In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Pharmacology Study Report

Title:	A Study to evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of Darapladib and its Metabolites in Healthy Volunteers

Phase: I

Compound Number: SB-480848

Effective Date: 15-JUN-2009

Description:

Darapladib (SB-480848) is a novel, selective and orally active inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) in development for the treatment of atherosclerosis.

This was an open label study where each subject participated in 2 study sessions, a Single Dose Session and a Repeat Dose Session. All subjects received 160 mg of EC micronized free-base darapladib as a single dose and as repeated daily doses for 28 days.

The purpose of this study was to characterize the pharmacokinetics of single and repeat oral doses of darapladib and its metabolites (M10, M3 and M4) in healthy adult subjects. Safety and tolerability of darapladib in healthy volunteers was also monitored.

Subject: darapladib, healthy volunteer, SB-480848 metabolite characterization

Author(s): [redacted] (CSSO); [redacted] (MDC); [redacted] (DB); [redacted] (CPMS)

Initiation Date: 12 SEP 2008

Completion Date: 02 DEC 2008

Date of Report: JUN 2009

Sponsor Signatory: [redacted] MD
(and Medical Officer) SVP, Drug Discovery
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
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
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-x)	Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
BA	Bioavailability
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
BPM	Beat Per Minute
BQL	Below the quantification limit
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence Interval
CIB	Clinical Investigator's Brochure
CLr	Renal clearance
CL	Systemic clearance of parent drug
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
Ct	Last observed quantifiable concentration
CDMP	Clinical Document Management and Publishing
CO_2	Carbon dioxide
CPDM	Clinical Pharmacology and Discovery Medicine
CPDS	Clinical Pharmacology Data Sciences
CPK	Creatine phosphokinase
CPKMS	Clinical Pharmacokinetics Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CP-RAP	Clinical Pharmacology Reporting and Analysis Plan
CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSSO	Clinical Science and Study Operations
CV	Coefficient of variance
DB	Discovery Biometrics

DBP	Diastolic blood pressure
DMPK	Discovery Medicine Pharmacokinetics
ECG	Electrocardiogram
EDC	Electronic data capture
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
Kg	Kilogram
λz	Terminal phase rate constant
L	Liter
LFTs	Liver function tests
ln	Naperian (natural) logarithm
LOQ	Limit of quantification
LLQ	Lower limit of quantification
µg	Microgram
µL	Microliter
MAT	Mean absorption time
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRT	Mean residence time
MSDS	Material Safety Data Sheet
msec	Milliseconds
NQ	Non-quantifiable concentration measured as below LLQ
PCI	Potential clinical importance
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic

PSRI	Periodic Safety Reports for Investigators
QC	Quality control
QD	Once daily
RAP	Reporting and Analysis Plan
RBC	Red blood cells
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SD	Standard deviation
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
T	Infusion duration
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
τ	Dosing interval
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
US	United States
Vd/F	Apparent volume of distribution after extravascular (e.g., oral) administration
WBC	White blood cells

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1. INVESTIGATOR INFORMATION AND STUDY ADMINISTRATION

1.1. List of Investigators

Investigator	Investigator/ Site/Center Number.	Institution and Address
[redacted] MD	[redacted]	[redacted]

2. ETHICAL CONDUCT OF THE STUDY

The study protocol (dated 26 Aug 2008), the informed consent, and other information that required pre-approval were reviewed and approved by the institutional review board (IRB):

[redacted]

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable subject privacy and regulatory requirements, including a US IND, and, the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. Electronic case report forms (CRFs) were provided for each subject's data to be recorded.

3. OBJECTIVES & ENDPOINTS

3.1. Objectives

3.1.1. Primary

To characterize the pharmacokinetics of single and repeat oral doses of darapladib and its metabolites (M10, M3 and M4) in healthy adult subjects

To monitor the safety and tolerability of single and repeat oral doses of darapladib in healthy adult subjects

3.1.2. Secondary

To evaluate the inhibition of plasma Lp-PLA_2 activity after repeat dosing of 160 mg of enteric-coat free base (micronised) darapladib

3.2. Endpoints

3.2.1. Primary

The primary PK endpoints were AUC and Cmax of darapladib and its metabolites (M10, M3 and M4) following single and repeat oral doses. Metabolite to parent AUC and Cmax ratio for each metabolite was calculated as data permit.

Clinical safety data (spontaneous AE reporting, vital signs, nursing/physician observation, and clinical laboratory tests) was the primary safety endpoint.

3.2.2. Secondary

Secondary PK endpoints were tmax and t½ of darapladib and its metabolites (M10, M3 and M4) as data permit.

Plasma Lp-PLA_2 activity, expressed in terms of percent inhibition relative to baseline, as data permit.

4. STUDY RATIONALE AND DESIGN

4.1. Study Rationale

Data from a previous human ADME study [GlaxoSmithKline Document Number ZM2007/00048/00] showed that the principal radioactive component in all plasma samples following single and repeat oral administration was unchanged darapladib, SB-480848. Five and eight metabolites were identified in plasma following single and repeat oral administration, respectively. Three noteworthy metabolites were observed in plasma, the result of hydroxylation of the cyclo penta pyrimidinone moiety (M3, SB-823094), N-deethylation (M4, SB-553253) and the formation of a uracil derivative following loss of the fluorobenzylthiol group (M10, SB-554008). M4, which is pharmacologically active, has been quantified in all preclinical toxicity studies, as well as in all clinical studies.

Darapladib is known to undergo acid hydrolysis, with the major acid degradant being M10. The clinical formulation of darapladib is enteric coated to minimize acid hydrolysis in the stomach. Formation of M10 following administration of the enteric coated formulation with food was likely to be substantially less than that observed in the human ADME study considering the radiolabelled [^{14}C]SB-480848 was formulated as a solution and administered with food in the human ADME study.

This study was thus designed to further assess the pharmacokinetics of darapladib and its metabolites (M10, M3 and M4) using the enteric coated formulation of darapladib and a newly developed sensitive LC/MS assay to quantify M10 and M3 following single and 28 days of repeat dosing of darapladib.

4.2. Study Design

This was an open label study where each subject participated in 2 study sessions, a Single Dose Session and a Repeat Dose Session. All subjects were assigned to receive 160 mg of EC micronized free-base darapladib as a single dose subsequently as repeated daily doses for 28 days.

There were 4 days between dosing in the Single Dose Session and the first dose of the Repeat Dose Session due to the PK sampling period following the single dose. PK samples were collected over a 96-hour period after single dose in Session 1, and over a 24-hour period after Days 10 and 28 of repeat dosing, as well as over a 28-day duration following the last day of dosing of the repeat dose session. PD samples were collected over a 24-hour period after Days 10 and 28 of repeat dosing, as well as over the 28-day duration following the last day of dosing of the repeat dose session.

Subjects returned approximately 28 days after the last dose of study medication for a follow-up visit. The total study duration for each subject including the screening, treatment and follow-up periods was approximately 12 weeks.

5. DIAGNOSIS AND CRITERIA FOR INCLUSION

A sufficient number of subjects were screened and enrolled so that at least 10 subjects completed the study.

5.1. Inclusion Criteria

A subject was considered eligible for inclusion in this study only if all of the following criteria applied:

1. Subject was healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and ECG. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may have been included only if the Investigator and the GSK Medical Monitor agreed that the finding was unlikely to introduce additional risk factors and did not interfere with the study procedures.
2. Male or female who were between 18 and 65 years of age inclusive, at the time of signing the informed consent.
3. A female subject was eligible to participate if she was of:
    - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MlU/ml and estradiol < 40 pg/ml (<140 pmol/L) is confirmatory].

- Child-bearing potential and agreed to use one of the contraception methods listed in Section 8.1 of the protocol 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 were to agree to use contraception until the follow-up visit.

4. Body weight ≥ 50 kg and BMI within the range 19 – 30 kg/m^2 (inclusive).
5. Capable of giving written informed consent, which included compliance with the requirements and restrictions listed in the consent form.
6. QTcB or QTcF < 450 msec; or QTc < 480 msec in subjects with Bundle Branch Block.

5.2. Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. A positive pre-study drug/alcohol screen.
2. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening
3. A positive test for HIV antibody.
4. 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 was 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.
5. The subject had participated in a clinical trial and had 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 was longer).
6. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
7. 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 would not interfere with the study procedures or compromise subject safety.
8. Consumption of grapefruit or grapefruit juice within 7 days prior to first dose of study medication.
9. History of drug abuse.
10. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicated their participation.

11. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions, or severe allergic responses.
12. History of cholecystectomy or biliary tract disease, or a history of liver disease with elevated liver function tests of known or unknown etiology.
13. History of sensitivity to heparin or heparin-induced thrombocytopenia (if heparin was to be used for flushing a cannula).
14. Where participation in the study resulted in donation of blood or blood products in excess of 500 mL within a 56 day period.
15. Use of oral, injected and implanted hormonal methods of contraception for female subjects.
16. Pregnant females as determined by positive serum hCG test at screening or prior to dosing.
17. Lactating females.
18. Unwillingness or inability to follow the procedures outlined in the protocol.
19. Subject was mentally or legally incapacitated.

5.3. Permitted Medications

All concomitant medications taken during the study were recorded in the CRF with indication, dose information, and dates of administration. The minimum requirement was that drug name and the dates of administration were recorded. Acetaminophen at doses of ≤ 2 grams/day was permitted.

5.4. Prohibited Medications

Subjects abstained from using all prescription or over-the-counter medications (other than acetaminophen at doses of ≤ 2 grams per day) within 7 days or 5 half-lives (whichever was longer) prior to Day 1 of Session 1 and until the end of the study. The investigator was to be informed as soon as possible about any medication taken from the time of screening until completion of follow-up procedures.

Use of oral, injected and implanted hormonal methods of contraception for female subjects was prohibited.

6. TREATMENT ADMINISTRATION

6.1. Treatments Administered

All subjects received 160 mg of EC micronized free-base darapladib as a single dose and subsequently as repeated daily doses for 28 days. All doses were administered after a meal by study personnel and were given orally with 240 mL of tepid water.

6.2. Identity of Investigational Product (s)

Product name:	darapladib
Dosage form:	Enteric coated , free base (micronized) tablet
Unit dose strength(s)/Dosage level(s):	160 mg
Route/ Administration/ Duration:	Route: oral Administered: daily Duration: Single dose, followed by 28 days of repeat dosing
Dosing instructions:	Take with food. Swallow whole, do not chew.
Manufacturer/ source of procurement:	GSK
Lot number: Batch number:	081164493 081164493

7. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures were performed by study personnel as described in the Time and Events Table (see Attachment 1).

Subjects were screened within 30 days prior to administration of the first dose of study medication in Session 1 to confirm they met the entrance criteria for the study. The investigator or a sub-investigator discussed with each subject the nature of the study, its requirements, and its restrictions. Written informed consent was obtained prior to performance of any protocol-specific procedures.

Subjects were not to eat or drink anything for at least 4 hours before the screening visit. At the screening visit, Inclusion and Exclusion Criteria were evaluated and the procedures summarized in the Time and Events Table (Attachment 1) were performed.

Demographic information collected for this study included date of birth, age, gender, and race. Medical history included any information regarding any known allergies to drugs, use of concomitant medications, history of smoking and alcohol consumption, and history of blood donation or participation in other clinical trials. Information on additional screening assessments is provided in Attachment 1, Time and Events Table for LPL112498, and in Section 7.1 below.

7.1. Safety Assessments

7.1.1. Adverse Events and Serious Adverse Events

Adverse event (AE) data were collected and recorded on the CRF starting with the dosing in Session 1 and continuing until the last PK sample collection in Session 2. From the time a subject consented to participate in the study until he or she had completed the study (including any follow-up period), all serious adverse events (SAEs) assessed as related to study participation (eg, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, were to be reported promptly to GSK. The investigator was responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in the study protocol.

When an AE or SAE occurred, it was the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event and record all relevant information regarding an AE or SAE in the appropriate data collection tool. The diagnosis was to be documented as the AE/SAE and not the individual signs/symptoms. Once an investigator became aware that an SAE had occurred in a study subject, she or he was to report the information to GSK within 24 hours and provide an assessment of causality.

7.1.2. Clinical Laboratory Evaluations

Clinical laboratory assessments were performed at the times indicated in Attachment 1, Time and Events Table for LPL112498, and as deemed necessary by the principal investigator or medical monitor. Table 1 lists the clinical laboratory parameters assessed during the study.

Table 1 Clinical Laboratory Assessments

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Other tests

HIV
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result)
FSH and estradiol (as appropriate)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

Laboratory values of potential clinical concern were to be reported and discussed with the medical monitor, and those abnormal findings judged by the Investigator as clinically significant were to be recorded as AEs or SAEs, as appropriate.

Liver chemistry threshold stopping criteria were designed to assure subject safety. When subjects met the following liver chemistry threshold criteria, investigational product was permanently withdrawn, additional testing performed, and the subject monitored until liver chemistries resolved, stabilized, or returned to baseline values. The subject was then permanently withdrawn from the study:

- ALT ≥ 3x upper limit of normal (ULN) and bilirubin ≥ 1.5xULN (> 35% direct)
- ALT ≥ 3xULN.

Subjects with ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (> 35% direct bilirubin; bilirubin fractionation required) were immediately and permanently withdrawn from investigational product. Every attempt was to be made to have the subject return to clinic (within 24 hours) for repeat liver chemistries and additional testing, and monitored closely (with specialist or hepatology consultation recommended). This event was to be reported to GSK within 24 hours of learning of its occurrence. Subjects were monitored twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, and bilirubin) resolved, stabilized or returned to within baseline values. Upon completion of the safety follow-up, the subject was then withdrawn from the study.

Subjects with ALT ≥ 3xULN were to be permanently withdrawn from investigational product and monitored weekly until liver chemistries (ALT, AST, alkaline phosphatase, and bilirubin) resolved, stabilized or returned to within baseline values. This event was to be reported to GSK within 24 hours of learning of its occurrence.

In all the above situations, every attempt was to be made to obtain:

- 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 (if subject resided outside the United States of America [USA] or Canada, or had travelled outside USA or Canada in past 3 months).
- Blood sample for PK analysis, obtained within ~33 hours of last dose. Recorded the date and time of the PK blood sample draw and the last dose of investigational product prior to blood sample draw on the CRF.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if bilirubin ≥ 1.5xULN.
- Recorded the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form.
- Recorded use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, putative hepatotoxins, or alcohol on the concomitant medications report form.

The following were required for subjects with ALT ≥ 3xULN and bilirubin ≥ 1.5xULN but were optional for other abnormal liver chemistries:

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

7.1.3. Other Safety Assessments

7.1.3.1. Physical Examination

A complete medical exam was performed including assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities. Height and weight were measured and recorded. Abnormal physical examination findings that were judged by the Investigator as clinically significant were recorded as AEs or SAEs, as appropriate.

7.1.3.2. Vital Signs Measurements

Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured at the times indicated in Attachment 1, Time and Events Table for LPL112498, and as deemed necessary by the Investigator or medical monitor. All measurements were obtained after the subject had rested in a supine position for at least 5 minutes. Abnormalities of potential clinical concern were reported and discussed with the medical monitor, and those abnormal findings judged by the Investigator as clinically significant were recorded as AEs or SAEs, as appropriate.

7.1.3.3. Electrocardiograms

Standard 12-lead ECGs were obtained at the time points indicated in Attachment 1, Time and Events Table for LPL112498. All 12-lead ECGs were obtained after the subject had rested in a supine position for at least 5 minutes. Whenever 12-lead ECGs were performed at the same nominal time as a blood draw or vital signs measurement, the 12-lead ECG was to be obtained first, followed by vital signs and then blood draws.

Abnormalities of potential clinical concern were reported, and those abnormal findings judged by the Investigator as clinically significant were recorded as AEs or SAEs, as appropriate.

7.2. Pharmacokinetic Assessments

7.2.1. Collection and Sample Preparation

Pharmacokinetic samples were collected at time-points outlined in the Time and Events Tables (Attachment 1).

Blood samples were taken via an indwelling cannula (or by direct venapuncture), collected into an ethylenedinitrotetraacetic acid (EDTA) tube and immediately placed on crushed ice. All samples were centrifuged at 1000x g (approximately 3000 rpm) for approximately 10-15 minutes under refrigeration (4ºC) within 30 minutes of collection. Supernatant plasma was transferred to a polypropylene tube and stored at -20 °C before shipment. Samples were shipped frozen on dry ice (or refrigerated as appropriate) at agreed timepoints throughout the study to: GlaxoSmithKline, King of Prussia, PA, USA

7.2.2. Assay Methodology

Plasma SB-480848 (darapladib), SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) concentrations were determined by Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, King of Prussia, PA, USA. Human plasma samples were analysed for SB-480848, SB-553253, SB-554008 and SB-823094 concentrations using a validated method. SB-480848, SB-553253, SB-554008 and SB-823094 were extracted from human plasma by liquid-liquid extraction. Extracts were analysed by liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). The assay was validated over the SB-480848, SB-553253, SB-554008 and SB-823094

concentration range of 0.10 ng/mL to 50 ng/mL in human plasma [GlaxoSmithKline Document Number CD2008/01347/00].

Quality controls were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. For the analysis to be acceptable, no more than one third of the quality control results were to deviate from the nominal concentration by more than 15%, with at least one quality control result acceptable at each concentration. Quality control results from this study met these acceptance criteria. All data are stored in the Archive, GlaxoSmithKline, King of Prussia, PA, USA.

7.3. Pharmacodynamic Assessments

Blood samples to determine Lp-PLA_2 plasma activity were collected into EDTA tubes at the time points listed in Attachment 1, Time and Events Table for LPL112498. Plasma was separated by centrifugation at approximately 1500x g for 10 minutes under refrigeration (4ºC) and plasma samples were transferred to a polypropylene tube and stored at approximately -70ºC prior to shipment to Quest Diagnostics.

All samples were analyzed by Quest Nichols Institute, San Juan Capistrano, CA using a validated colorimetric assay method (CAM) with an LLQ of 1.8 nmol/min/mL. Any results less than LLQ were reported as <1.8 nmol/min/mL.

7.4. Pharmacogenetic Assessments

A blood sample for PGx analysis was collected into an EDTA tube at any time after the subject provided consent for PGx testing. Samples were stored at -20°C prior to shipment to Quest Diagnostic Clinical Trials, Van Nuys, CA.

All PGx samples were labeled (or "coded") with a study-specific number that could be traced or linked back to the subject by the investigator or site staff, but did not carry personal identifiers (such as name or social security number).

Deoxyribonucleic acid (DNA) extraction was performed by Quest Diagnostic Clinical Trials.

As of the date of this report, PGx analyses for the V279F polymorphism for Lp-PLA_2 have not been performed.

The need to conduct additional PGx analyses may be identified after further study(ies) of darapladib have been completed and the study data reviewed. For this reason, all PGx samples from the current study may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner.

The results of any PGx analyses will be documented in a separate report.

8. METHODS

8.1. Data Quality Assurance

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors contacted 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 included identification, agreement and documentation of data items for which the CRF served as the source document.

- GSK monitored the study consistent with the demands of the study and site activity to verify that the Data were authentic, accurate, and complete.
- Safety and rights of subjects were being protected.
- Study was conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

To ensure compliance with GCP and all applicable regulatory requirements, GSK could conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections could have occurred at any time during or after completion of the study. If an audit or inspection occurred, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The database was released when all subjects completed the study, all data were entered, and all queries had been resolved. All planned analyses were performed after the database was frozen.

8.2. Data Analysis Methods

8.2.1. Sample size considerations

Sample size was based on feasibility. The plan for this study was to enroll 20 subjects to have 10 subjects evaluable. Based on study SB480848/015, the maximum within subject standard deviation (SD) for metabolite to parent ratio was 3.1%. Assuming similar variability of metabolite to parent ratio in current study, the half width of 90% confidence interval (CI) of metabolite to parent ratio would be about 1.8%. Based on study LPL107988, the CVw% for SB-480848 Cmax was 26.0%, and the CVw% for AUC was 18.3%. Based on the CVs and 10 subjects, the half width of 90% CI for Rcmax would be within 22.4% of point estimate and for Ro, Rp and Rs would be within 15.1% of point estimate.

8.2.2. Interim Analyses

No interim analysis was planned for this study. After the last dose of darapladib and before database freeze, Clinical Pharmacology Modeling and Simulation assessed preliminary pharmacokinetic data based on nominal time. This was to provide preliminary results of metabolite to parent exposure ratio to begin dialogue with the FDA on the need to conduct further toxicological testing on the metabolites, particularly M10 and M3.

8.2.3. Final Analyses

Following the completion of the study, all planned analyses outlined in the RAP were conducted after the database was frozen.

Statistical analyses were performed under the direct auspices of Discovery Biometrics, GlaxoSmithKline Pharmaceuticals, Philadelphia, PA.

8.2.3.1. Safety Analyses

No formal inferential analyses of safety data were planned or conducted. Safety endpoints, including clinical laboratory test results, 12-lead ECG parameters, and vital sign measurements were tabulated and listed by treatment.

8.2.3.2. Pharmacokinetic Analyses

PK analyses were conducted by Covance Laboratories Inc, Madison, WI, USA, under the direction of Clinical Pharmacology/Modeling and Simulation, Quantitative Sciences, GlaxoSmithKline. All PK analyses were performed and archived in accordance with GSK and CP/MS Standard Operating Procedures (SOPs) and guidance documents.

8.2.3.2.1. Drug Concentration Data

Plasma SB-480848 (darapladib), SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) concentrations, along with the actual blood sampling dates and times were listed by subject and planned sampling time. Plasma SB-480848, SB-553253, SB-554008 and SB-823094 concentrations were summarised by planned sampling time. Figures of individual and mean/median plasma SB-480848 concentration-time profiles were produced on both semi-log and linear scales.

For the calculation of individual PK profiles, if an NQ (not quantifiable) value occurred in a profile before the first measurable concentration, it was assigned a value of zero concentration. Additionally, if an NQ value occurred after a measurable concentration in a profile and was followed by a value above the LLQ (lower limit of quantification), then NQ was generally omitted. If two NQ values occurred in succession (after Cmax) the profile was deemed to have terminated at the first NQ value and any subsequent concentrations were omitted from PK calculations.

For the calculation of mean and median profiles, when estimating the mean and median values for the concentration at a given time point, NQ values were handled in a manner consistent with calculation of individual PK profiles (i.e., all NQ values were set to zero except when an individual NQ fell between two quantifiable values, in which case it was omitted). The mean/median value at a time with one or more NQ values was reported (in tabular or graphical fashion) unless the resulting mean/median value was below the LLQ of the assay, in which case the value was assigned NQ.

8.2.3.2.2. Pharmacokinetic Parameters

PK analyses of plasma SB-480848, SB-553253, SB-554008 and SB-823094 concentration-time data were conducted using non-compartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.2 (Pharsight Corporation, Mountain View, CA) according to the guidance described in Non-Compartmental Analysis of Pharmacokinetic Data (GUI-CPK-3001 v01, 28-Sep-07). Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects. Values for the following PK parameters were estimated following administration of single and multiple doses of SB-480848, as appropriate.

