
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<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Safety Assessment** (order of assessments if at same nominal time: 12-lead ECG, vital signs, blood draws)

- Complete physical: X
- Brief physical: X
- Medical/medication/drug/alcohol history: X
- 12-lead ECG: X
- Vital signs² (BP&HR): X
- Vital signs² (RR): X
<table>
<thead>
<tr>
<th>Study Assessments</th>
<th>Screening</th>
<th>Study Days</th>
<th>Follow-up 1 (10-14 days post last dose)</th>
<th>Follow-up 2 (35± 7 days post last dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Window (relative to Day 1)</td>
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<td>24 to 28 days</td>
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<td>42 to 56 days</td>
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<td>Oxygen saturation/ Pulse Ox³</td>
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<tr>
<td>AE assessment⁴</td>
<td>X X X X X X X X X X X X X X X X X X</td>
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<tr>
<td>Con.Medication Review⁵</td>
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<td></td>
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<tr>
<td>Lab Assessments (blood draws should always be collected at exact nominal time)</td>
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</tr>
<tr>
<td>HIV, Hep B and Hep C screen</td>
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</tr>
<tr>
<td>Hema/Chem/Urinalysis tests⁶</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Drug/alcohol screen</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test⁷</td>
<td>X X</td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>PGx blood sample⁸</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK blood sample⁹</td>
<td>X X X X</td>
<td></td>
<td></td>
<td>X X X X</td>
</tr>
</tbody>
</table>

1. Refer to Section 4.3.2
2. BP and HR are taken predose on Days 1, 3, 8 and 14. Respiration rate will be recorded predose, 1, 2 and 4 hours after dosing. Refer to Section 6.3.2
3. Oxygen saturation will be monitored continuously from 15 minutes before dosing through 4hrs after dosing. If continuous oxygen saturation monitoring is not available, then it will be measured every 15 minutes by pulse oximetry beginning 15 minutes prior to dosing until 90 minutes after dosing and at 2, 3, and 4 hours after dosing with midazolam.
4. Refer to Section 7
5. Refer to Section 5.11
6. Subjects must fast for a minimum of 8 hours and abstain from alcohol use for 24 hours prior to any blood draws for safety laboratory testing. Refer to Section 6.3.5
7. Informed consent for optional PGx (pharmacogenetics) research must be obtained before collecting a sample.
8. Blood samples for midazolam PK will be collected on: Day 1 at predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose; Day 3 at predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose; Days 12 and 13 predose; Day 14 at predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Blood samples collected on Days 3, 12, 13 and 14 will also be analyzed for darapladib concentrations.
6.2. Demographic/Medical History Assessments

After giving written informed consent, subjects will undergo a medical screen within 30 days prior to Day 1.

The following demographic parameters will be captured: year of birth, gender, race and ethnicity.

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2.

6.3. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 6.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

6.3.1. Physical Exams

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

6.3.2. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate and respiration rate.

Systolic and diastolic blood pressure and pulse rate measurements will be recorded after the subject has been resting in a semi-supine or supine position for at least 10 minutes at the time points indicated in the Time and Events Table (Section 6.1).

Respiration rate (number of breaths) will be measured over one minute and recorded at the timepoints indicated in the Time and Events Table (Section 6.1). Additional vital signs measurements may be performed during the study if considered appropriate by the Principle Investigator.

6.3.3. Oxygen Saturation

Oxygen saturation will be monitored continuously from 15 minutes before dosing through 4hrs after dosing with midazolam. If continuous oxygen saturation monitoring is not available, then it will be measured every 15 minutes by pulse oximetry beginning 15 minutes prior to dosing until 90 minutes after dosing and at 2, 3, and 4 hours after dosing with midazolam.
6.3.4. Electrocardiogram (ECG)

Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.3.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

6.3.5. Clinical Laboratory Assessments

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below. Details for the preparation and shipment of samples will be provided by the local laboratory. Reference ranges for all safety parameters will be provided to the site by the laboratory.

If additional non-protocol specified laboratory assessments are performed at the site’s local laboratory and result in a change in subject management or are considered clinical significant by the Investigator (for example SAE or AE or dose modification) the results must be captured and sent to GSK along with other study data as defined in Appendix 4.

### Hematology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Automated WBC Differential:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td></td>
</tr>
<tr>
<td>RBC Count</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>WBC Count (absolute)</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Reticulocyte Count</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Basophils</td>
</tr>
</tbody>
</table>

### Clinical Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>Potassium</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Chloride</td>
</tr>
<tr>
<td>Glucose, fasting</td>
<td>Total CO₂</td>
</tr>
<tr>
<td>Sodium</td>
<td>Calcium</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>ALT (SGPT)</td>
</tr>
<tr>
<td>Total and direct bilirubin</td>
<td>Uric Acid</td>
</tr>
<tr>
<td>GGT</td>
<td>Albumin</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Total Protein</td>
</tr>
</tbody>
</table>

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.3.1

### Routine Urinalysis

<table>
<thead>
<tr>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific gravity</td>
</tr>
<tr>
<td>pH, glucose, protein, blood and ketones by dipstick</td>
</tr>
<tr>
<td>Microscopic examination (if blood or protein is abnormal)</td>
</tr>
</tbody>
</table>
### Other laboratory tests

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Test (β-HcG at Screening, urine or serum at Baseline and Follow-up)</td>
</tr>
<tr>
<td>HIV (Screening)</td>
</tr>
<tr>
<td>Hepatitis B (HBsAg) (Screening)</td>
</tr>
<tr>
<td>Hepatitis C (Screening)</td>
</tr>
<tr>
<td>FSH and estradiol (as needed in women of non-child bearing potential only) (Screening)</td>
</tr>
<tr>
<td>Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).</td>
</tr>
<tr>
<td>PGx (optional)</td>
</tr>
</tbody>
</table>

### 6.4. Pharmacokinetics

#### 6.4.1. Blood Sample Collection

Blood samples for pharmacokinetic analysis of darapladib, midazolam will be collected at the time points indicated in Section 6.1, Time and Events Table. At each time point, collect 2mL of whole blood in a properly labelled EDTA evacuated blood tube.

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided separately.

#### 6.4.2. Sample Analysis

Plasma sample analysis will be performed under the management of Worldwide Bioanalysis, DMPK, GlaxoSmithKline. Concentrations of midazolam will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be stored in GLP Archives, GlaxoSmithKline.

Once the plasma has been analyzed for midazolam any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol.

### 6.5. Pharmacogenetics

Information regarding pharmacogenetic (PGx) research is included in Appendix 2. The IRB/IEC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. In some cases, approval of the PGx 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 PGx assessments is being deferred and in most cases, the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.
7. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PREGNANCY AND MEDICAL DEVICES

7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

7.1.1. Time period for collecting AE and SAE information

AEs will be collected from the start of Study Treatment and until the follow-up contact. Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions CRF.

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., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product 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 recorded and reported to GSK within 24 hours, as indicated in Appendix 4.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify GSK.

NOTE: The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.1.2. Definition of Adverse Events

An AE is 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:

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

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

- Any clinically significant abnormal laboratory findings or other abnormal 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.
- 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.
- 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.

7.1.3. Definition of Serious Adverse Events

If an event is not an AE per Section 7.1.2, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

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

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin * ≥ 2xULN (>35% direct), or
- ALT ≥ 3xULN and INR ** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
7.1.4. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 hours. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Appendix 4.

7.1.5. Regulatory Reporting Requirements for SAEs

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

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.2. Pregnancy

7.2.1. Time period for collecting pregnancy information

All pregnancies in female subjects will be collected after the start of dosing and until the final follow-up visit.

7.2.2. Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.
A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 7.1.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. 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. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses and Treatment Comparisons

This study is designed to estimate the effect of repeat oral doses of darapladib on the single dose pharmacokinetics of midazolam AUC\((0-\infty)\) and Cmax. There are no formal hypotheses to be tested. Point estimates and corresponding 90% confidence intervals will be constructed for the ratio of geometric mean of the test treatment (darapladib + midazolam Day 14) to the geometric mean of the reference treatment (midazolam Day 1), \(\mu(\text{test}) - \mu(\text{reference})\).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

A within subject CV of 13.5%, 29.0% was estimated for midazolam AUC\((0-\infty)\) and 21.7%, 45.0% for midazolam Cmax in the studies NKF10007 and NKD10006, respectively.