- The maximum observed plasma concentration (Cmax) and the first time to reach Cmax (tmax) were the actual observed values.
- Where possible, the terminal plasma elimination rate-constant (λz) was estimated from log-linear regression analysis of the terminal phase of the plasma concentration-time profile following repeat dosing on Day 28. The number of points included in the terminal phase was determined by visual inspection of the semi-log plots of the plasma concentration-time profiles. The associated apparent terminal elimination half-life (t1/2) was calculated as $\ln 2/\lambda z$.
- The area under the plasma concentration-time curve from time zero to the last quantifiable time point [AUC(0-t)], the area from time zero to infinity [AUC(0-∞)], and the area over the dosing interval [AUC(0-τ)] were calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method was used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method was used for those arising from decreasing concentrations. AUC(0-∞) on Day 1 was estimated by extrapolating the AUC(t-∞) using Clast/λz where Clast is the last measurable analyte concentration in the profile and λz was the terminal elimination rate constant.

Plasma SB-480848, SB-553253, SB-554008 and SB-823094 PK parameter estimates were listed by subject and study day. Individual plasma SB-480848, SB-553253, SB-554008 and SB-823094 parameter estimates were plotted by treatment on linear scales. Plasma SB-480848, SB-553253, SB-554008 and SB-823094 PK parameter values were summarized by treatment and study day.

For plasma concentration-time profiles where only few or sporadic samples had quantifiable concentrations, Cmax and tmax were reported for profiles with at least 1 quantifiable value, and AUC(0-t) was calculated for profiles with at least 3 quantifiable values.

In accordance with GlaxoSmithKline SOP-NPD-0003 v01, Management of the Sponsor's Clinical Study Documents (Sponsor Study Records)**,** all PK analyses were stored in the Archive, GlaxoSmithKline, Research and Development under protocol LPL112498.

8.2.3.3. Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic/Pharmacodynamic aspects of this study were conducted at the Department of Clinical Pharmacology/Modeling & Simulation, Quantitative Sciences, GlaxoSmithKline, King of Prussia, PA. Pharmacokinetic/Pharmacodynamic data are stored in the Archive, GlaxoSmithKline, R&D, King of Prussia, Pennsylvania, USA under protocol LPL112498.

The relationship between SB-480848 plasma concentration and plasma Lp-PLA_2 activity data was explored graphically. The results suggested a decrease in plasma Lp-PLA_2 activity with an increase in SB-480848 plasma concentration. Based on graphical assessment and historical data, a direct effect inhibitory Emax model was used to describe the relationship. The PK/PD model was parameterized for baseline plasma Lp-PLA_2 activity (Eo) and the SB-480848 plasma concentration causing 50% inhibition of Lp-PLA_2 activity (IC_{50}). Sigmoid Emax model with the addition of Hill coefficient (γ) was also investigated. The PK/PD data were analyzed using Nonlinear Mixed Effect Modeling as implemented in the computer program NONMEM (Version V, level 1.0). The First- Order Conditional Estimation with interaction (FOCE-I) method was employed in the model development process.

The following criteria were used to compare and select different candidate models:

- A significant reduction in the objective function value (≥ 6.64, $\chi^2 < 0.01$) for FOCE-I based on the likelihood ratio test
- Increase in the precision of the estimated PK/PD parameters
- Decrease in the interindividual and/or residual errors
- Improvement in the fits of the diagnostic scatter plots (e.g., more random distribution in the weighted residual plots vs. predicted concentration and time plots; random distribution of the observed versus predicted concentrations values across the identity line)
- Model performance parameters (i.e., convergence of the minimization, termination of the covariance step without warning messages, and correlation between model parameters < 0.95)

8.2.3.4. Statistical Analyses

The statistical analyses of pharmacokinetic data were performed under the direct auspices of Discovery Biometrics, Quantitative Sciences, GlaxoSmithKline.

Details of the plans for data analysis, data handling and the specific statistical analyses to be performed are provided in the Reporting and Analysis Plan (RAP) (Attachment 2).

Following loge-transformation, AUC and Cmax of SB-480848 and its metabolites SB-553253 (M4), SB-554008 (M10), SB-823094 (M3) were separately analyzed using a mixed effect model, fitting day as a fixed effect and subject as a random effect. Point estimates and associated 90% confidence intervals for the comparison of interests were constructed using the residual variance. The point estimates and associated 90% confidence intervals were then exponentially back-transformed to provide point estimates and 90% confidence intervals for the ratios (e.g., Ro, Rs and Rcmax). Similar analysis was done with day 1 AUC (0 - ∞) and AUC (0 - τ) data fitting PK parameter as fixed effect and subject as random effect to provide point estimate and 90% confidence intervals for the ratio of Rp.

The accumulation ratios (Ro, Rp, Rs, and Rcmax) were derived as shown in the equations below:

Observed Accumulation Ratio (Ro) =AUC(0-τ) of Day 10 or 28 / AUC(0-τ) of Day 1

Predicted Accumulation Ratio (Rp) = AUC(0-∞) of Day 1 / AUC(0-τ) of Day 1

Steady-State Accumulation Ratio (Rs) = AUC(0-τ) of Day 10 or 28/ AUC(0-∞) of Day 1

Cmax Accumulation Ratio (Rcmax) = Cmax of Day 10 or 28/ Cmax of Day 1

The within-subject coefficients of variation (CVw) for AUC and Cmax were calculated based on the loge –normal distribution.

For $\log_e$-transformed parameters, estimates of within subject (CVw) was calculated as

CVw = sqrt[exp(MSE)-1]*100,

where MSE is the residual mean squared error from the model.

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

Descriptive statistics (n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum, CVb%) was calculated for all pharmacokinetic endpoints by day. In addition, for AUC (0-t), AUC (0 - ∞), AUC (0 - τ), Cmax, t½, and Cτ, geometric means and their 95% confidence intervals were calculated. Cτ on Days 26, 27 and 28 data were presented graphically for visual assessment of steady state.

8.2.4. Changes in Conduct of the Study or Planned Analyses

There were no changes made to the planned analyses.

9. STUDY POPULATION RESULTS

9.1. Subject Disposition and Demographics

Subject disposition and demographic characteristics are summarized in Table 2. A total of 20 healthy volunteers were enrolled into the study. Seventeen (85%) subjects completed both single and repeat dosing sessions as planned, and three subjects discontinued the study early because they withdrew consent.

Table 2 Summary of Subject Disposition and Demographic Characteristics

Number of Subjects	LPL112498
Number of subjects planned, N:	10
Number of subjects entered, N:	20
Number of subjects included in All subjects (safety) population, n (%):	20
Number of subjects included in PK population, n (%):	20 (100%)
Number of subjects completed as planned, n (%):	17 (85%)
Number of subjects withdrawn (any reason), n (%):	3 (15%)
Number of subjects withdrawn for SAE, n (%):	0 (0%)
Number of subjects withdrawn for AE, n (%):	0 (0%)
Reasons for subject withdrawal, n (%)	
Withdrew consent	3 (15%)
Demographics	LPL112498
Age in Years, Mean (SD)	31.7 (11.4)
Sex, n (%)	
Female:	6 (30%)
Male:	14 (70%)
BMI (kg/m^2), Mean (SD)	25.6 (3.1)
Height (cm), Mean (SD)	174.1 (8.3)
Weight (kg), Mean (SD)	78.3 (15.1)
Ethnicity, n (%)	
Hispanic or Latino:	2 (10%)
Not Hispanic or Latino:	18 (90%)
Race, n (%)	
African American/African Heritage	3 (15%)
American Indian or Alaskan Native	1 (5%)
Asian – South East Asian Heritage	1 (5%)
White – White/Caucasian/European Heritage	14 (70%)
Mixed Race	1 (5%)

Source Data: Table 9.1., Table 9.2., Table 9.3.

9.2. Protocol Deviations

There were no subjects with major deviations from the protocol eligibility criteria.

All other protocol deviations were considered minor and unlikely to affect the safety of the subjects or the interpretation of the study data, and the subjects were permitted to continue in the study.

9.3. Populations of Interest

Safety: All subjects who received at least one dose of darapladib were included in the Safety Population.

Pharmacokinetic: All subjects who received at least one dose of darapladib and provided evaluable pharmacokinetic data were included in the formal statistical analysis of the pharmacokinetic data. The impact of subjects with incomplete data was to be evaluated.

Pharmacodynamic: Subjects were included in the summary statistics if they provided sufficient data to calculate percent inhibition of plasma Lp-PLA2 activity, i.e. provide data from baseline and at least one post-dose sample.

9.4. Concomitant Medications

Two subjects received protocol approved concomitant medication during this study.

No subjects received any other concomitant medications during this study.

9.5. Treatment Compliance

Treatment compliance was 100% as confirmed by study staff responsible for administering all doses of medication during the study.

10. SAFETY RESULTS

10.1. Extent of Exposure

All 20 subjects randomized into the study received 160 mg of enteric coated micronized free-base darapladib as a single dose. All 20 subjects randomized into the study received 160 mg of EC micronized free-base darapladib daily as a repeat dose for at least 5 days. 17 subjects finished the planned repeat dose regimen of 28 days.

10.2. Adverse Events

A summary of all AEs, regardless of causality, is presented by system organ class and preferred term for each treatment in Table 3. There were five subjects with AEs reported during the single dose portion of this study. Twelve (12) out of twenty (20) subjects experienced AEs during the 28 day repeat dose regimen of the study. The most common AEs were headache (6 subjects), diarrhea (6 subjects) and fatigue (4 subjects). Most AEs were assessed by the investigator as mild to moderate in intensity. [redacted] The AE was noted as severe in intensity, related to study medication and resolved after approximately 6 days.

Table 3 Summary of All AEs in Study LPL112498

Preferred Term	Single Dose 160 mg darapladib N=20	Repeat Dose 160 mg darapladib N=20
	n (%)	n (%)
Subjects with Any AE	5 (25)	12 (60)
Gastrointestinal disorders		
Diarrhoea	2 (10)	4 (20)
Abdominal Pain	0 (0)	2 (10)
Abdominal Distension	0 (0)	1 (5)
Nausea	0 (0)	1 (5)
Nervous system disorders		
Headache	2 (10)	4 (20)
Disturbance in attention	1 (5)	0 (0)
Somnolence	1 (5)	0 (0)
General disorders		
Fatigue	2 (10)	2 (10)
Irritability	0 (0)	1 (5)
Musculoskeletal disorders		
Arthralgia	0 (0)	1 (5)
Back pain	0 (0)	1 (5)
Flank pain	0 (0)	1 (5)
Pain in extremity	0 (0)	1 (5)
Renal and urinary disorders		
Urine odour abnormal	2 (10)	0 (0)
Bladder neck obstruction	0 (0)	1 (5)
Glycosuria	1 (5)	0 (0)
Infections and infestations		
Pharyngitis	0 (0)	1 (5)
Viral upper respiratory tract infection	0 (0)	1 (5)
Metabolism and nutrition disorders		
Anorexia	0 (0)	1 (5)
Decreased appetite	0 (0)	1 (5)
Psychiatric disorders		
Abnormal dreams	1 (5)	0 (0)
Reproductive system and breast disorders		
Dysmenorrhoea	0 (0)	1 (5)
Respiratory, thoracic and mediastinal disorders		
Rhinorrhoea	0 (0)	1 (5)

Source Data: Data Table 10.2.

10.3. Drug-Related Adverse Events

Table 4 Summary of Drug-Related AEs in Study LPL112498

Preferred Term	Single Dose 160 mg darapladib N=20	Repeat Dose 160 mg darapladib N=20
	n (%)	n (%)
Subjects with Any AE	5 (25)	7 (35)
Gastrointestinal disorders		
Diarrhoea	2 (10)	3 (15)
Abdominal Pain	0 (0)	2 (10)
Abdominal Distension	0 (0)	1 (5)
Nervous system disorders		
Headache	1 (5)	1 (5)
Disturbance in attention	1 (5)	0 (0)
Somnolence	1 (5)	0 (0)
General disorders		
Fatigue	2 (10)	2 (10)
Musculoskeletal disorders		
Back pain	0 (0)	1 (5)
Renal and urinary disorders		
Urine odour abnormal	2 (10)	0 (0)
Glycosuria	1 (5)	0 (0)
Psychiatric disorders		
Abnormal dreams	1 (5)	0 (0)

Source Data: Data Table 10.4.

10.4. Serious Adverse Events and Adverse Events Leading to Withdrawal

No subject died, experienced an SAE, or withdrew due to an AE during the study.

10.5. Pregnancies

There were no reported pregnancies in female subjects participating in the study, or in female partners of male subjects during the study.

10.6. Clinical Laboratory Evaluations

Chemistry, hematology and urinalysis parameters are summarized descriptively by treatment and timepoint in Data Table 10.5 to Data Table 10.8. There were no mean changes over time of clinical concern for any analyte.

10.7. Vital Signs

There were no clinically significant mean changes over time in vital sign parameters (HR, SBP, and DBP) on any treatment, and no individual vital sign results of potential clinical importance (PCI) (Data Table 10.20).

10.8. ECGs

There were no clinically significant mean changes over time in ECG parameters (HR, QRS duration, PR, QT, QTc, QTcF and QTcB) on any treatment, and no 12-lead ECG abnormal findings of clinical significance were reported for any subject during the study (Data Table 10.13).

A total of 5 individual ECG values of PCI were reported in 5 subjects during the study (Data Table 10.16). The ECG abnormalities, which included increases in QRS duration (3 subjects), and slight increases in corrected QT interval (2 subjects), were not considered clinically significant by the principal investigator.

11. PHARMACOKINETIC RESULTS

11.1. Drug Concentration Data

Individual plasma SB-480848 (darapladib), SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) concentration listings and associated summary statistics were prepared. Individual plasma SB-480848, SB-553253, SB-554008 and SB-823094 concentration-time profiles are displayed with actual time on both semi-logarithmic and linear scales by subject and treatment. Descriptive statistics for plasma SB-480848, SB-553253, SB-554008 and SB-823094 concentration data at each planned relative time are presented by treatment. Mean and median steady-state plasma SB-480848, SB-553253, SB-554008 and SB-823094 concentration-time profiles for all treatments are displayed with scheduled time and are presented on both semi-logarithmic and linear scales.

All concentration data for SB-554008 were below the limit of quantitation following single dosing in Session 1.

[redacted]

11.2. Plasma Pharmacokinetic Parameters

11.2.1. SB-480848, SB-553253, SB823094, and SB-554008 Plasma PK Parameters

SB-480848, SB-553253, SB823094, and SB-554008 plasma PK parameters are summarized in Data Table 11.5, Table 11.6, Table 11.7, Table 11.8, Table 11.9, Table 11.10, Table 11.11, Table 11.12, and Table 11.13. Selected PK parameters are also summarized in Table 5, Table 6, and Table 7, below.

Following single dose administration, SB-554008 (M10) was not quantifiable in any samples at any time point from any subject. For SB-823094 (M3), mean plasma $AUC_{(0-t)}$ and Cmax were 3.6% (range 1.2 – 7.6%) and 11.3% (range 4.5 – 17.8%) of parent, respectively. Consistent with historical data, SB-553253 (M4) was present in plasma at an average of 3.2% (range 1.2 – 5.4%) of parent $AUC_{(0-t)}$ and 9.0% (range 3.3 – 15.2%) of parent Cmax (Table 5).

Table 5 Pharmacokinetic Parameters Following Single Oral Dose of 160 mg Enteric Coated Tablets of Micronized Free-base darapladib (SB-480848) in Healthy Volunteers

	AUC(0-t)		Cmax		Tmax
n = 20	Ng•hr/mL	% Parent	ng/mL	% Parent	hr
SB-480848	456.1 (48.9%)	--	18.6 (65.3%)	--	9.0 (4.0 – 24.0)
SB-553253 (M4)	14.6[1] (82.7%)	3.2%[1] (1.2 – 5.4%)	1.6 (109.7%)	9.0% (3.3–15.2%)	7.5 (6.0 – 24.0)
SB-823094 (M3)	16.2[1] (83.7%)	3.6%[1] (1.2 – 7.6%)	2.0 (107.5%)	11.3% (4.5–17.8%)	9.0 (6.0 – 24.0)
SB-554008 (M10)	Not quantifiable				

AUC(0-t) and Cmax values are presented as geometric mean (CV%); Tmax presented as median (range); % Parent as mean (range);
1. n = 18
Source Data: Data Table 11.5, Table 11.6, Table 11.7, Table 11.8, Table 11.9, Table 11.10, Table 11.11, Table 11.12, and Table 11.13

Following 10 day repeat dosing, SB-480848 and all three metabolites (M10, M3 and M4) were quantifiable in human plasma. M10 had the lowest exposure with plasma $AUC_{(0-24)}$ and Cmax at an average of 1.5% (range 0.8 – 2.7%) and 1.1% (range 0.7 – 1.6%) of parent, respectively. M3 was circulating in plasma at an average of 5.8% (range 3.1 – 9.1%) of parent $AUC_{(0-24)}$ and 11.1% (range 6.5 – 19.6%) of parent Cmax. M4 was present at levels similar to M3 and was consistent with historical data (Table 6).

Table 6 Pharmacokinetic Parameters Following 10-day Repeat Oral Doses of 160 mg Enteric Coated Tablets of Micronized Free-base darapladib (SB-480848) in Healthy Volunteers

	AUC(0-τ)		Cmax		Tmax
n =a 19	ng•hr/mL	% Parent	ng/mL	% Parent	hr
SB-480848	362.2 (33.7%)	--	25.1 (38.9%)	--	9.0 (0.0 – 23.9)
SB-553253 (M4)	17.0 (51.0%)	4.9% (2.6 – 6.7%)	2.0 (69.0%)	8.8% (3.6–16.7%)	9.0 (4.1 – 23.9)
SB-823094 (M3)	20.2 (53.9%)	5.8% (3.1 – 9.1%)	2.7 (61.2%)	11.1% (6.5–19.6%)	9.0 (0.0 – 23.9)
SB-554008 (M10)	5.3 (41.4%)	1.5% (0.8 – 2.7%)	0.3 (41.0%)	1.1% (0.7 – 1.6%)	9.0 (0.0 – 23.9)

AUC(0-τ) and Cmax values are presented as geometric mean (CV%); Tmax presented as median (range); % Parent as mean (range)
Source Data: Data Table 11.5, Table 11.6, Table 11.7, Table 11.8, Table 11.9, Table 11.10, Table 11.11, Table 11.12, and Table 11.13

Following 28 day repeat dosing, exposures of M10 and M3 were low relative to parent and similar to Day 10 results. Exposure to M10 in all subjects was lower than 5% of parent and only 1 out of 19 subjects had an AUC of M3 above 10% of parent (10.7%) (Table 7). Exposure to M4 was low and the metabolite to parent ratio was below 10% in all subjects. Half-life was estimated in 15 out of 19 subjects and M4 was observed to circulate in plasma for a prolonged period of time following repeat dosing (t1/2 was on average 285 hours).

Based on visual inspection of trough data collected on Days 26 through 28, steady-state appears to have been achieved for SB-480848, M10 and M3 by Day 28.

Table 7 Pharmacokinetic Parameters Following 28-day Repeat Oral Doses of 160 mg Enteric Coated Tablets of Micronized Free-base darapladib (SB-480848) in Healthy Volunteers

	AUC(0-τ)		Cmax		Tmax	t1/2
n = 19	ng•hr/mL	% Parent	ng/mL	% Parent	hr	hr
SB-480848	315.1 (40.5%)	--	17.5 (49.8%)	--	6.0 (0.5–12.0)	126.3 (29.7%)
SB-553253 (M4)	14.7 (59.2%)	4.8% (2.9-8.7%)	1.2 (99.3%)	7.5% (3.1-20.8%)	6.0 (0.0–12.0)	285.2[1] (25.2%)
SB-823094 (M3)	15.1 (73.5%)	5.1% (3.1-10.7%)	1.4 (105.6%)	8.7% (3.7-22.3%)	6.0 (0.0-9.0)	96.4[2] (27.9%)
SB-554008 (M10)	7.7 (34.8%)	2.5% (1.7-4.0%)	0.4 (36.2%)	2.2% (1.4-3.8%)	9.0 (0.0-12.2)	148.2[2] (36.6%)

AUC(0-τ) and Cmax values are presented as geometric mean (CV%); Tmax presented as median (range); % Parent as mean (range);
1. n = 15;
2. n = 16;
Source Data: Data Table 11.5, Table 11.6, Table 11.7, Table 11.8, Table 11.9, Table 11.10, Table 11.11, Table 11.12, and Table 11.13

11.3. Statistical Analyses of Pharmacokinetic Parameters

11.3.1. Assessment of Accumulation for SB-480848, SB-553253, and SB-823094

In general, SB-480848 displayed evidence of accumulation after repeat dosing, as the accumulation ratio was greater than unity, and the corresponding 90% confidence interval of observed accumulation ratio (Ro) ranged from 1.76 to 3.25 on Day 10 and 1.53 to 2.82 on Day 28. The Cmax accumulation ratio was greater than unity on Day 10, with corresponding 90% confidence interval excluding one, while on Day 28, the accumulation ratio was 0.94, on average, with 90% confidence interval from 0.76 to 1.17. The predicted accumulation ratio (Rp) was significantly greater than unity. The steady state accumulation ratio (Rs) was significantly lower than unity, implying a deviation from linearity and/or time-invariance.

In general, both SB-553253 (M4) and SB-823094 (M3) exhibited moderate level of accumulation following repeat dosing (generally 35-40%).

A summary of these results is presented in Table 8 below.

Table 8 Assessment of Accumulation for SB-480848, SB-553253, and SB-823094 Plasma PK Parameters

Analyte	Parameter	Comparison	Ratio[1]	90% Conference Interval	%CVw
SB-480848	Rcmax	Day 10 : Day 1	1.35	(1.08, 1.67)	41.76
		Day 28 : Day 1	0.94	(0.76, 1.17)	
	Ro	Day 10 : Day 1	2.39	(1.76, 3.25)	61.09
		Day 28 : Day 1	2.08	(1.53, 2.82)	
	Rp	Day 1 AUC(0-∞) : Day 1 AUC(0-τ)	3.70	(2.89, 4.72)	47.11
	Rs	Day 10 : Day 1	0.64	(0.55, 0.76)	30.40
		Day 28 : Day 1	0.56	(0.48, 0.66)	
SB-553253 (M4)	Rcmax	Day 10 : Day 1	1.29	(0.92, 1.80)	68.19
		Day 28 : Day 1	0.76	(0.54, 1.06)	
	Ro	Day 10 : Day 1	1.46	(1.17, 1.82)	36.22
		Day 28 : Day 1	1.27	(1.02, 1.58)	
SB-823094 (M3)	Rcmax	Day 10 : Day 1	1.35	(0.95, 1.91)	71.71
		Day 28 : Day 1	0.70	(0.49, 0.99)	
	Ro	Day 10 : Day 1	1.35	(1.03, 1.77)	46.85
		Day 28 : Day 1	1.01	(0.77, 1.33)	

1. Ratio: Adjusted geometric mean ratio

Source Data: Table 11.14, Table 11.15

11.3.2. Statistical Analysis Details

Statistical analyses of pharmacokinetic data were performed under the direct auspices of Discovery Biometrics, GlaxoSmithKline Pharmaceuticals, Philadelphia.