Based upon the mean values observed (20.7% for AUC\((0-\infty)\) and 33.4% for Cmax) and with 20 subjects completing the study, it is estimated that the half-width of the 90% confidence interval for the ratio of geometric means (darapladib + midazolam / midazolam alone) should be no more than 11.9% for AUC\((0-\infty)\) and 19.5% for Cmax of the point estimates. Assuming an observed ratio of one, the corresponding 90%
confidence interval for the ratio of geometric means would be 0.89 to 1.12 for AUC(0-∞) and 0.84 to 1.20 for Cmax.

9.2.2. Sample Size Sensitivity

In case of a within subject CV of 29% for AUC(0-∞) and 45.0% for Cmax (the maximum values observed) and with 20 subjects completing the study, the half-width of the 90% confidence interval for the ratio of geometric means (darapladib + midazolam / midazolam alone) should be no more than 16.8% for AUC(0-∞) and 26.5% for Cmax of the point estimates. Assuming an observed ratio of one, the corresponding 90% confidence interval for the ratio of geometric means would be 0.86 to 1.17 for AUC(0-∞) and 0.79 to 1.27 for Cmax.

9.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Interim Analysis

No interim analysis is planned.

9.3.2. Final Analyses

9.3.2.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK’s Integrated Data Standards Library (IDSL) standards.

9.3.2.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling & Simulation department within GlaxoSmithKline. Midazolam plasma concentration-time data will be analyzed by non-compartmental methods with WinNonlin Professional Edition. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-∞), AUC(0-t) if AUC(0-∞) could not be estimated], and apparent terminal phase half-life (t1/2). Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state of darapladib.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline.
Following log$_e$-transformation, AUC(0-∞) and Cmax of midazolam will be separately analyzed using a mixed effects model with fixed effect terms for day. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, Day 14 – Day 1 (darapladib + midazolam) – (midazolam). The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, (darapladib + midazolam) : (midazolam).

Secondary objectives will include the following comparisons: midazolam following repeat dosing of darapladib (Day 14) versus midazolam following a single dose of darapladib + midazolam (Day 3); midazolam following a single dose of darapladib + midazolam (Day 3) versus a single dose of midazolam (Day 1). For each comparison, a similar model to that used for the primary comparison will be used.

For each comparison, point estimates and their associated 90% confidence intervals will be constructed for the differences in means. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios.

The within-subject coefficients of variation (CV$_w$) for AUC(0-∞) and Cmax will be calculated based on the log$_e$-normal distribution where:

$$CV_w(\%) = \sqrt{\exp(MSE) - 1} \times 100$$

MSE is the residual mean squared error from the model. CV$_w$ represents a pooled measure of within-subject variability across regimens.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of the residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

If data permit, Tmax will be analyzed nonparametrically using the Wilcoxon's Matched Pairs Method [Steinijans, 1983]. The point estimates and 90% confidence intervals for the median differences will be derived for (darapladib + midazolam) – (midazolam).

Further details of the planned analyses will be provided in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.
10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

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

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

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each subject prior to participation in the study.

Information regarding pharmacogenetic research is included in Appendix 2. In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency must also approve the PGx assessments (i.e., approval of Appendix 2), unless otherwise indicated. Where permitted by regulatory authorities, approval of the PGx 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 PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including 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 also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify 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

10.4. Quality Assurance

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

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned,
electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide 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.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject’s last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a summary statement will be added to the register to explain the reason for not publishing.
11. REFERENCES


12. **APPENDICES**

12.1. **Appendix 1: Liver Safety Process**

**Scenario 1 Healthy Volunteer Studies**

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 5.3.1:

- Immediately withdraw the subject from study treatment
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject’s study treatment cessation and follow-up.
- Complete the “Safety Follow-Up Procedures” listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 7.1.3), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required.
- Do not restart investigational product.
- Refer to the Flow chart for a visual presentation of the procedures listed below.