Data was released to Discovery Biometrics on 28-JAN-2009 by CPMS via HARP. Main results of the statistical analyses (point estimates and 90% confidence intervals) are presented to 2 decimal places. All statistical analyses were carried out using SAS 9.1 for UNIX running under the HARP environment.

A total of 20 subjects were enrolled, with 17 subjects completing the study. [redacted] All subjects provided evaluable pharmacokinetic data from at least one study day and thus were included in the statistical analysis and summary statistics. [redacted] There is no observed significant influence on the result (data on file, GSK). Therefore, the final statistical analysis results were based on data from all subjects.

No pharmacokinetic parameters for SB-554008 (M10) could be derived and AUC(0-∞) for SB-553253 (M4) and SB-823094 (M3) could not be derived due to the low concentration of metabolites in the single dose session. Therefore the analysis for SB-554008 (M10) and the analyses of Rp and Rs for SB-553253 (M4) and SB-823094 (M3) were not performed.

Distributional assumptions of the formal statistical analyses were assessed by visual examination of residual plots. Homogeneity of variance was examined by plots of residuals versus predicted values, while normality was assessed by plots of normal order scores versus predicted values. [redacted] The analyses were re-run excluding these potential outliers. Removal of these outliers from the analysis did not change statistical inferences and conclusions. However, there were notable reductions in the point estimates and within subject variability was reduced. The interpretation should be based on results with full data since there is no clinically relevant reason to remove those outliers. There were no other gross distributional assumption violations in the analyses.

12. PHARMACODYNAMIC RESULTS

12.1. Pharmacodynamic Results

Summary statistics for Lp-PLA_2 activity, and maximum and trough percent inhibition of plasma Lp-PLA_2 enzyme activity, using CAM assay, are presented in Pharmacodynamic Source Table 12.1 and Table 12.2. Summary statistics for the CAM assay are summarized in Table 9.

Table 9 Summary Statistics for Maximum and Trough % Inhibition of Plasma Lp-PLA_2 Enzyme Activity by Regimen (CAM Assay)

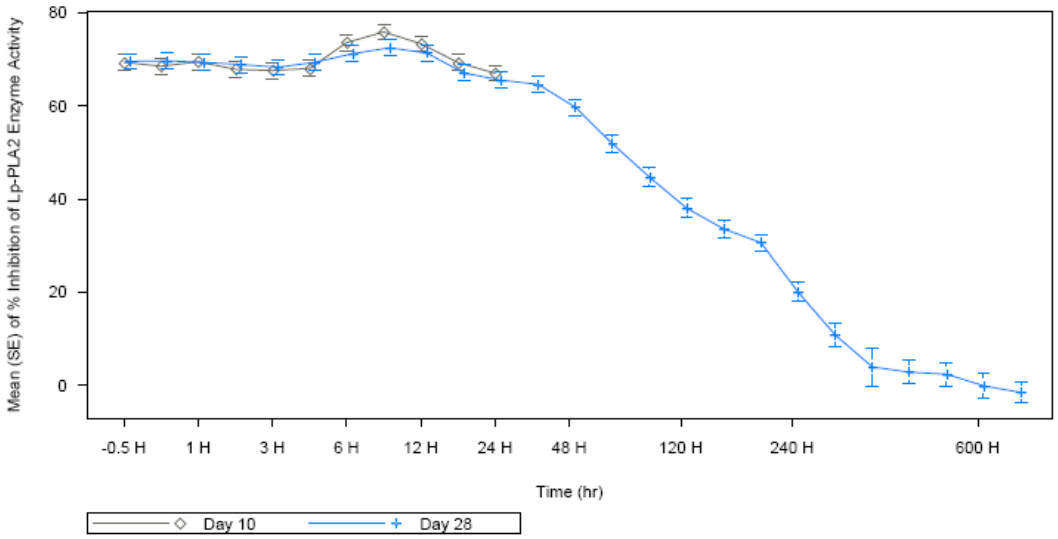
Day 10 Maximum			Day 10 Trough		
n	mean	95% CI	n	mean	95% CI
19	75.8	(73.5, 78.2)	19	67.0	(63.6, 70.4)
Day 28 Maximum			**Day 28 Trough**		
n	mean	95% CI	n	mean	95% CI
18	72.5	(70.1, 74.8)	18	65.5	(63.3, 67.7)

Regimen:
160mg enteric-coated free base (micronised) SB-480848
Source data: Table 12.2

Average maximum Lp-PLA_2 enzyme inhibition occurred at approximately 6 hours post dose and was approximately 70-75% using the CAM assay.

Figure 1 presents the time course of Lp-PLA_2 activity after repeat dosing. There are similar levels of inhibition observed after 10 days of repeat dosing and 28 days of repeat dosing. Inhibition of Lp-PLA_2 enzyme activity returned to baseline approximately 28 days after last dose.

Figure 1 Time Course of Percent Inhibition of Lp-PLA$_2$ Activity



Note: X-axis is a representative scale. % Inhibition was calculated with Session1 Day1 as baseline.
Day 1: 160 mg of EC micronized free-base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 10
Day28: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 28

13. RELATIONSHIP BETWEEN PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

The relationship between plasma darapladib concentrations and plasma Lp-PLA_2 activity has been described previously in healthy volunteers (data on file, GSK). The PK/PD relationship was best described by a direct-effect inhibitory Emax relationship. Based on these historical data, the same structural PK/PD model was first fit to the plasma Lp-PLA_2 activity and concentration data obtained from the current study with varying error models. Amongst the additive, proportional, and combined additive and proportional error models tested, the combined additive and proportional error model (Model 5) showed the lowest objective function with reasonable precision in parameter estimation and was thus progressed further in model building. The next two models involved removal of inter-individual variability (IIV) from the two PK/PD parameters: E_0 (Model 7) and IC_{50} (Model 8). Removal of IIV on E_0 and IC_{50} resulted in 568 and 120 points increase in objective function, respectively, with little improvement in precision of parameter estimation. Addition of a Hill coefficient was tested with (Model 6) and without (Model 9) an IIV estimates. Although inclusion of a Hill coefficient without an IIV estimate (Model 9) resulted in more than 62 points decrease in objective function compared to Model 5, the fits of the diagnostic plots were more biased with less random distribution in the weighted residual vs. predicted concentration plot and the precision of the estimated PK/PD parameters has decreased. Therefore, Model 5 was considered as the final PK/PD model with its parameter estimates given in Table 10 below. The model estimated population mean of darapladib IC_{50} is 5.41 ng/mL with 22.3% inter-individual variability associated with it. The baseline Lp-PLA_2 activity (population mean of 166 nmol/min/mL) is slightly more variable between individuals (32.6%). The population PK/PD parameters were estimated with high precision with coefficient of variation (%CV) being less than 10% for both parameters.

Table 10 Population PK/PD Parameter Estimates in Healthy Volunteers

	Pop. Mean (% CV*)	Interindividual Variability (IIV) %** (% CV*)
IC_{50} (ng/mL)	5.41 (5.27)	22.3 (26.5)
E_0 (nmol/min/mL)	166 (7.23)	32.6 (32.8)
Residual Variability** (%CV)	8.91 (20.8)	
Residual Variability*** (%CV)	4.12 (21.7)	

* precision expressed as % coefficient of variation, ** expressed as % coefficient of variation, *** expressed as nmol/min/mL
N.E. – Not Estimated
IC_{50}: SB-480848 plasma concentration causing 50% inhibition of plasma Lp-PLA_2 activity; E_0: baseline plasma Lp-PLA_2 activity.

14. DISCUSSION AND CONCLUSIONS

14.1. Discussion

Darapladib (SB-480848) is a novel, selective and orally active inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) in development for the treatment of atherosclerosis.

This study was designed to fully characterize the pharmacokinetics (PK) of darapladib and its metabolites SB-553253 (M4), SB-554008 (M10), and SB-823094 (M3) in healthy volunteers using enteric coated tablets, the clinical trial and proposed commercial product, of SB-480848 and a newly developed sensitive LC/MS assay to quantify M10 and M3 following single and repeat dosing.

Darapladib was well tolerated in this study by the healthy volunteers in both single and repeat dose regimens. The most common AEs, regardless of causality, were headache, diarrhoea, fatigue, abdominal pain and abnormal urine odor. All odor AEs were considered relative to treatment. The most common AEs, including the odor AEs are not new and have been seen in previous studies with this compound. Fatigue was reported as a drug related AE in 3 subjects, diarrhoea was reported as a drug related AE in 2 subjects and headache was reported as a drug related AE in 2 subjects. Most AEs were mild to moderate in intensity, and there were no deaths, SAEs, or withdrawals due to AEs. No clinically significant changes in laboratory, vital sign, or 12-lead ECG parameters were reported during the study.

In this study, darapladib was rapidly converted to M4 and M3 following single oral dose and to M4, M3 and M10 following repeat oral doses of enteric coated darapladib. M3 was present at low levels (mean Cmax 1.4 ng/mL and mean $AUC_{(0-24)}$ of 5.1% of parent at steady-state) but was seen at >10% of parent in one of 19 subjects (10.7%). M10 was only seen at low levels in human (mean Cmax of 0.4 ng/mL, and mean $AUC_{(0-24)}$ of 2.5% of parent at steady state) with the highest individual value of 4.0% of parent in one of 19 subjects. Exposure of M4 in this study was similar to results from studies conducted historically.

Some key design differences between this study and the previously conducted human ADME study are discussed below.

An oral solution formulation was used in the human ADME study due to the need for radiolabelled [^{14}C]SB-480848 administration. Darapladib is known to undergo hydrolysis, with the major degradant being M10. The clinical trial and proposed commercial tablet of darapladib is enteric coated to minimize acid hydrolysis in the stomach. It was therefore considered that the formation of M10 from enteric coated darapladib would be less than that observed in the human ADME study. Results from this study confirm that following administration of the enteric coated darapladib, M10 is a minor metabolite with very low circulating levels (mean Cmax of 0.4 ng/mL) and mean $AUC_{(0-24)}$ at steady state of 2.5% (range 1.7-4.0%) of parent.

In addition, in this study with the clinical trial and proposed commercial product, the time course of darapladib and its metabolites was characterized at steady state in healthy volunteers with a sensitive LC/MS/MS assay and accurate estimates of pharmacokinetic parameters were made for each metabolite using traditional methods. This is in contrast to the human ADME study, in which, due to the low radioactive concentrations, Accelerator Mass Spectrometry was utilized, and for radio-profiling and metabolite identification, area under the curve was approximated from one sample by pooling appropriate aliquots of plasma samples from all time points.

It is known that darapladib undergoes metabolic transformation by CYP3A4 and M3 is one of the metabolites formed by CYP3A4. As expected, exposure to M3 was not significantly different from that observed in the human ADME study with metabolite to parent ratio at an average of 5.8% and 5.1% on Days 10 and 28, respectively, with only one subject exceeding 10% (10.7%). The average Cmax in plasma was 2.7 and 1.4 ng/mL on Days 10 and 28, respectively. The overall exposure of M3 in human is low.

Following single oral dose and 10-day repeat dosing, exposure of M4 was similar to historical data. Exposure of M4 was similar following 10-day and 28-day repeat dosing. Given the long sampling duration post Day 28 dosing, we were able to definitively estimate the half-life of M4 in 15 out of 19 subjects. M4 was observed to circulate in plasma at low concentrations for a prolonged period of time (t1/2 was on average 285 hours post repeat dosing).

One other objective of this study was to definitively estimate the half-lives of darapladib and its metabolites following extended duration of sampling (672 hours) after 28-day repeat dosing. The average estimated half-life of darapladib following repeat dosing is 126 hours in this study. This is considerably longer than that estimated from previous studies (approximately 45 hours) when sampling was truncated at 96 hours post-dose and can be explained by the triexponential disposition profile shown in the plasma concentration-time curve of darapladib following 672-hour sampling on day 28. Based on visual inspection of trough data collected on days 26, 27 and 28 and the estimated half-life in this study, steady-state of darapladib has been reached by day 28. However, it should be noted that exposures following 28-day dosing were not higher than that following 10-day dosing ($AUC_{(0-24)}$ was 315.1 ng.h/mL on day 28 and 362.2 ng.h/mL on day 10; Cmax was 17.5 ng/mL on day 28 and 25.1 ng/mL on day 10). Therefore, the long half-life estimated from this study does not contribute significantly to the accumulation of darapladib.

Based on trough data obtained on days 26, 27 and 28 and the estimated half-lives, M3 and M10 have achieved steady-state by day 28 in the study.

Lp-PLA_2 activity, and Percent Inhibition of Plasma Lp-PLA_2 Enzyme Activity were measured in this study using CAM assay as in previous studies. The results of this study at the 160 mg dose were consistent with previous data, demonstrating similar levels of enzyme activity inhibition.

The PK/PD relationship between plasma concentrations of darapladib and Lp-PLA_2 activity described in this study is similar to historical data. The extended sampling for 28 days post repeat dosing did not reveal a different PK/PD relationship compared to

truncated sampling collected historically for up to 96 hours post dose. A direct-effect inhibitory Emax model best described the concentration-effect relationship. All population PK/PD parameters were well estimated with high precision.

14.2. Conclusions

The following can be concluded from this study:

- There were no deaths, SAEs or withdrawals due to AEs, and no clinically significant changes in laboratory, vital sign, or 12-lead ECG parameters in any subjects during the study.

- After single oral dose of enteric-coated darapladib at a dose level of 160 mg, darapladib was rapidly converted to M4 and M3. The mean metabolite to parent ratios for AUC(0-t) and Cmax were 3.2% and 9.0% for M4 and 3.6% and 11.3% for M3, respectively. No M10 was detected in any plasma sample following single oral dose of darapladib.

- After steady-state dosing of enteric-coated darapladib at a dose level of 160 mg for 28 days, M4, M3 and M10 were circulating in the plasma at low concentrations. The mean metabolite to parent ratios for AUC(0-τ) and Cmax were 4.8% and 7.5% for M4, 5.1% and 8.7% for M3, 2.5% and 2.2% for M10, respectively.

- Mean half-lives of darapladib, M4, M3 and M10 were 126, 285, 96 and 148 hour, respectively. Although the half-life of darapladib following 28-day sampling was longer than noted in previous studies, exposure following 28-day dosing is not higher than that following 10-day dosing and therefore, the longer half-life does not contribute significantly to the accumulation of darapladib beyond 10-day dosing.

- Modest accumulation was observed for darapladib in plasma following repeat daily dosing as shown by the observed accumulation ratios for AUC(0- τ) on Day 10 and Day 28 of 2.39 and 2.08, respectively. Consistent with historical data, darapladib appears to exhibit time-dependent pharmacokinetics as the observed accumulation was considerably less than that predicted from single dose pharmacokinetic data (3.70)

- Similar to the parent compound, M4 exhibited modest accumulation following repeat daily dosing of SB-480848. The accumulation of M3 was minimal. It was not possible to quantitate the accumulation of M10 as this metabolite was not present following single dose of darapladib.

- Inhibition of Lp-PLA_2 activity (approximately 75%) was observed following repeat oral administration of darapladib. Levels of Lp-PLA_2 activity returned to baseline approximately 28 days after last dose.

- The PK/PD relationship between darapladib and plasma Lp-PLA_2 activity was described by a sigmoid inhibitory Emax model.

15. REFERENCES

GlaxoSmithKline Document Number CD2008/01347/00. The Validation of a Method for the Determination of SB-480848, SB-553253, SB-554008 and SB-823094 in Human Plasma (range 0.10 to 50 ng/mL) using LC/MS/MS. Effective Date: 07-April-2009

GlaxoSmithKline Document Number ZM2007/00048/00 Study ID 480848/015. A Study to Determine the Balance/Excretion, Pharmacokinetics and Biotransformation of [^{14}C]-SB-480848 Following Single Oral and Intravenous Doses and Repeat Oral Doses of SB-480848. Effective Date: 07-DEC-2007

Study Population Data Source Tables

Table 9.1
Summary of Demographic Characteristics

		Total (N=20)
Age (y)	n	20
	Mean	31.7
	SD	11.38
	Median	28.0
	Min.	20
	Max.	54
Sex	n	20
	Female	6 (30%)
	Male	14 (70%)
Ethnicity	n	20
	Hispanic/Latino	2 (10%)
	Not Hispanic/Latino	18 (90%)
Height (cm)	n	20
	Mean	174.1
	SD	8.27
	Median	175.5
	Min.	158
	Max.	184
Weight (kg)	n	20
	Mean	78.32
	SD	15.061
	Median	75.65
	Min.	54.0
	Max.	99.3

Table 9.1
Summary of Demographic Characteristics

		Total (N=20)
Body Mass Index (kg/m^2)	n	20
	Mean	25.613
	SD	3.1074
	Median	25.755
	Min.	20.20
	Max.	30.01
Child-bearing Potential	n	20
	not applicable	14 (70%)
	Potentially able to bear children	6 (30%)

Table 9.2
Summary of Race and Racial Combination Details

Race	Total (N=20)
n	20
African American/African Heritage	3 (15%)
American Indian or Alaska Native	1 (5%)
Asian - South East Asian Heritage	1 (5%)
White - White/Caucasian/European Heritage	14 (70%)
Mixed Race	1 (5%)

Table 9.3
Summary of Subject Disposition

	Total (N=20)
Completion Status	
Completed	17 (85%)
Prematurely Withdrawn	3 (15%)
Primary reason for withdrawal	
Withdrew consent	3 (15%)

Safety Data Source Tables

Table 10.1
Summary of Exposure to Study Drug

		A1 (N=20)	A2 (N=20)
Duration (days)	n	20	20
	Mean	1.0	26.9
	SD	0.00	5.14
	Median	1.0	28.0
	Min.	1	5
	Max.	1	28

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.2
Summary of All Adverse Events

System Organ Class Preferred Term	A1 (N=20)	A2 (N=20)
ANY EVENT	5 (25%)	12 (60%)
Gastrointestinal disorders		
Any event	2 (10%)	6 (30%)
Diarrhoea	2 (10%)	4 (20%)
Abdominal pain	0	2 (10%)
Abdominal distension	0	1 (5%)
Nausea	0	1 (5%)
General disorders and administration site conditions		
Any event	2 (10%)	3 (15%)
Fatigue	2 (10%)	2 (10%)
Vessel puncture site pain	0	0
Irritability	0	1 (5%)
Nervous system disorders		
Any event	3 (15%)	4 (20%)
Headache	2 (10%)	4 (20%)
Disturbance in attention	1 (5%)	0
Somnolence	1 (5%)	0
Musculoskeletal and connective tissue disorders		
Any event	0	3 (15%)
Arthralgia	0	1 (5%)
Back pain	0	1 (5%)
Flank pain	0	1 (5%)
Pain in extremity	0	1 (5%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.2
Summary of All Adverse Events

System Organ Class Preferred Term	A1 (N=20)	A2 (N=20)
Renal and urinary disorders		
Any event	2 (10%)	1 (5%)
Urine odour abnormal	2 (10%)	0
Bladder neck obstruction	0	1 (5%)
Glycosuria	1 (5%)	0
Infections and infestations		
Any event	0	2 (10%)
Pharyngitis	0	1 (5%)
Viral upper respiratory tract infection	0	1 (5%)
Metabolism and nutrition disorders		
Any event	0	2 (10%)
Anorexia	0	1 (5%)
Decreased appetite	0	1 (5%)
Psychiatric disorders		
Any event	1 (5%)	0
Abnormal dreams	1 (5%)	0
Reproductive system and breast disorders		
Any event	0	1 (5%)
Dysmenorrhoea	0	1 (5%)
Respiratory, thoracic and mediastinal disorders		
Any event	0	1 (5%)
Rhinorrhoea	0	1 (5%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.3
Summary of Adverse Events Leading to Withdrawal

No data to report

Table 10.4
Summary of All Drug Related Adverse Events

System Organ Class Preferred Term	A1 (N=20)	A2 (N=20)
ANY EVENT	5 (25%)	7 (35%)
Gastrointestinal disorders		
Any event	2 (10%)	4 (20%)
Diarrhoea	2 (10%)	3 (15%)
Abdominal pain	0	2 (10%)
Abdominal distension	0	1 (5%)
General disorders and administration site conditions		
Any event	2 (10%)	2 (10%)
Fatigue	2 (10%)	2 (10%)
Nervous system disorders		
Any event	3 (15%)	1 (5%)
Headache	1 (5%)	1 (5%)
Disturbance in attention	1 (5%)	0
Somnolence	1 (5%)	0
Renal and urinary disorders		
Any event	2 (10%)	0
Urine odour abnormal	2 (10%)	0
Glycosuria	1 (5%)	0
Musculoskeletal and connective tissue disorders		
Any event	0	1 (5%)
Back pain	0	1 (5%)
Psychiatric disorders		
Any event	1 (5%)	0
Abnormal dreams	1 (5%)	0

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.5
Summary of Chemistry Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Albumin (G/L)	SCREENING	20	SCREENING	20	42.0	2.42	42.0	37	46
	A1	20	S1D-1	20	41.6	2.26	41.0	37	47
		20	S1D1	20	42.0	2.54	42.0	37	47
	FOLLOW-UP	20	FOLLOW-UP	20	42.5	2.35	42.0	39	48
Alkaline Phosphatase (IU/L)	SCREENING	20	SCREENING	20	65.5	13.30	66.5	40	92
	A1	20	S1D-1	20	64.3	13.46	64.0	40	88
		20	S1D1	20	64.0	13.18	65.5	39	88
	FOLLOW-UP	20	FOLLOW-UP	20	66.5	17.35	65.5	34	103
Alanine Amino Transferase (IU/L)	SCREENING	20	SCREENING	20	20.7	10.46	19.0	10	50
	A1	20	S1D-1	20	18.3	7.55	17.5	8	38
		20	S1D1	20	20.8	15.93	18.0	8	84
	FOLLOW-UP	20	FOLLOW-UP	20	19.9	10.38	18.5	8	49
Aspartate Amino Transferase (IU/L)	SCREENING	20	SCREENING	20	20.5	5.95	19.0	13	34
	A1	20	S1D-1	20	18.8	5.01	18.5	12	33
		20	S1D1	20	18.6	7.47	17.0	13	49
	FOLLOW-UP	20	FOLLOW-UP	20	18.8	4.99	17.5	11	32
Direct Bilirubin (UMOL/L)	SCREENING	20	SCREENING	20	4.874	1.8629	5.130	1.71	8.55
	A1	20	S1D-1	20	5.216	1.7077	5.130	3.42	8.55
		20	S1D1	20	5.216	1.8794	5.130	3.42	10.26
	FOLLOW-UP	20	FOLLOW-UP	20	4.532	1.6896	5.130	1.71	8.55

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.5
Summary of Chemistry Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Total Bilirubin (UMOL/L)	SCREENING	20	SCREENING	20	12.056	4.6904	11.115	5.13	22.23
	A1	20	S1D-1	20	10.773	3.8875	8.550	6.84	18.81
		20	S1D1	20	11.201	4.5573	10.260	5.13	23.94
	FOLLOW-UP	20	FOLLOW-UP	20	9.576	4.0920	8.550	3.42	18.81
Calcium (MMOL/L)	SCREENING	20	SCREENING	20	2.35528	0.055140	2.35778	2.2455	2.4701
	A1	20	S1D-1	20	2.38772	0.066801	2.42015	2.2705	2.4950
		20	S1D1	20	2.41142	0.080247	2.42015	2.2455	2.5449
	FOLLOW-UP	20	FOLLOW-UP	20	2.40393	0.055658	2.39520	2.2954	2.4950
Chloride (MMOL/L)	SCREENING	20	SCREENING	20	105.3	2.59	105.5	99	111
	A1	20	S1D-1	20	105.0	2.34	105.0	99	108
		20	S1D1	20	104.7	1.59	104.0	103	108
	FOLLOW-UP	20	FOLLOW-UP	20	104.7	1.78	105.0	99	108
Creatinine (UMOL/L)	SCREENING	20	SCREENING	20	81.770	12.7863	83.980	61.88	97.24
	A1	20	S1D-1	20	82.212	14.6525	83.980	61.88	106.08
		20	S1D1	20	82.654	14.9787	83.980	61.88	106.08
	FOLLOW-UP	20	FOLLOW-UP	20	78.234	14.4190	79.560	53.04	97.24
Gamma Glutamyl Transferase (IU/L)	SCREENING	20	SCREENING	20	25.2	14.99	20.5	11	68
	A1	20	S1D-1	20	24.0	12.42	20.5	11	56
		20	S1D1	20	24.7	13.39	20.5	12	61
	FOLLOW-UP	20	FOLLOW-UP	20	23.3	10.92	19.5	11	44
Glucose (MMOL/L)	SCREENING	20	SCREENING	20	5.01533	0.455714	4.96815	4.2188	5.7175
	A1	20	S1D-1	20	4.80717	0.293400	4.77386	4.3853	5.4400
		20	S1D1	20	4.93761	0.333777	4.88488	4.3853	5.4400
	FOLLOW-UP	20	FOLLOW-UP	20	5.25957	0.625404	5.05141	4.5518	6.8277

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.5
Summary of Chemistry Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Bicarbonate (MMOL/L)	SCREENING	20	SCREENING	20	24.5	1.91	24.5	21	28
	A1	20	S1D-1	20	25.5	1.61	25.0	23	29
		20	S1D1	20	26.1	1.62	26.0	23	29
	FOLLOW-UP	20	FOLLOW-UP	20	26.9	1.57	27.0	23	29
Potassium (MMOL/L)	SCREENING	20	SCREENING	20	4.15	0.332	4.10	3.7	4.9
	A1	20	S1D-1	20	4.10	0.340	4.10	3.6	4.8
		20	S1D1	20	4.42	0.390	4.30	3.7	5.3
	FOLLOW-UP	20	FOLLOW-UP	20	4.21	0.393	4.25	3.4	5.0
Sodium (MMOL/L)	SCREENING	20	SCREENING	20	139.2	1.96	139.5	133	142
	A1	20	S1D-1	20	139.1	1.79	139.0	134	142
		20	S1D1	20	139.5	1.24	139.0	138	142
	FOLLOW-UP	20	FOLLOW-UP	20	139.7	1.26	140.0	137	142
Total Protein (G/L)	SCREENING	20	SCREENING	20	70.0	3.78	69.0	63	78
	A1	20	S1D-1	20	69.2	3.91	68.5	62	78
		20	S1D1	20	71.8	4.55	70.5	63	82
	FOLLOW-UP	20	FOLLOW-UP	20	70.1	4.06	71.5	62	77
Urea/BUN (MMOL/L)	SCREENING	20	SCREENING	20	4.1234	1.26603	3.9270	1.785	7.497
	A1	20	S1D-1	20	4.5518	0.90370	4.6410	2.856	6.069
		20	S1D1	20	4.8374	0.99283	4.8195	3.213	7.140
	FOLLOW-UP	20	FOLLOW-UP	20	4.7481	1.17036	4.4625	3.570	8.211
Uric acid (UMOL/L)	SCREENING	20	SCREENING	20	264.3886	82.08909	273.6080	89.220	440.152
	A1	20	S1D-1	20	266.1730	94.00405	288.4780	77.324	463.944
		20	S1D1	20	281.9352	89.21791	276.5820	101.116	481.788
	FOLLOW-UP	20	FOLLOW-UP	20	264.6860	78.58993	282.5300	65.428	440.152

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.6
Summary of Haematology Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Basophils (GI/L)	SCREENING	20	SCREENING	20	0.01	0.031	0.00	0.0	0.1
	A1	20	S1D-1	20	0.01	0.022	0.00	0.0	0.1
		20	S1D1	20	0.00	0.000	0.00	0.0	0.0
	FOLLOW-UP	20	FOLLOW-UP	20	0.01	0.022	0.00	0.0	0.1
Basophils (percentage) (%)	SCREENING	20	SCREENING	20	0.46	0.211	0.40	0.1	1.0
	A1	20	S1D-1	20	0.43	0.198	0.40	0.1	0.9
		20	S1D1	20	0.42	0.191	0.40	0.1	0.8
	FOLLOW-UP	20	FOLLOW-UP	20	0.43	0.200	0.40	0.2	1.0
Eosinophils (GI/L)	SCREENING	20	SCREENING	20	0.14	0.088	0.10	0.0	0.4
	A1	20	S1D-1	20	0.14	0.093	0.10	0.0	0.4
		20	S1D1	20	0.16	0.076	0.10	0.1	0.3
	FOLLOW-UP	20	FOLLOW-UP	20	0.17	0.103	0.10	0.1	0.4
Eosinophils (percentage) (%)	SCREENING	20	SCREENING	20	2.42	1.846	2.05	0.2	8.3
	A1	20	S1D-1	20	2.32	1.560	2.05	0.5	6.8
		20	S1D1	20	2.33	1.015	2.25	1.1	5.4
	FOLLOW-UP	20	FOLLOW-UP	20	2.77	1.317	2.55	1.0	6.0
Hemoglobin (G/L)	SCREENING	20	SCREENING	20	143.5	12.11	146.5	116	162
	A1	20	S1D-1	20	141.0	13.72	143.5	111	160
		20	S1D1	20	148.1	14.07	154.5	116	170
	FOLLOW-UP	20	FOLLOW-UP	20	143.0	14.72	149.0	112	164
Hematocrit (1)	SCREENING	20	SCREENING	20	0.4287	0.02999	0.4320	0.365	0.473
	A1	20	S1D-1	20	0.4188	0.03342	0.4235	0.345	0.464
		20	S1D1	20	0.4404	0.03336	0.4515	0.368	0.498
	FOLLOW-UP	20	FOLLOW-UP	20	0.4231	0.03509	0.4340	0.351	0.475

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.6
Summary of Haematology Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Lymphocytes (GI/L)	SCREENING	20	SCREENING	20	1.78	0.474	1.75	0.8	2.9
	A1	20	S1D-1	20	1.82	0.417	1.75	1.0	2.7
		20	S1D1	20	1.82	0.451	1.90	0.9	2.6
	FOLLOW-UP	20	FOLLOW-UP	20	1.99	0.499	2.00	1.1	3.2
Lymphocytes (percentage) (%)	SCREENING	20	SCREENING	20	29.90	6.801	29.50	16.9	41.3
	A1	20	S1D-1	20	30.75	5.310	31.20	19.3	41.6
		20	S1D1	20	29.44	5.571	28.80	19.9	38.7
	FOLLOW-UP	20	FOLLOW-UP	20	32.71	5.844	32.55	21.8	47.1
Mean Corpuscle Hemoglobin concentration (G/L)	SCREENING	20	SCREENING	20	334.5	9.61	337.5	311	351
	A1	20	S1D-1	20	336.3	10.77	339.0	316	355
		20	S1D1	20	335.7	9.98	338.5	315	348
	FOLLOW-UP	20	FOLLOW-UP	20	337.5	11.15	338.0	319	357
Mean Corpuscle Hemoglobin (PG)	SCREENING	20	SCREENING	20	29.29	2.110	29.50	23.5	32.0
	A1	20	S1D-1	20	29.28	2.162	29.60	23.2	32.3
		20	S1D1	20	29.34	2.104	29.80	23.1	32.2
	FOLLOW-UP	20	FOLLOW-UP	20	29.49	2.207	29.80	23.6	32.3
Mean Corpuscle Volume (FL)	SCREENING	20	SCREENING	20	87.51	5.120	87.40	71.5	93.6
	A1	20	S1D-1	20	86.97	4.774	87.85	72.4	93.5
		20	S1D1	20	87.33	4.881	88.55	73.0	93.9
	FOLLOW-UP	20	FOLLOW-UP	20	87.32	4.772	88.85	74.2	94.5

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.6
Summary of Haematology Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Monocytes (GI/L)	SCREENING	20	SCREENING	20	0.55	0.128	0.50	0.3	0.8
	A1	20	S1D-1	20	0.52	0.114	0.50	0.4	0.8
		20	S1D1	20	0.56	0.150	0.50	0.3	1.0
	FOLLOW-UP	20	FOLLOW-UP	20	0.58	0.196	0.55	0.3	0.9
Monocytes (percentage) (%)	SCREENING	20	SCREENING	20	9.30	2.179	9.80	6.3	15.0
	A1	20	S1D-1	20	9.12	2.412	9.05	4.9	14.9
		20	S1D1	20	9.21	1.949	8.80	5.7	12.7
	FOLLOW-UP	20	FOLLOW-UP	20	9.61	2.430	9.75	5.4	16.0
Total Neutrophils (GI/L)	SCREENING	20	SCREENING	20	3.62	1.482	3.25	1.8	7.7
	A1	20	S1D-1	20	3.45	1.012	3.35	2.2	5.9
		20	S1D1	20	3.69	0.998	3.95	2.2	5.7
	FOLLOW-UP	20	FOLLOW-UP	20	3.37	1.077	3.00	2.0	5.8
Total Neutrophils (percentage) (%)	SCREENING	20	SCREENING	20	57.92	8.305	59.25	44.3	75.3
	A1	20	S1D-1	20	57.39	6.496	55.25	43.4	72.5
		20	S1D1	20	58.61	6.095	59.60	46.8	68.8
	FOLLOW-UP	20	FOLLOW-UP	20	54.49	5.958	54.65	44.6	67.0
Platelet count (GI/L)	SCREENING	20	SCREENING	20	248.4	47.62	236.5	183	367
	A1	20	S1D-1	20	231.4	41.00	222.0	152	323
		20	S1D1	20	237.0	42.46	225.0	145	311
	FOLLOW-UP	20	FOLLOW-UP	20	248.7	43.25	235.0	179	334
Red Blood Cell count (TI/L)	SCREENING	20	SCREENING	20	4.914	0.4320	4.950	4.21	5.79
	A1	20	S1D-1	20	4.830	0.4748	4.970	4.00	5.69
		20	S1D1	20	5.059	0.4765	5.220	4.11	5.93
	FOLLOW-UP	20	FOLLOW-UP	20	4.858	0.4755	4.965	3.83	5.50

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.6
Summary of Haematology Laboratory Values

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
RDW - Red Cell Distribution Width (%)	SCREENING	20	SCREENING	20	12.74	0.694	12.75	11.6	14.1
	A1	20	S1D-1	20	12.57	0.777	12.30	11.6	14.2
		20	S1D1	20	12.58	0.799	12.40	11.6	14.5
	FOLLOW-UP	20	FOLLOW-UP	20	12.91	0.777	12.75	12.0	14.6
Reticulocytes (TI/L)	SCREENING	20	SCREENING	20	0.053	0.0208	0.050	0.02	0.09
	A1	20	S1D-1	20	0.045	0.0161	0.040	0.02	0.08
		20	S1D1	20	0.054	0.0209	0.050	0.02	0.11
	FOLLOW-UP	20	FOLLOW-UP	19	0.057	0.0229	0.050	0.03	0.13
Reticulocytes (percentage) (1)	SCREENING	20	SCREENING	20	0.01069	0.003694	0.01055	0.0055	0.0170
	A1	20	S1D-1	20	0.00940	0.002827	0.00870	0.0057	0.0162
		20	S1D1	20	0.01061	0.003830	0.00970	0.0049	0.0202
	FOLLOW-UP	20	FOLLOW-UP	19	0.01168	0.004354	0.01090	0.0061	0.0255
White Blood Cell count (GI/L)	SCREENING	20	SCREENING	20	6.11	1.717	5.95	3.6	10.2
	A1	20	S1D-1	20	5.93	1.233	5.90	4.0	8.8
		20	S1D1	20	6.24	1.364	6.15	3.7	8.4
	FOLLOW-UP	20	FOLLOW-UP	20	6.11	1.526	5.80	3.8	9.0

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.7
Summary of Urinalysis Categorical Results

Lab Test	Visit	Planned Relative Time	Result	SCREENING (N=20)	A1 (N=20)	FOLLOW-UP (N=20)
Urine Appearance	SCREENING	SCREENING	n	20		
			CLEAR	19 (95%)		
			TURBID	1 (5%)		
	S1D-1	DAY -1	n		20	
			CLEAR		20 (100%)	
	S1D1	48 H	n		20	
			CLEAR		14 (70%)	
			TURBID		6 (30%)	
	FOLLOW-UP	FOLLOW-UP	n			20
			CLEAR			20 (100%)
Urine Microscopy - Bacteria	S1D1	48 H	n		1	
			PRESENT		1 (100%)	
	FOLLOW-UP	FOLLOW-UP	n			1
			PRESENT			1 (100%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.7
Summary of Urinalysis Categorical Results

Lab Test	Visit	Planned Relative Time	Result	SCREENING (N=20)	A1 (N=20)	FOLLOW-UP (N=20)
Urine Bilirubin (dipstick)	SCREENING	SCREENING	n	20		
			NEGATIVE	20 (100%)		
	S1D-1	DAY -1	n		20	
			NEGATIVE		20 (100%)	
	S1D1	48 H	n		20	
			NEGATIVE		20 (100%)	
	FOLLOW-UP	FOLLOW-UP	n			20
			NEGATIVE			20 (100%)
Urine Occult Blood (dipstick)	SCREENING	SCREENING	n	20		
			NEGATIVE	19 (95%)		
			TRACE	1 (5%)		
	S1D-1	DAY -1	n		20	
			3+		1 (5%)	
			NEGATIVE		19 (95%)	
	S1D1	48 H	n		20	
			1+		1 (5%)	
			3+		1 (5%)	
			NEGATIVE		18 (90%)	
	FOLLOW-UP	FOLLOW-UP	n			20
			3+			1 (5%)
			NEGATIVE			19 (95%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.7
Summary of Urinalysis Categorical Results

Lab Test	Visit	Planned Relative Time	Result	SCREENING (N=20)	A1 (N=20)	FOLLOW-UP (N=20)
Urine Colour	SCREENING	SCREENING	n	20		
			AMBER	2 (10%)		
			YELLOW	18 (90%)		
	S1D-1	DAY -1	n		20	
			YELLOW		20 (100%)	
	S1D1	48 H	n		20	
			YELLOW		20 (100%)	
	FOLLOW-UP	FOLLOW-UP	n			20
			AMBER			2 (10%)
			YELLOW			18 (90%)
Urine Microscopy - Epithelial Cells	S1D1	48 H	n		1	
			3.0-10.0		1 (100%)	
	FOLLOW-UP	FOLLOW-UP	n			1
			3.0-10.0			1 (100%)
Urine Microscopy - Mucous Threads	FOLLOW-UP	FOLLOW-UP	n			1
			PRESENT			1 (100%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.7
Summary of Urinalysis Categorical Results

Lab Test	Visit	Planned Relative Time	Result	SCREENING (N=20)	A1 (N=20)	FOLLOW-UP (N=20)
Urine Nitrite (dipstick)	SCREENING	SCREENING	n	20		
			NEGATIVE	20 (100%)		
	S1D-1	DAY -1	n		20	
			NEGATIVE		20 (100%)	
	S1D1	48 H	n		20	
			NEGATIVE		20 (100%)	
	FOLLOW-UP	FOLLOW-UP	n			20
			NEGATIVE			20 (100%)
Urine Microscopy - Red Blood Cells	SCREENING	SCREENING	n	1		
			0.0-2.0	1 (100%)		
	S1D-1	DAY -1	n		1	
			0.0-2.0		1 (100%)	
	S1D1	48 H	n		2	
			0.0-2.0		1 (50%)	
			3.0-10.0		1 (50%)	
	FOLLOW-UP	FOLLOW-UP	n			2
			0.0-2.0			1 (50%)
			3.0-10.0			1 (50%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.7
Summary of Urinalysis Categorical Results

Lab Test	Visit	Planned Relative Time	Result	SCREENING (N=20)	A1 (N=20)	FOLLOW-UP (N=20)
Urine Microscopy - White Blood Cells	SCREENING	SCREENING	n	1		
			0.0-2.0	1 (100%)		
	S1D-1	DAY -1	n		1	
			0.0-2.0		1 (100%)	
	S1D1	48 H	n		2	
			0.0-2.0		1 (50%)	
			3.0-10.0		1 (50%)	
	FOLLOW-UP	FOLLOW-UP	n			2
			0.0-2.0			1 (50%)
			3.0-10.0			1 (50%)
Urine Leukocyte Esterase test for detecting WBC (dipstick)	SCREENING	SCREENING	n	20		
			NEGATIVE	20 (100%)		
	S1D-1	DAY -1	n		20	
			NEGATIVE		20 (100%)	
	S1D1	48 H	n		20	
			NEGATIVE		20 (100%)	
	FOLLOW-UP	FOLLOW-UP	n			20
			NEGATIVE			19 (95%)
			TRACE			1 (5%)

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.8
Summary of Urinalysis Numerical Results

Lab Test (Unit)	Treatment Group	N	Visit	n	Mean	SD	Median	Min.	Max.
Urine Glucose (dipstick) (MG/DL)	SCREENING	20	SCREENING	20	0.0	0.00	0.0	0	0
	A1	20	S1D-1	20	0.0	0.00	0.0	0	0
		20	S1D1	20	12.5	55.90	0.0	0	250
	FOLLOW-UP	20	FOLLOW-UP	20	0.0	0.00	0.0	0	0
Urine Ketones (dipstick) (MG/DL)	SCREENING	20	SCREENING	20	1.0	3.48	0.0	0	15
	A1	20	S1D-1	20	0.5	1.54	0.0	0	5
		20	S1D1	20	0.0	0.00	0.0	0	0
	FOLLOW-UP	20	FOLLOW-UP	20	0.8	1.83	0.0	0	5
Urine pH ( )	SCREENING	20	SCREENING	20	6.15	0.975	6.25	5.0	8.0
	A1	20	S1D-1	20	6.13	0.901	6.50	5.0	7.0
		20	S1D1	20	5.65	0.651	6.00	5.0	7.0
	FOLLOW-UP	20	FOLLOW-UP	20	5.88	0.793	6.00	5.0	7.0
Urine Protein (dipstick) (MG/DL)	SCREENING	20	SCREENING	20	0.0	0.00	0.0	0	0
	A1	20	S1D-1	20	0.0	0.00	0.0	0	0
		20	S1D1	20	0.0	0.00	0.0	0	0
	FOLLOW-UP	20	FOLLOW-UP	20	0.0	0.00	0.0	0	0
Urine Specific Gravity ( )	SCREENING	20	SCREENING	20	1.0152	0.00819	1.0180	1.002	1.027
	A1	20	S1D-1	20	1.0143	0.00955	1.0140	1.002	1.028
		20	S1D1	20	1.0206	0.00548	1.0210	1.011	1.032
	FOLLOW-UP	20	FOLLOW-UP	20	1.0202	0.00639	1.0220	1.004	1.029
Urine Urobilinogen (quantitative) (UMOL/L)	SCREENING	20	SCREENING	20	16.930	0.0000	16.930	16.93	16.93
	A1	20	S1D-1	20	16.930	0.0000	16.930	16.93	16.93
		20	S1D1	20	16.930	0.0000	16.930	16.93	16.93
	FOLLOW-UP	20	FOLLOW-UP	20	16.930	0.0000	16.930	16.93	16.93

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.9
Listing of All Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance

No data to report

Table 10.10
Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance

No data to report

Table 10.11
Listing of Clinical Haematology Abnormalities of Potential Clinical Importance

No data to report

Table 10.12
Listing of All Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance

No data to report

Table 10.13
Summary of ECG Findings

Visit	Category	Total (N=20)
SCREENING	n	20
	Normal	19 (95.0%)
	Abnormal - Not clinically significant	1 (5.0%)
	Abnormal - Clinically significant	0
FOLLOW-UP	n	20
	Normal	20 (100.0%)
	Abnormal - Not clinically significant	0
	Abnormal - Clinically significant	0

Table 10.14
Summary of 12-Lead ECG Values

	Treatment	N	Pl.Time	n	Mean	SD	Median	Min.	Max.
Heart Rate (bpm)	SCREENING	20	SCREENING	20	57.9	8.46	58.0	43	78
	FOLLOW-UP	20	FOLLOW-UP	20	64.0	7.65	63.5	49	77
PR Interval (msec)	SCREENING	20	SCREENING	20	156.6	19.32	157.5	121	197
	FOLLOW-UP	20	FOLLOW-UP	20	161.9	17.51	163.5	134	194
QRS Duration (msec)	SCREENING	20	SCREENING	20	95.3	10.63	93.5	77	127
	FOLLOW-UP	20	FOLLOW-UP	20	96.1	11.50	94.0	80	124
QT Interval (msec)	SCREENING	20	SCREENING	20	404.5	21.76	405.0	362	442
	FOLLOW-UP	20	FOLLOW-UP	20	394.8	22.73	393.0	360	436
QTc Interval (msec)	SCREENING	20	SCREENING	20	397.6	20.35	397.5	354	446
	FOLLOW-UP	20	FOLLOW-UP	20	402.7	19.89	399.5	362	444
QTc (Bazett) (msec)	SCREENING	20	SCREENING	20	395.46925	24.437874	399.96287	345.2489	454.3915
	FOLLOW-UP	20	FOLLOW-UP	20	406.30675	22.747092	407.31701	354.2489	453.3348
QTc (Fridericia) (msec)	SCREENING	20	SCREENING	20	398.21654	19.280447	396.77290	358.3307	446.1110
	FOLLOW-UP	20	FOLLOW-UP	20	402.27914	19.735971	398.87713	366.4103	445.0736

Regimen Key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
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[redacted]

Table 10.15
Listing of ECG Data for Subjects with Abnormalities of Potential Clinical Importance

Inv./ Subj./ Seq.	Age(y)/ Sex/ Race	Test	Treatment/ Visit	Study Day/ Period Day	ECG Date	ECG Time	ECG Value	Clinical Relevance [1]	Chg from Baseline Low	Chg from Baseline High	Clinical Relevance BL	Clinical Relevance [2]	Chg from Baseline Low	Chg from Baseline High

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

[1] H=High I=Normal L=Low N=No F3 Criteria
[2] H=High I=Normal L=Low N=No F2 Criteria R=Baseline U=Missing Test or Baseline test value
Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

Table 10.16
Listing of ECG Values of Potential Clinical Importance

Inv./ Subj./ Seq.	Age(y)/ Sex/ Race	Test	Treatment/ Visit	Study Day/ Period Day	ECG Date	ECG Time	ECG Value	Clinical Relevance [1]	Chg from Baseline BL	Chg from Baseline [2]

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

[redacted]

[1] H=High I=Normal L=Low
[2] H=High I=Normal L=Low N=No F2 Criteria R=Baseline U=Missing Test or Baseline test value
Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.17
Summary of Vital Signs

	Treatment	N	Visit	Pl.Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	SCREENING	20	SCREENING	SCREENING	20	77.5	7.94	77.5	66	96
	A1	20	S1D-1	DAY -1	20	73.4	6.99	71.0	66	95
			S1D1	PREDOSE	20	68.4	7.21	68.0	57	88
				48 H	20	71.9	6.39	71.0	61	89
	A2	20	S2D14	PREDOSE	19	69.9	7.12	68.0	58	91
			S2D28	PREDOSE	19	68.2	7.99	67.0	58	94
	FOLLOW-UP	20	FOLLOW-UP	FOLLOW-UP	19	74.9	8.04	75.0	61	96
Heart rate (BPM)	SCREENING	20	SCREENING	SCREENING	20	65.3	8.85	66.0	45	84
	A1	20	S1D-1	DAY -1	20	67.6	9.67	68.0	52	95
			S1D1	PREDOSE	20	67.8	8.34	67.5	56	90
				48 H	20	66.3	8.91	67.5	51	85
	A2	20	S2D14	PREDOSE	19	73.1	9.45	72.0	56	95
			S2D28	PREDOSE	19	69.5	9.25	71.0	55	87
	FOLLOW-UP	20	FOLLOW-UP	FOLLOW-UP	19	68.1	8.22	68.0	53	83
Systolic BP (mmHg)	SCREENING	20	SCREENING	SCREENING	20	119.0	10.09	118.0	100	140
	A1	20	S1D-1	DAY -1	20	118.6	8.11	116.5	108	138
			S1D1	PREDOSE	20	114.2	10.12	113.5	92	136
				48 H	20	114.9	6.55	114.5	106	127
	A2	20	S2D14	PREDOSE	19	119.8	10.81	120.0	97	138
			S2D28	PREDOSE	19	114.3	9.04	112.0	99	133
	FOLLOW-UP	20	FOLLOW-UP	FOLLOW-UP	19	116.9	9.05	115.0	103	135

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 10.18
Summary of Change from Baseline for Vital Signs

	Treatment	N	Visit	Pl.Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	A1	20	S1D1	48 H	20	3.5	5.67	2.5	-6	20
	A2	20	S2D14	PREDOSE	19	1.6	5.06	1.0	-9	13
			S2D28	PREDOSE	19	-0.2	4.87	0.0	-8	11
Heart rate (BPM)	A1	20	S1D1	48 H	20	-1.5	5.15	-2.0	-9	11
	A2	20	S2D14	PREDOSE	19	5.4	6.91	5.0	-7	21
			S2D28	PREDOSE	19	1.8	5.67	1.0	-10	13
Systolic BP (mmHg)	A1	20	S1D1	48 H	20	0.7	7.31	1.0	-14	14
	A2	20	S2D14	PREDOSE	19	6.1	7.43	6.0	-7	21
			S2D28	PREDOSE	19	0.6	6.53	0.0	-16	10

Regimen key:
A1: 160 mg of EC micronized free-base darapladib as a single dose
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days
NOTE: Baseline is the Session 1 Day 1 Predose measurement.