**Safety Follow-Up Procedures for subjects with ALT ≥ 3xULN:**

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

**Safety Follow-Up Procedures for subjects with ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin); or ALT ≥ 3xULN and INR\(^1\) > 1.5:**

- This event is considered an SAE (see Section 7.1.3). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

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\(^1\) INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.
In addition, for all subjects with ALT $\geq 3\times$ULN, every attempt must be made to also obtain the following:

- **Viral hepatitis serology including:**
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody.

- **Blood sample for pharmacokinetic (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 study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject’s best approximation. If the date/time of the last dose cannot be approximated **OR** a PK sample cannot be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are provided separately.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin $\geq 2\times$ULN.

- Assess eosinophilia

- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.

- Record alcohol use on the Liver Events CRF.

The following are required for subjects with ALT $\geq 3\times$ULN and bilirubin $\geq 2\times$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.

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

Refer to the diagram below for a visual presentation of the procedures listed above.

- Instruct subject to **stop IP**
- Notify GSK within 24 hrs
- Obtain weekly liver chemistries until resolved, stabilized or returned to baseline values
- Perform liver event follow up assessments (serology, PK sample, etc as in protocol)
- Complete liver event CRF
- **Withdraw subject from study after liver chemistry monitoring complete + do not re-challenge with IP**

*INR threshold does not apply to subjects receiving anticoagulants.*
12.2. Appendix 2: Pharmacogenetic research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (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). Some reported examples of PGx associations with safety/adverse events include:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Gene Variant</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HIV</td>
<td>HLA-B* 57:01 (Human Leukocyte Antigen B)</td>
<td>Carriage of the HLA-B<em>57:01 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B</em>57:01 screening and exclusion of HLA-B<em>57:01 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B</em>57:01 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*57:01 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Seizure, Bipolar disorders &amp; Analgesia</td>
<td>Chung, 2010; Ferrell, 2008</td>
<td>Independent studies indicated that patients of East Asian ancestry who carry HLA-B<em>15:02 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B</em>15:02 prior to initiating treatment with carbamazepine.</td>
</tr>
</tbody>
</table>
Variations in the UGT1A1 gene can influence a patient’s ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to darapladib.

**Pharmacogenetic Research Objectives**

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to darapladib. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with darapladib, the following objectives may be investigated:

- Relationship between genetic variants and the pharmacokinetics of darapladib.
- Relationship between genetic variants and safety and/or tolerability of darapladib.
- Relationship between genetic variants and efficacy of darapladib.

**Study Population**

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

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

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx 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 is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

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

The need to conduct PGx analysis may be identified after a study (or a set of studies) of darapladib has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to darapladib.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) 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 PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx 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. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time.
when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

**Screen and Baseline Failures**

If a blood sample for PGx 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 should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

**Pharmacogenetics Analyses**

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. Candidate genes that may be investigated in this study could include, but not be limited to, *CYP3A4* and *ABCB1* (P-GP). They may also include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants and treatment response and/or tolerance.

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

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

**Informed Consent**

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.
Provision of Study Results and Confidentiality of Subject’s PGx Data

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject’s medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.
References


12.3. Appendix 3: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is likely when any one of the following 3 criteria is fulfilled [Sampson, 2006].

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, 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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

1. PEF, Peak expiratory flow; BP, blood pressure.
2. Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
12.4. Appendix 4: Procedures for Detection, Evaluation, Follow-Up and Reporting of Adverse Events and Medical Device Incidents

Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the subject’s medical records to GSK in lieu of completion of the GSK, AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.
An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as ‘serious’ when it meets at least one of the predefined outcomes as described in the definition of an SAE.

**Assessment of Causality**

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.
Reporting of SAEs to GSK

The primary mechanism for reporting SAEs to GSK will be the electronic data collection tool. If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the GSK Medical Monitor. Then the site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to their GSK protocol contact by telephone.

GSK contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.