[redacted]

Table 10.19
Listing of Vital Signs Data for Subjects with Abnormalities of Potential Clinical Importance

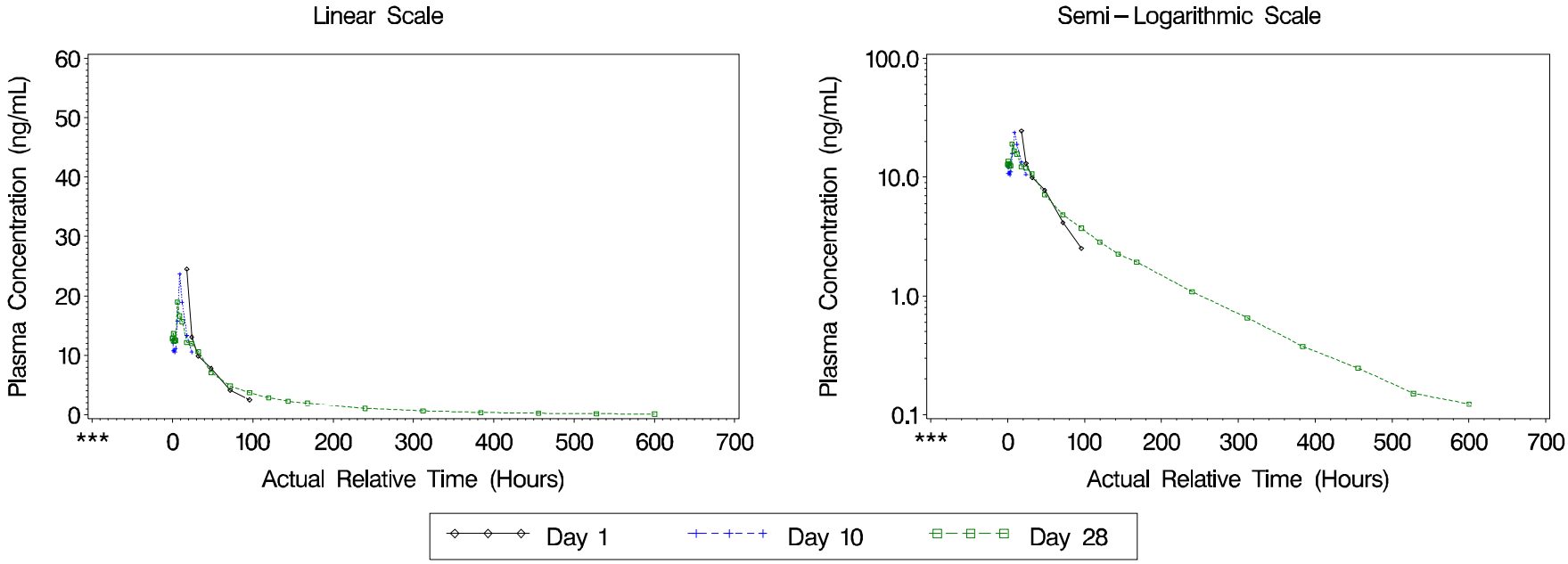
No data to report

Table 10.20
Listing of Vital Signs of Potential Clinical Importance

No data to report

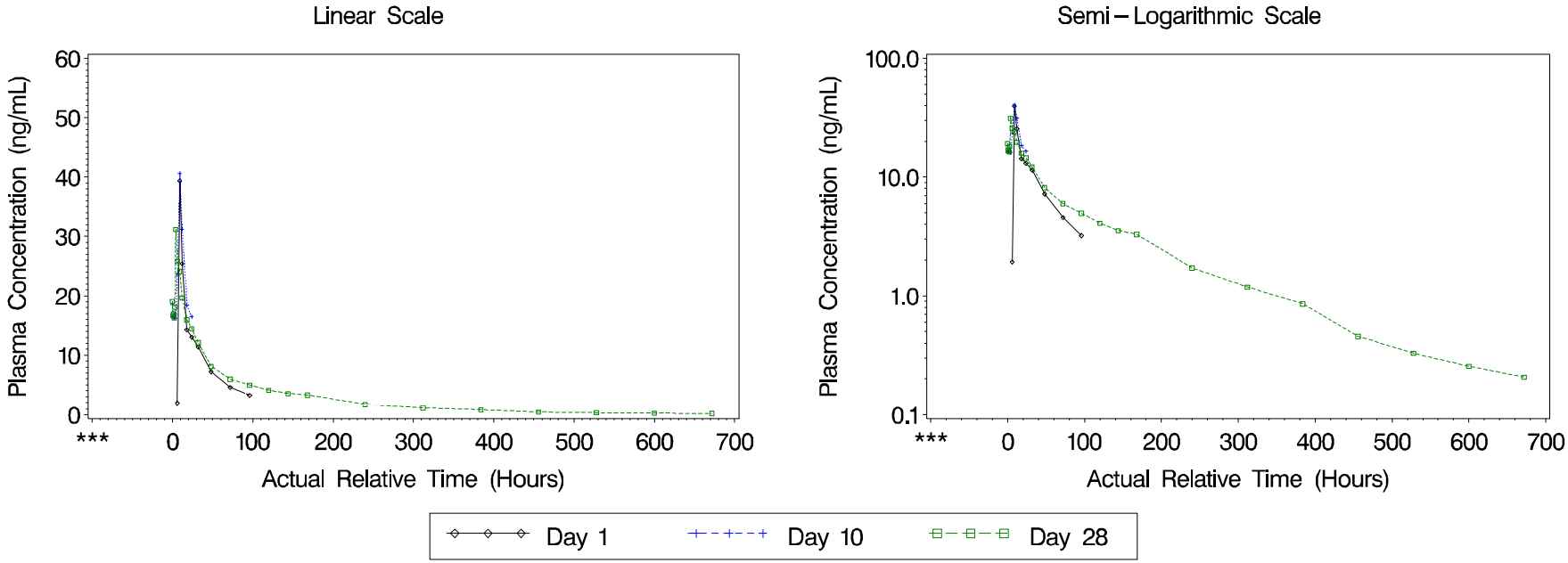
Pharmacokinetic Data Source Figures and Tables

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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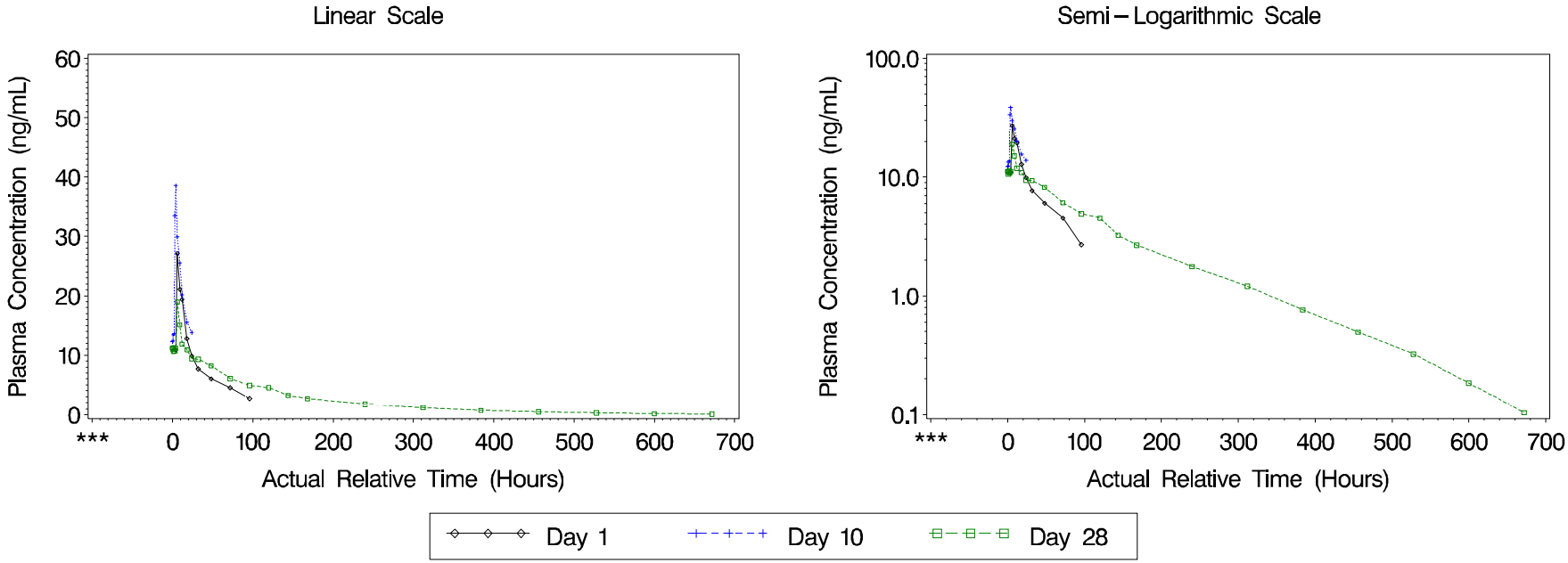
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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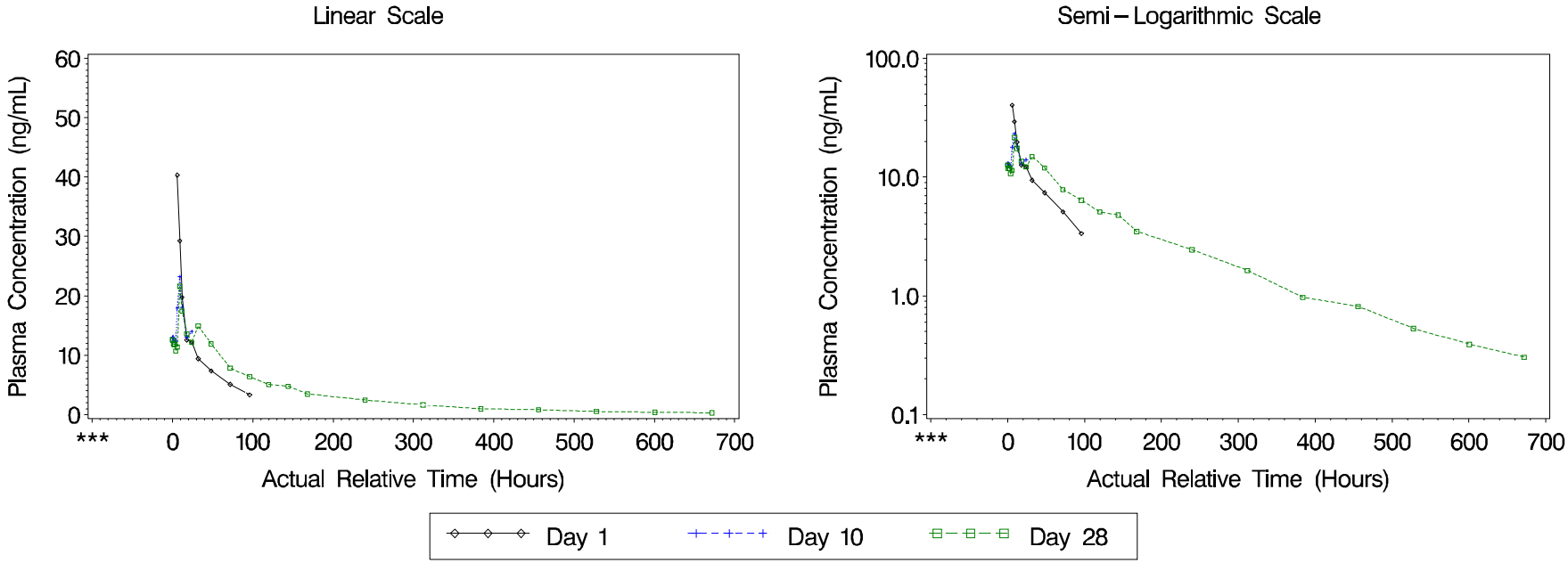
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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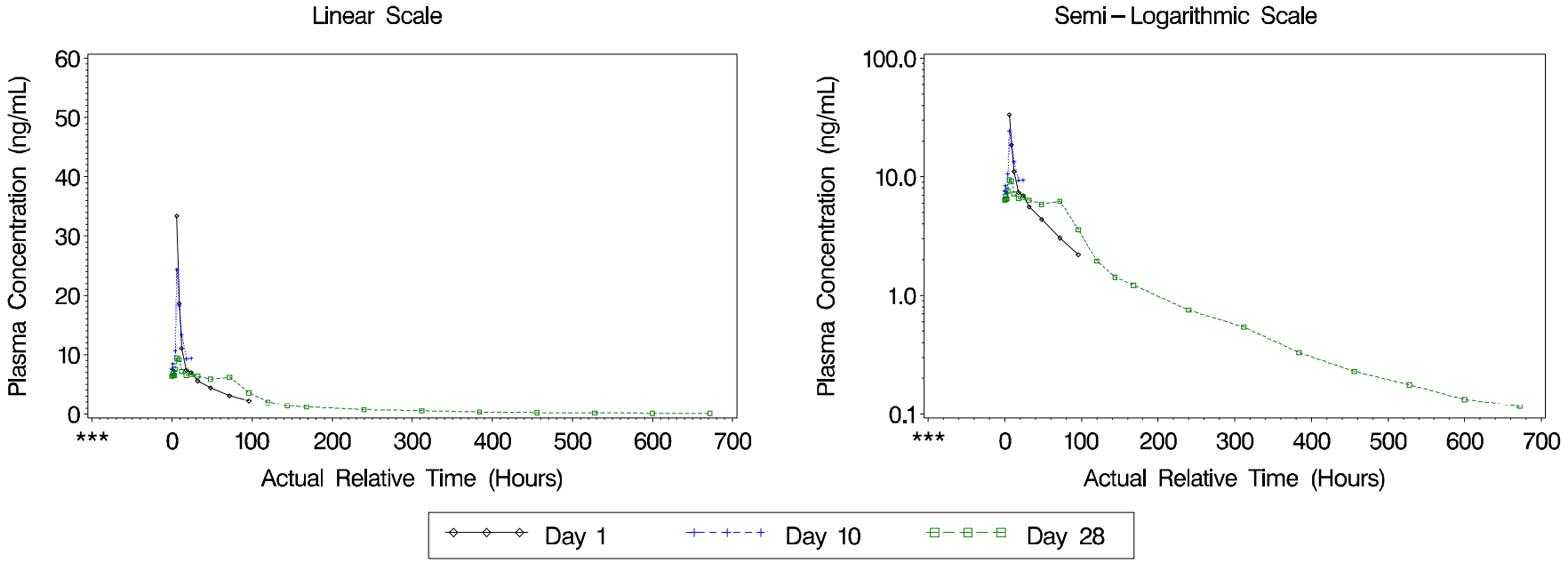
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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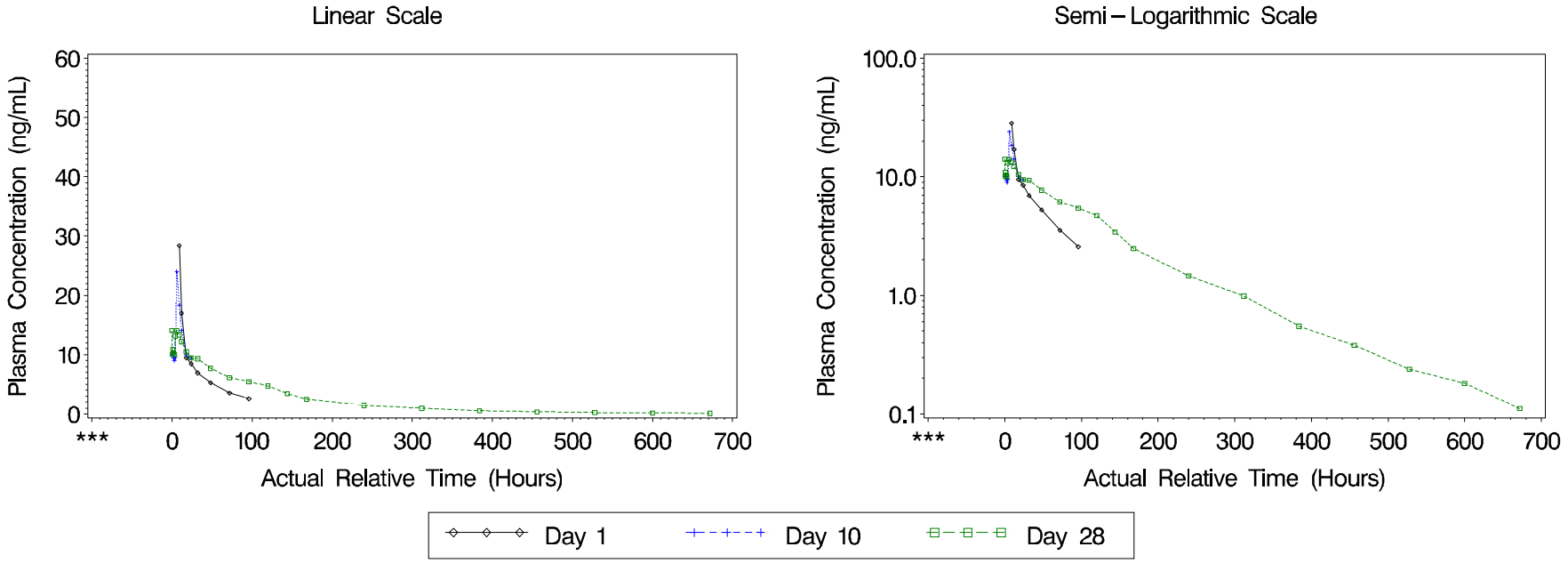
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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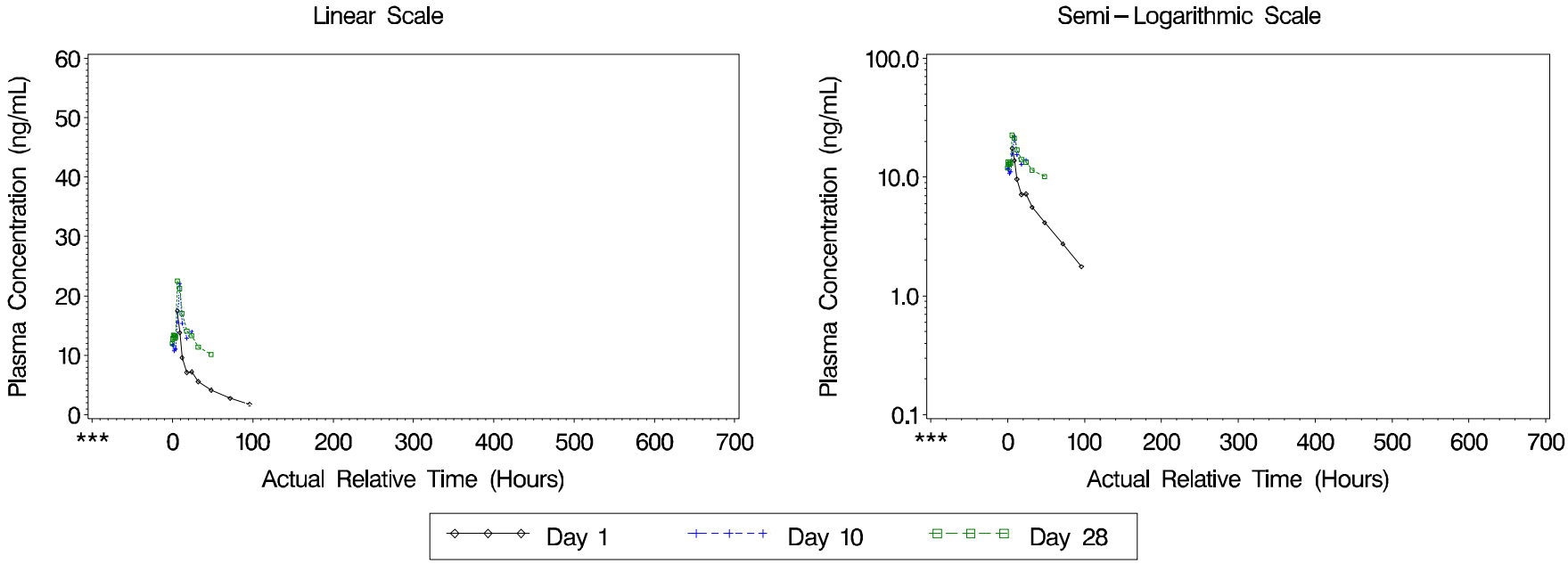
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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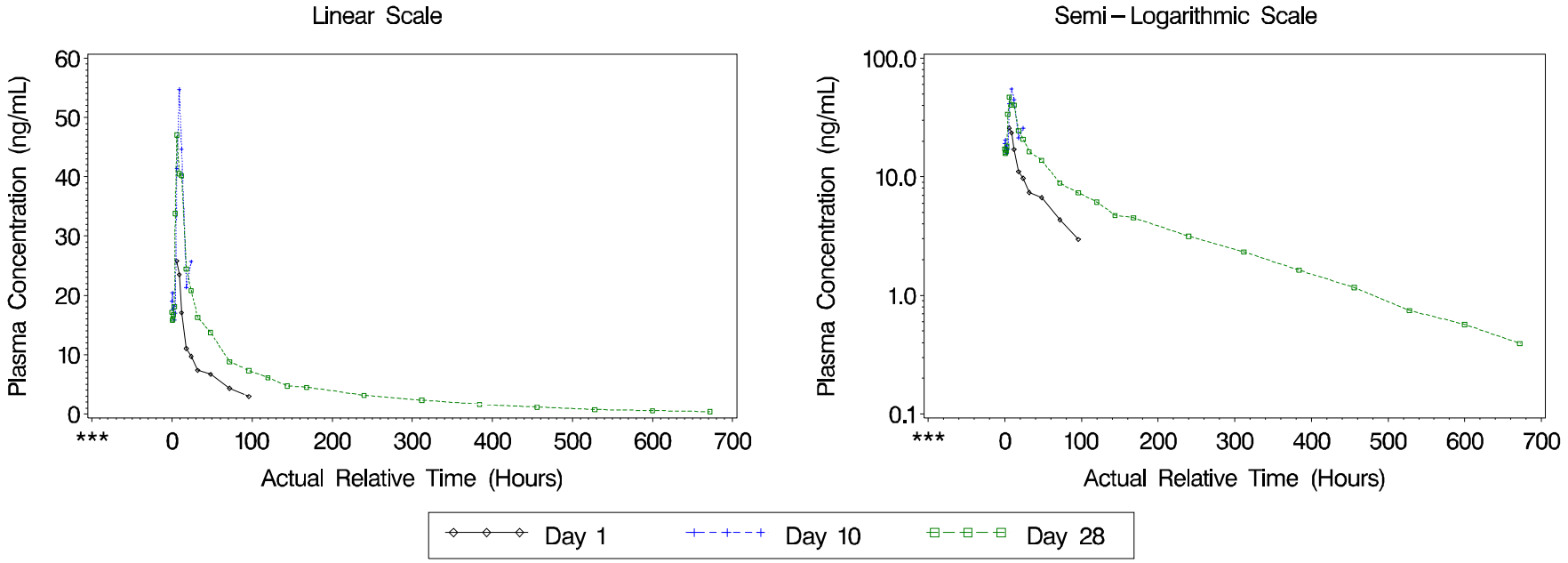
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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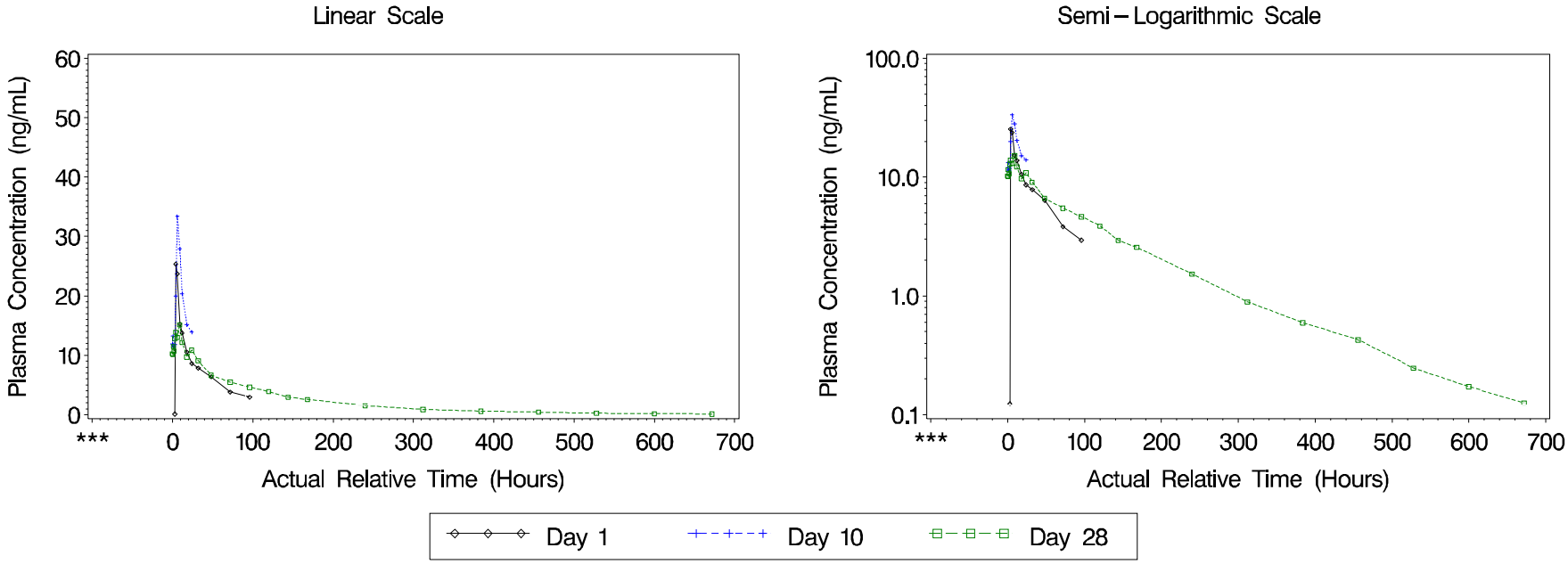
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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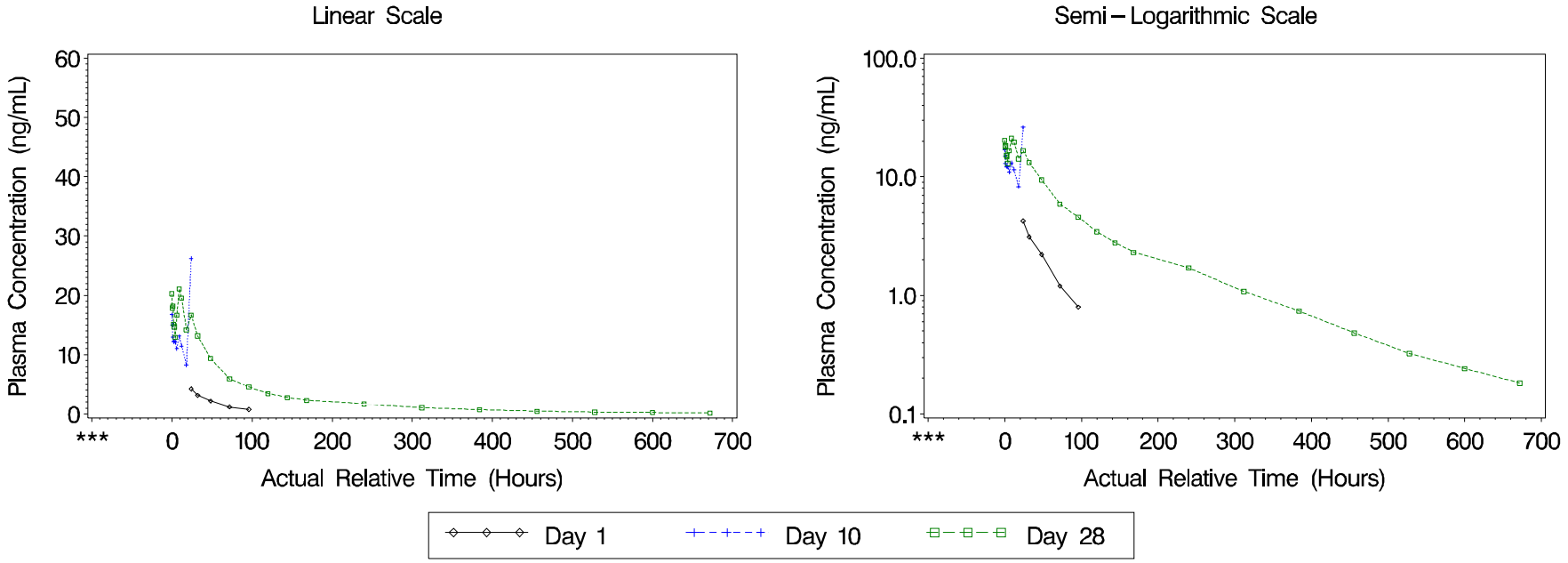
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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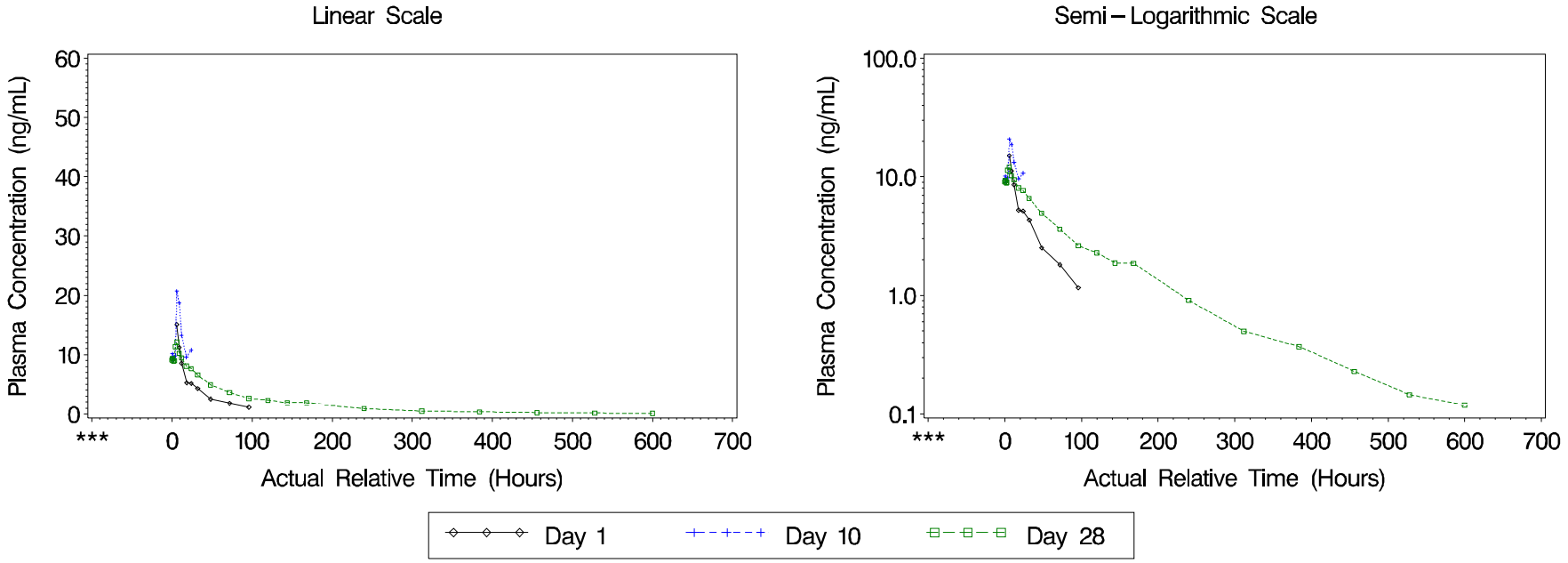
[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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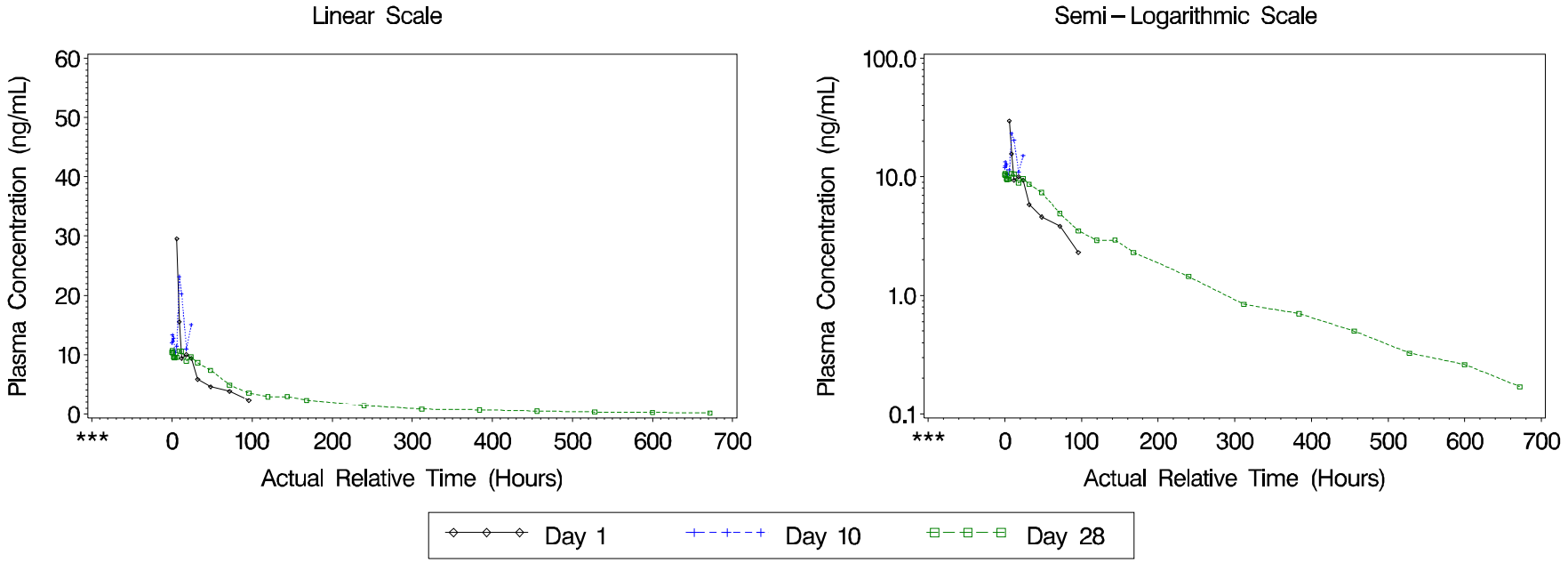
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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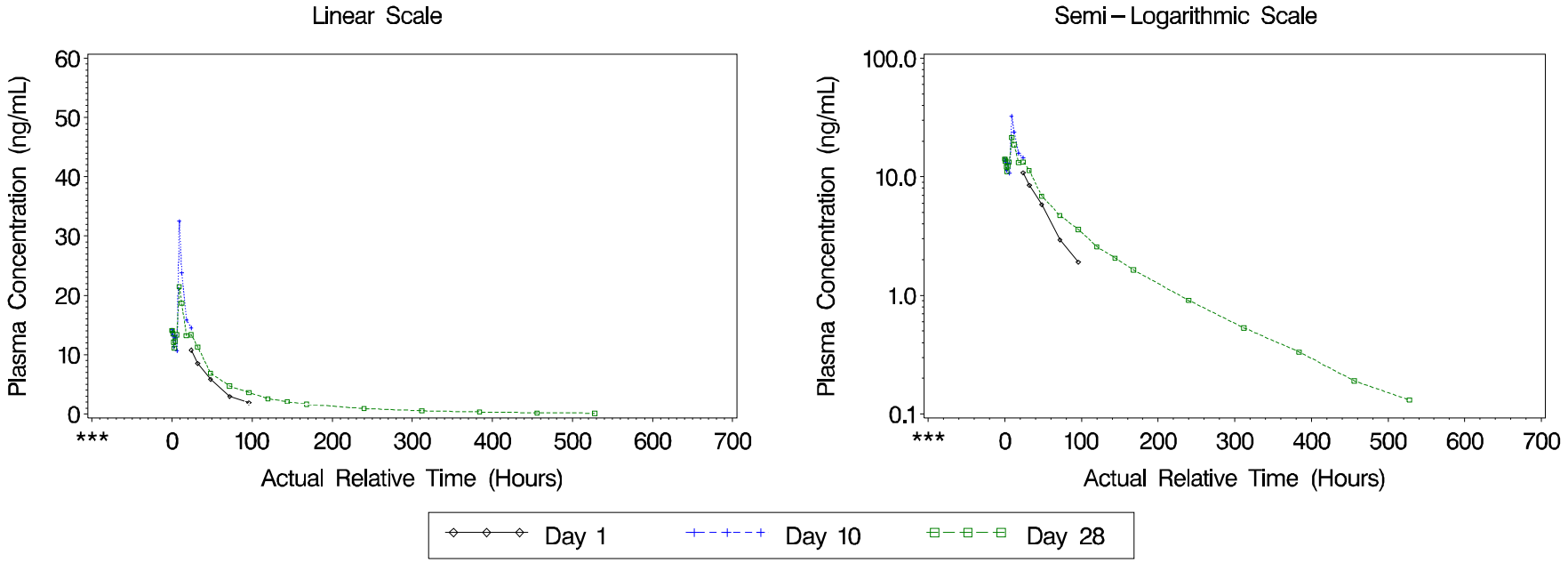
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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Individual Subject Plasma SB−480848 Concentration − Time Plot
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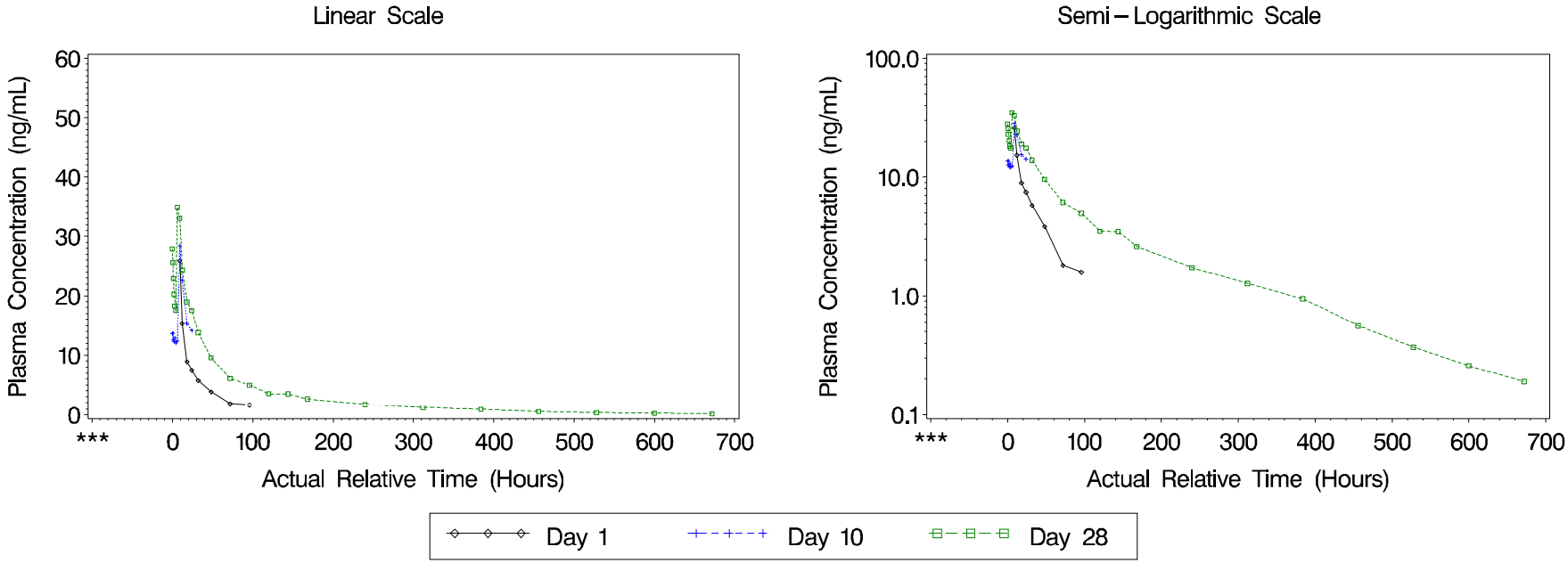

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[redacted]

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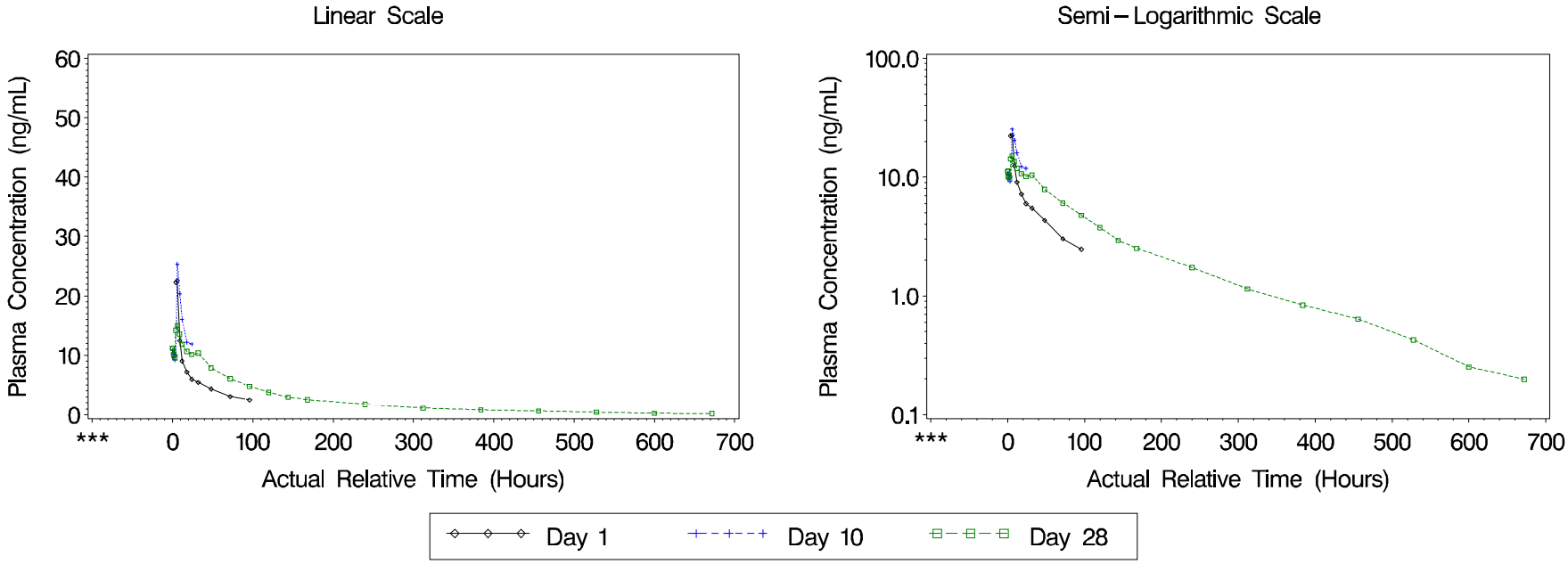
Subject ID=[redacted]



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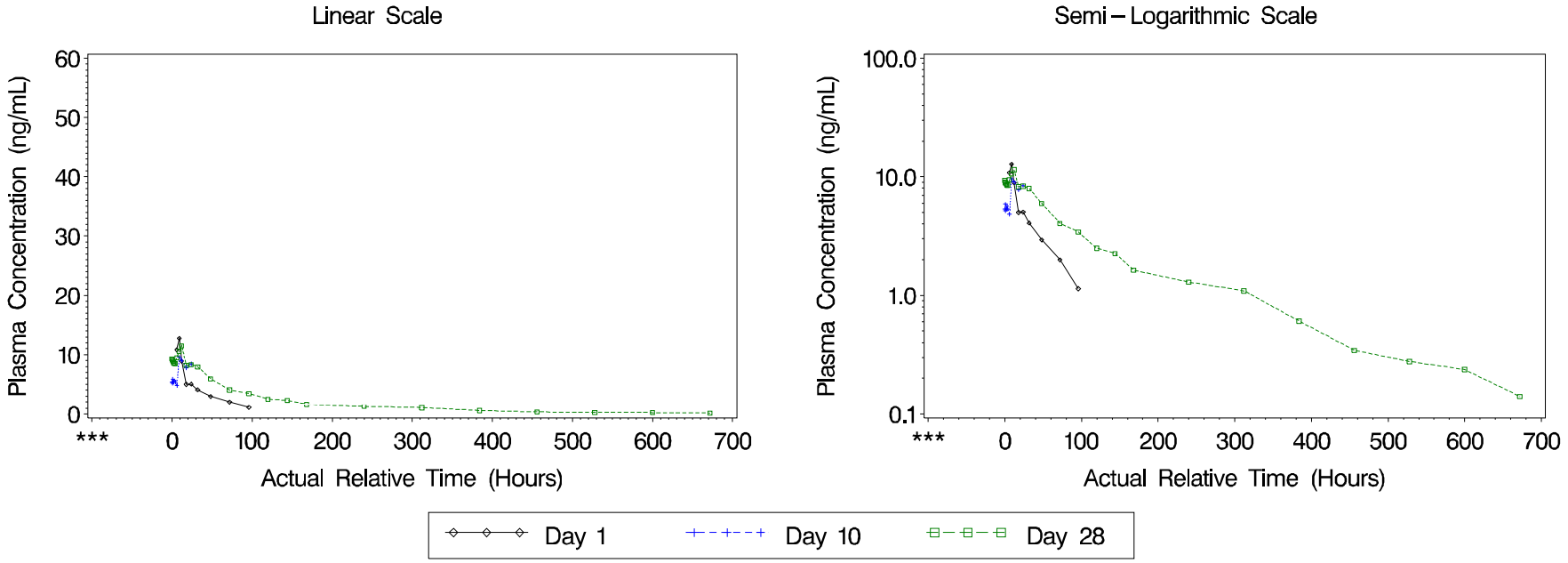
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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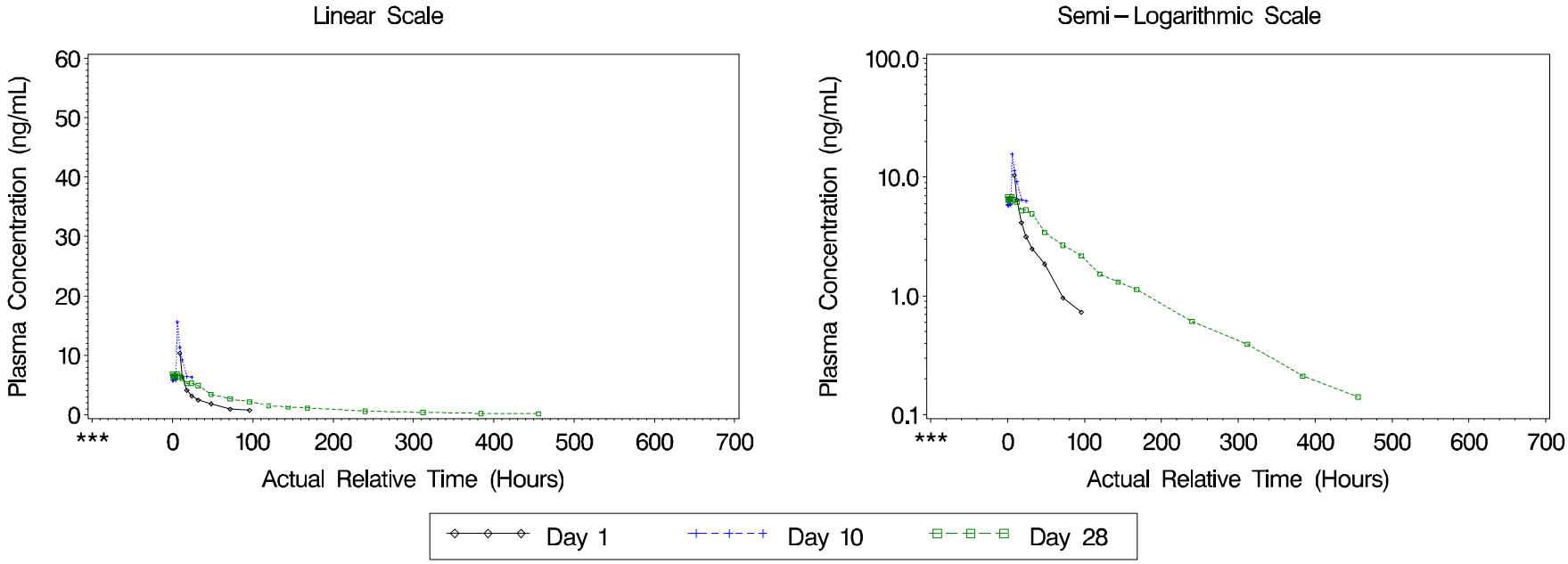
[redacted]

Figure 11.1
Individual Subject Plasma SB-480848 Concentration – Time Plot
Subject ID=[redacted]



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[redacted]

Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]

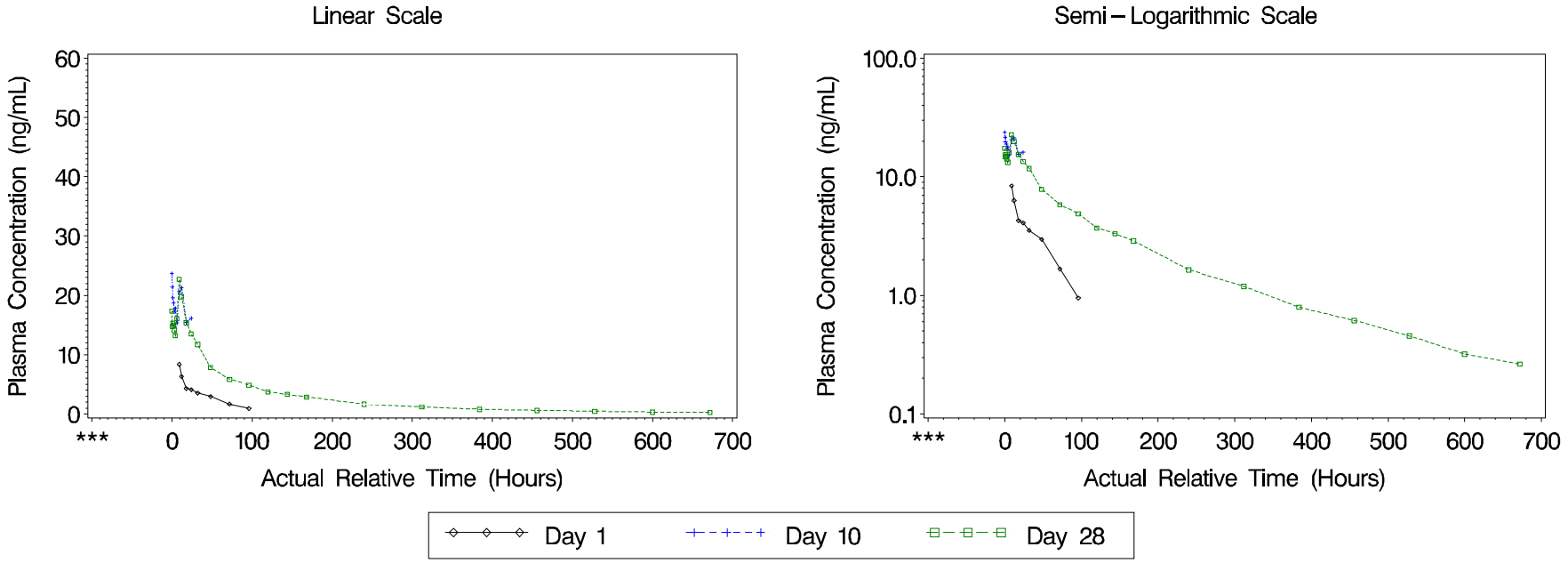

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Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]

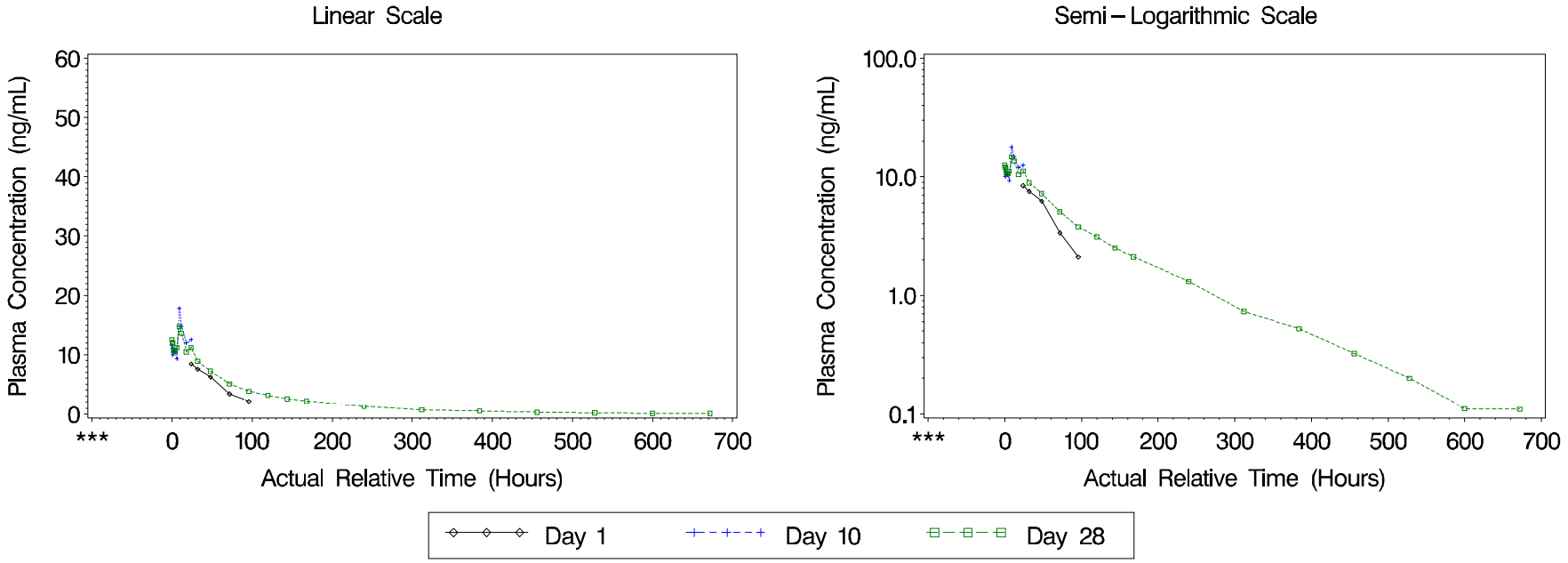

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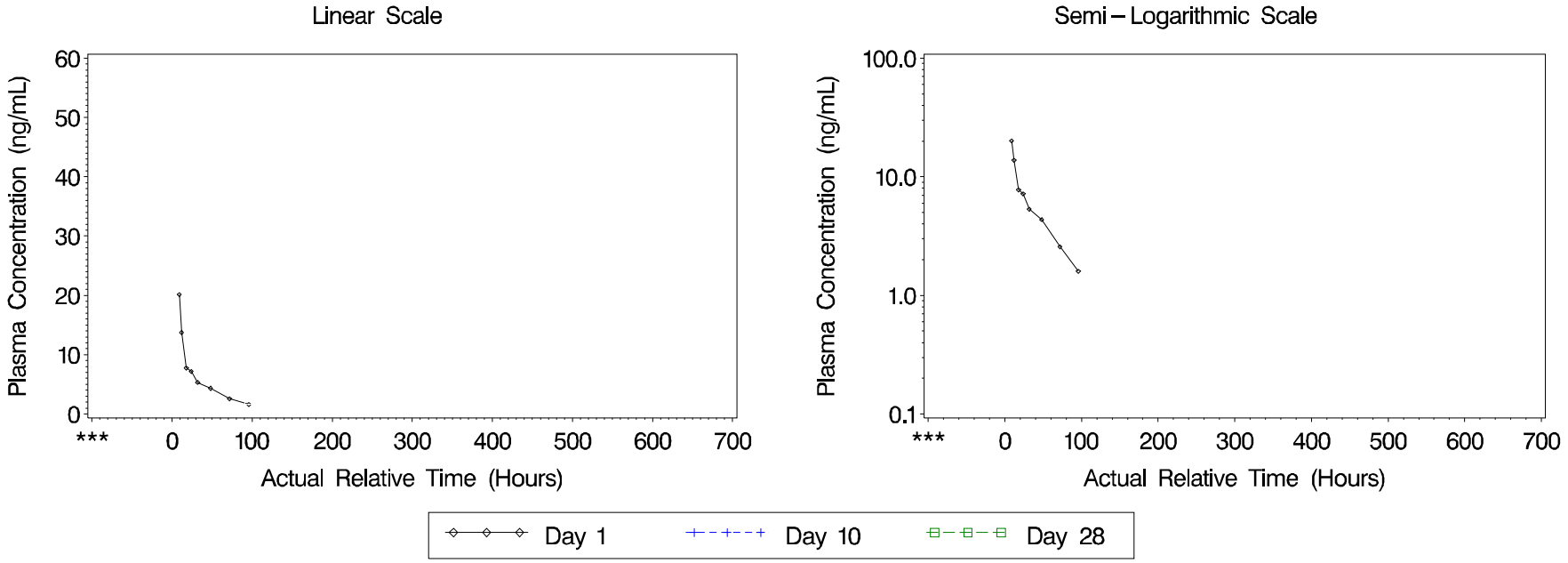
Figure 11.1
Individual Subject Plasma SB−480848 Concentration − Time Plot
Subject ID=[redacted]



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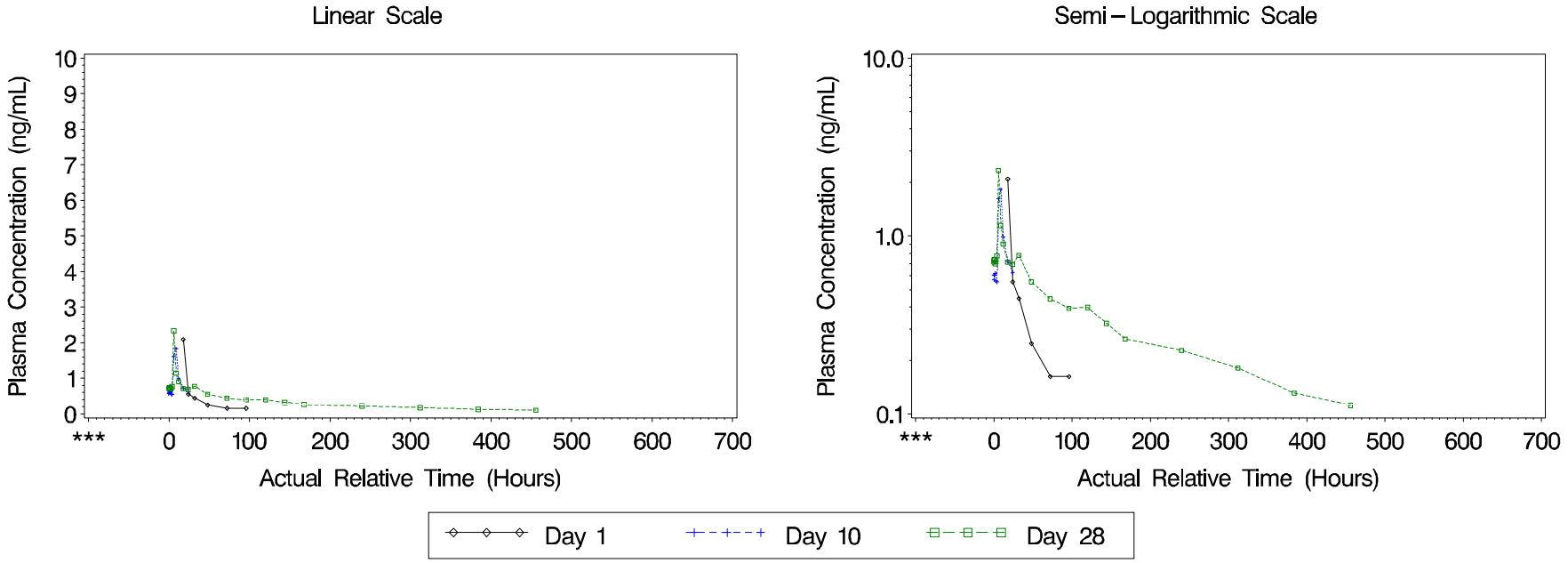
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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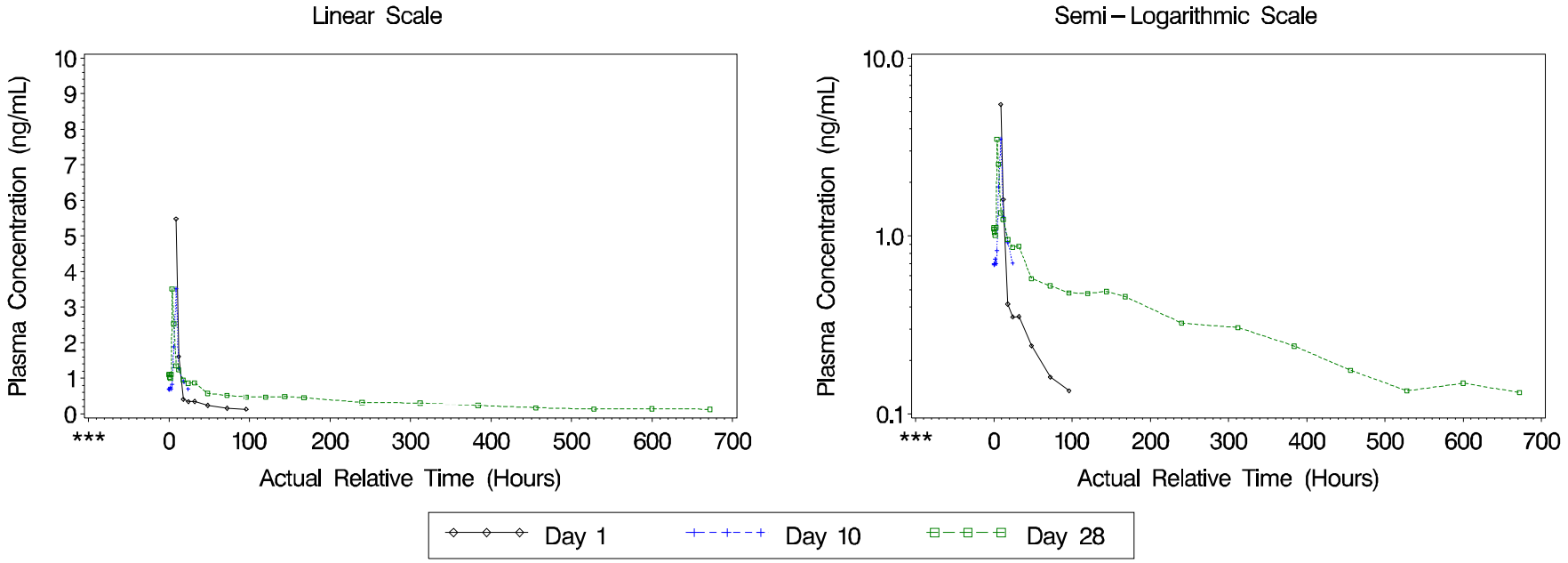
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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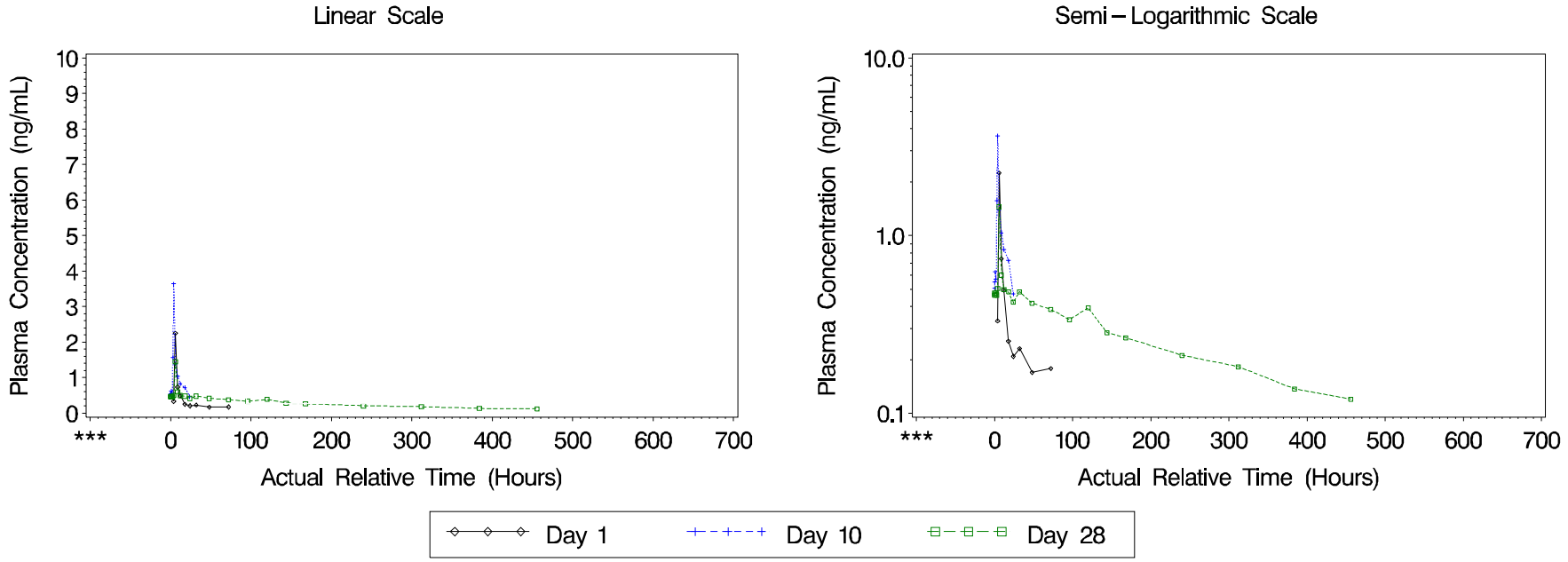
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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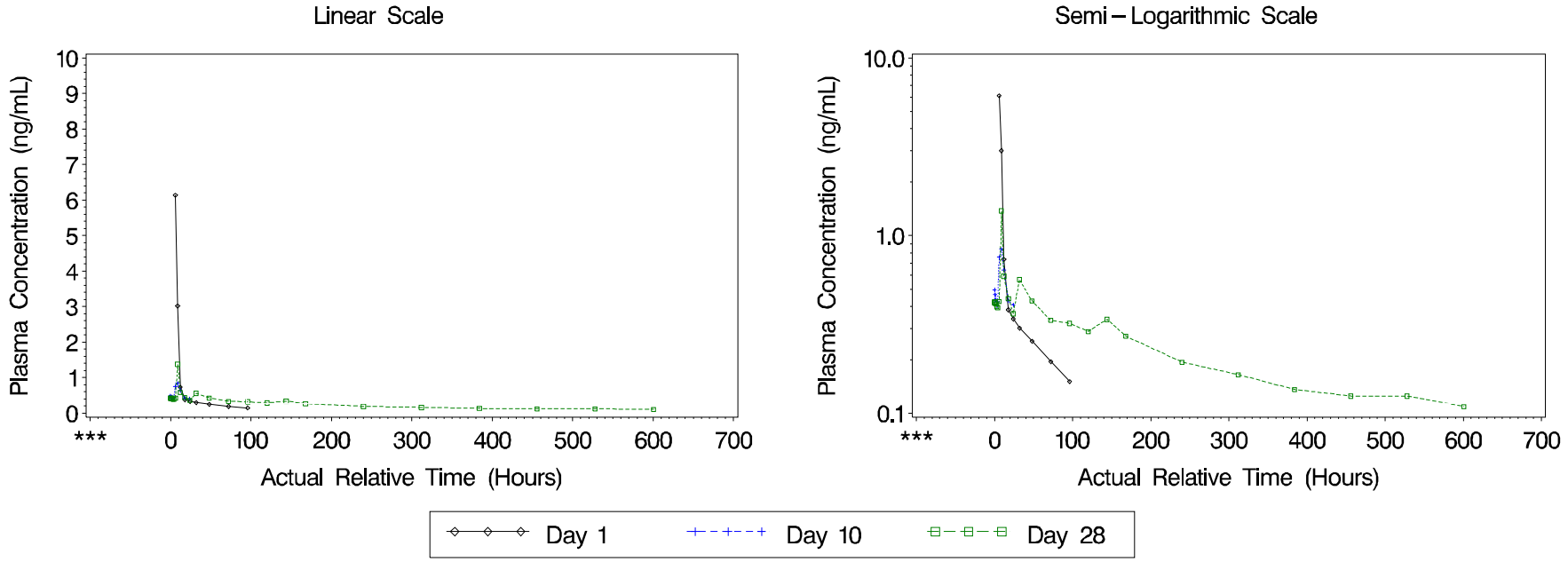
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]

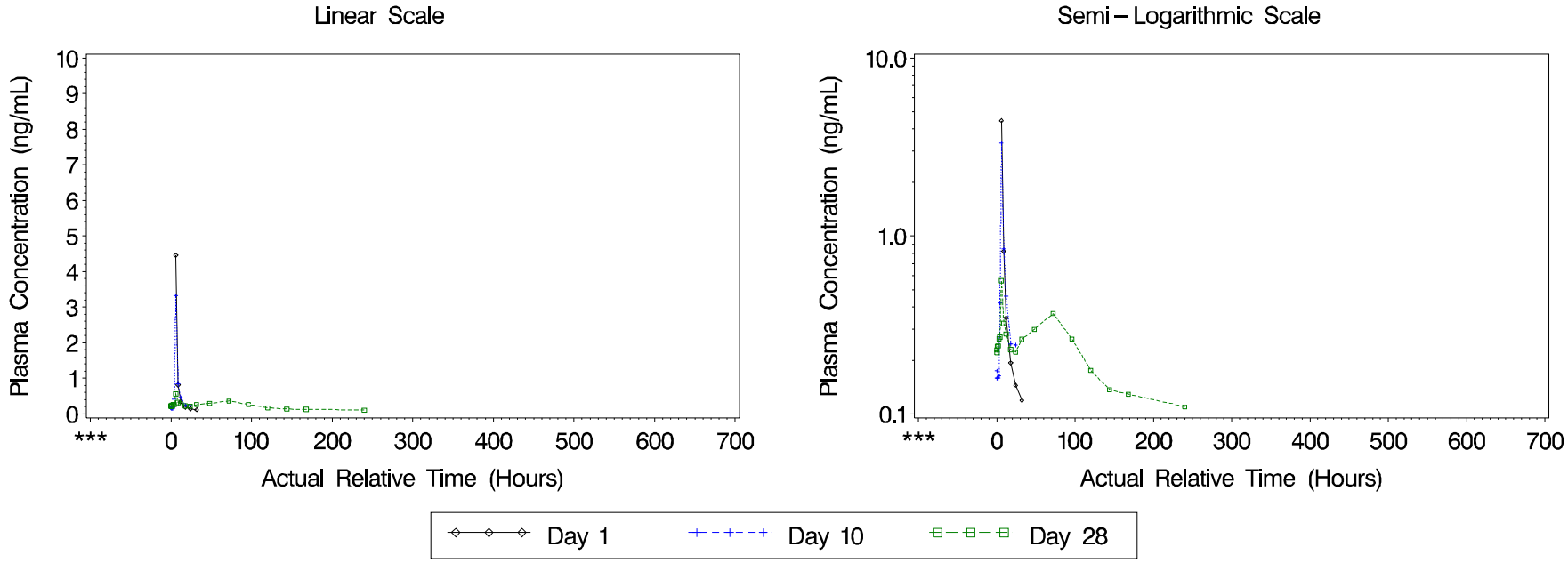

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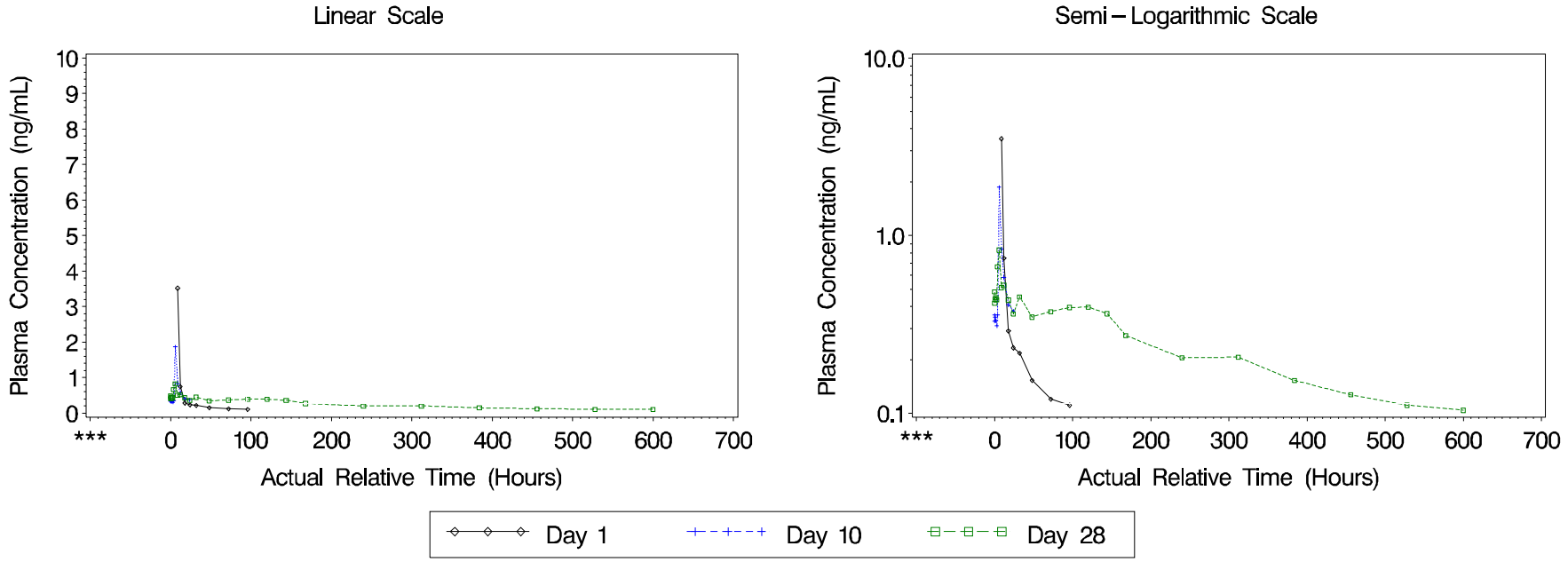
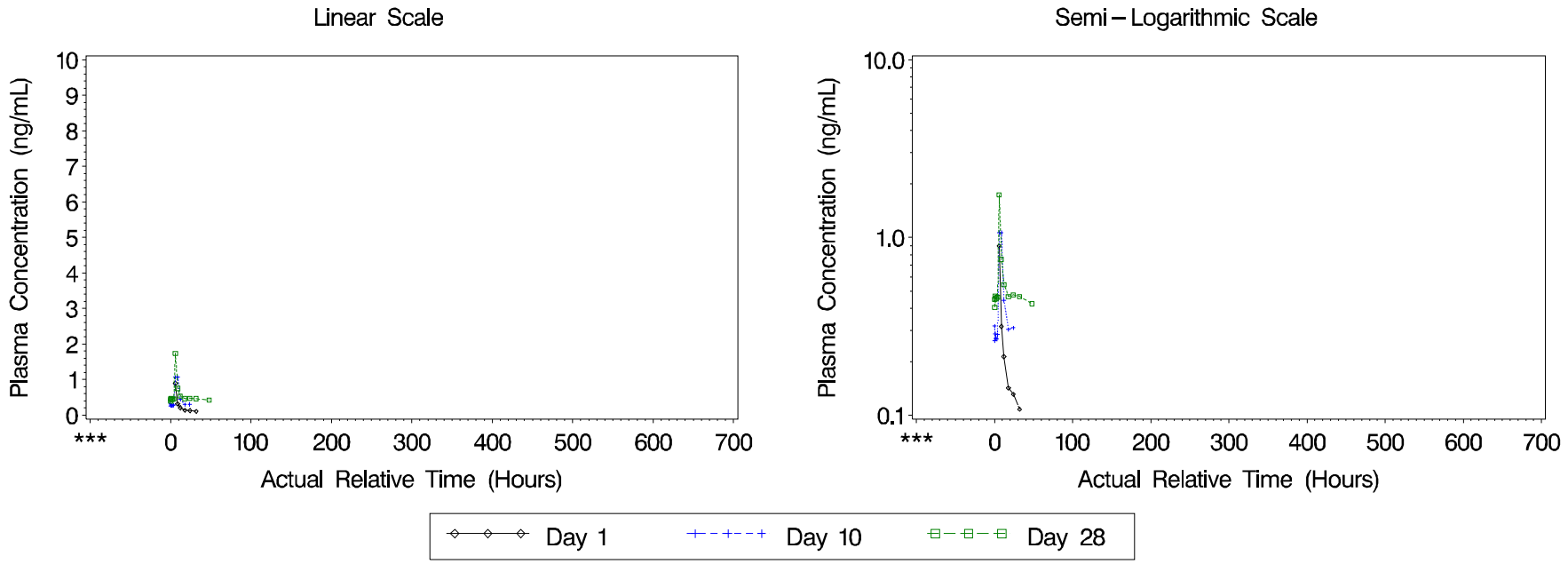
Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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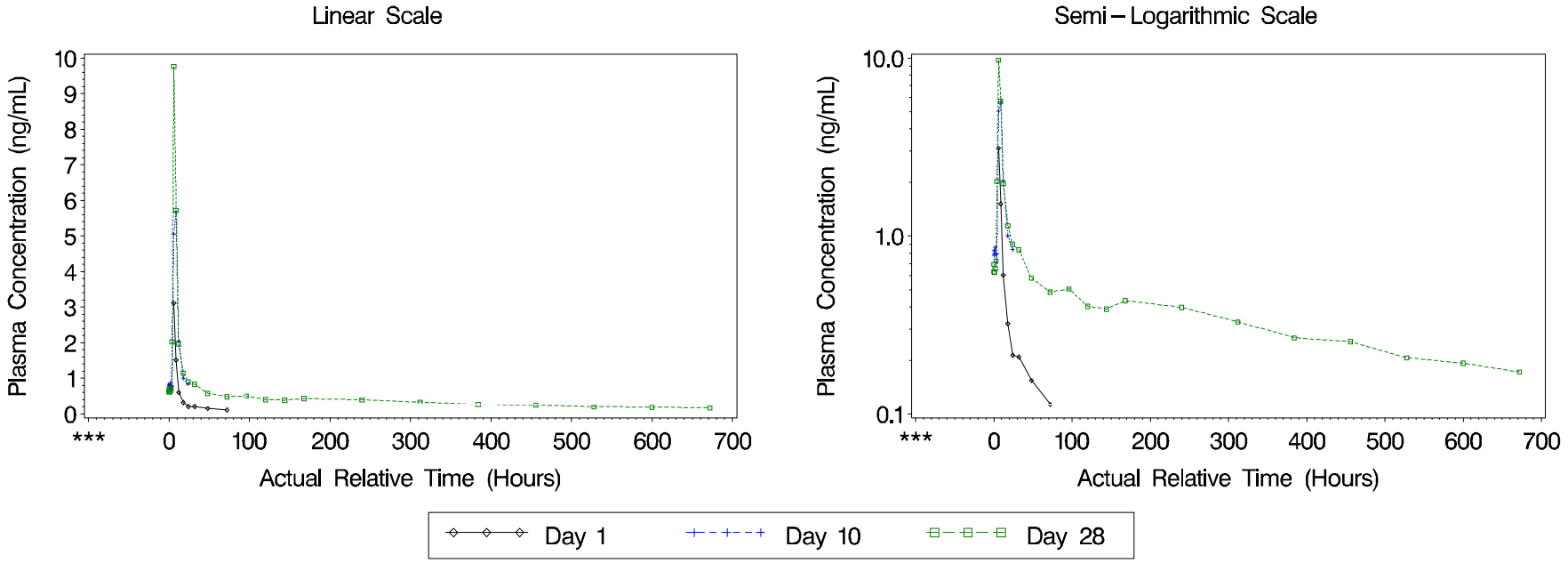
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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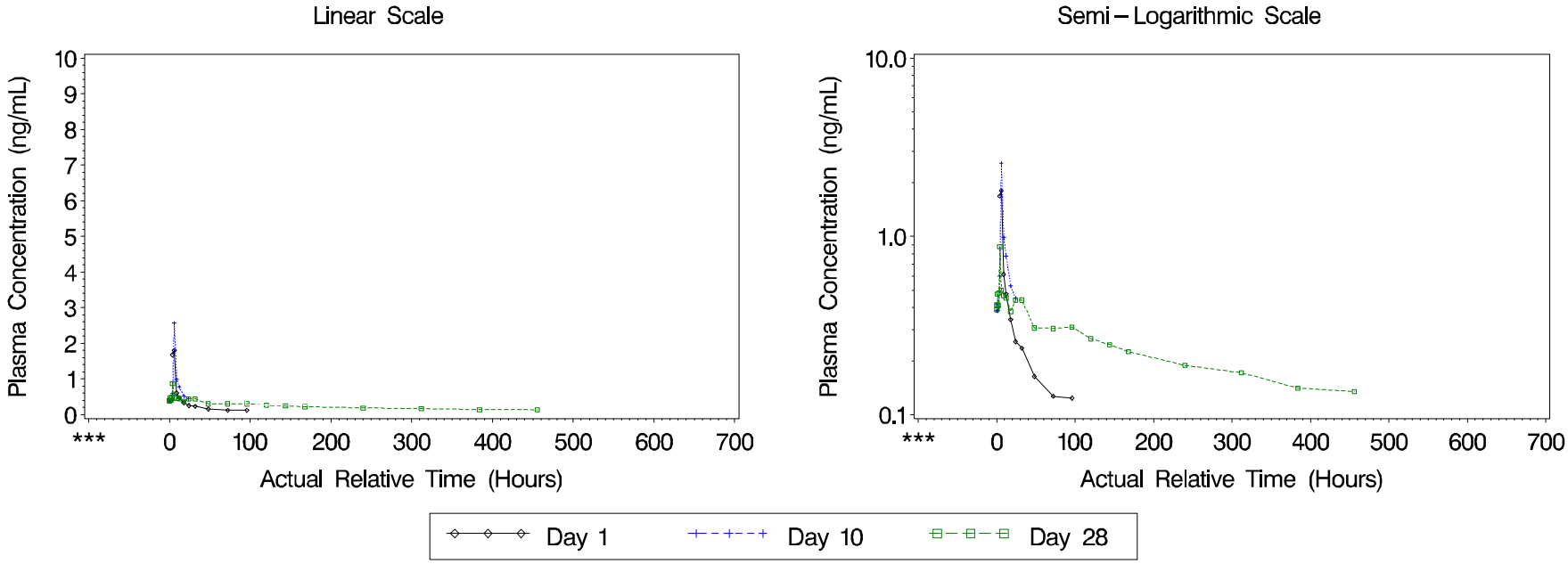
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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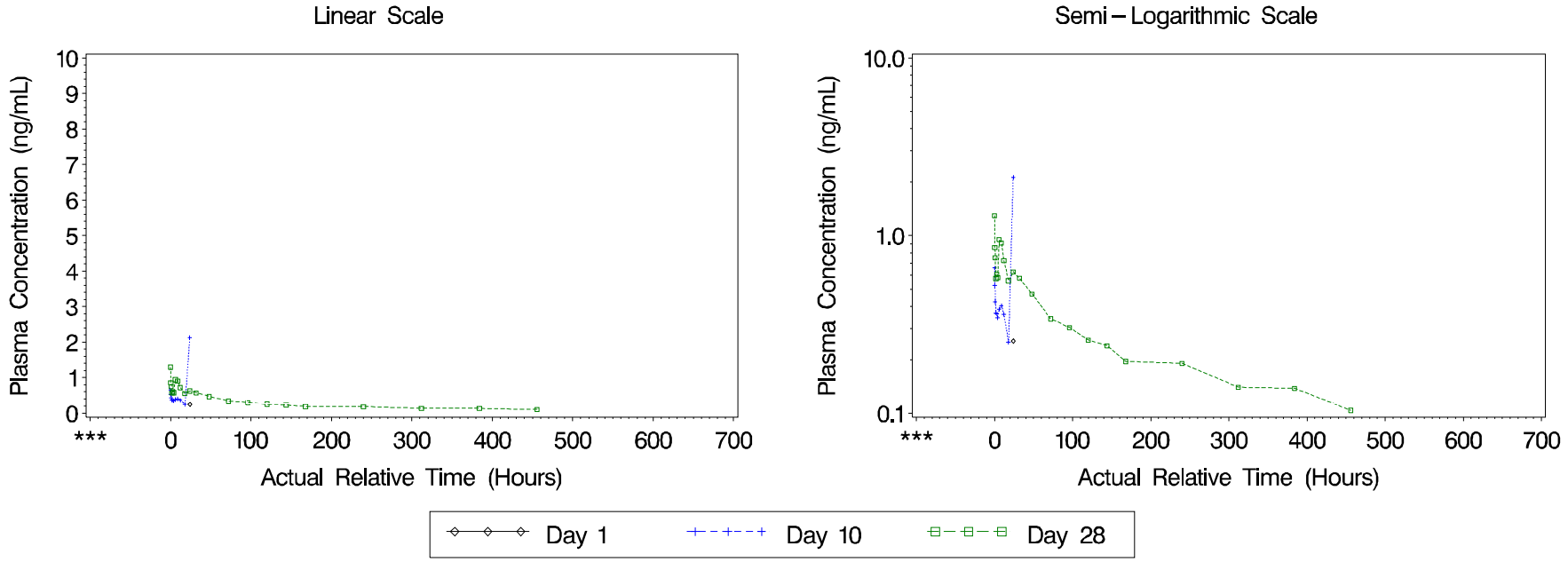
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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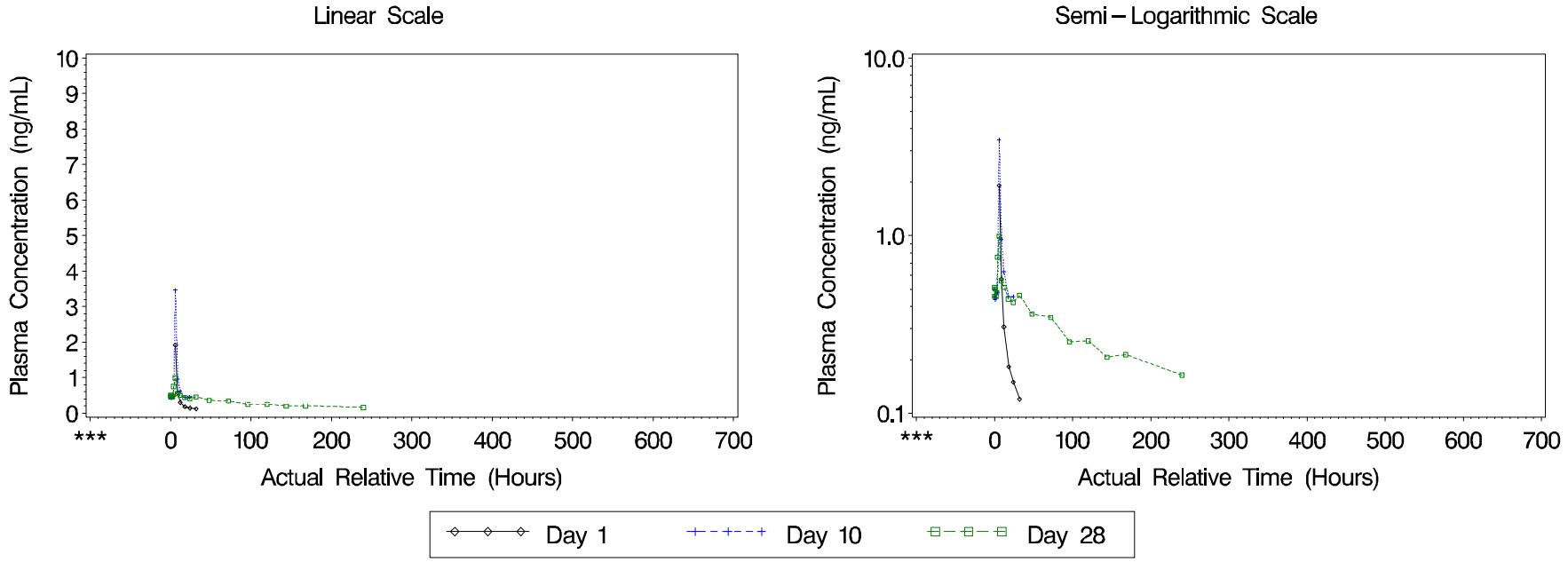
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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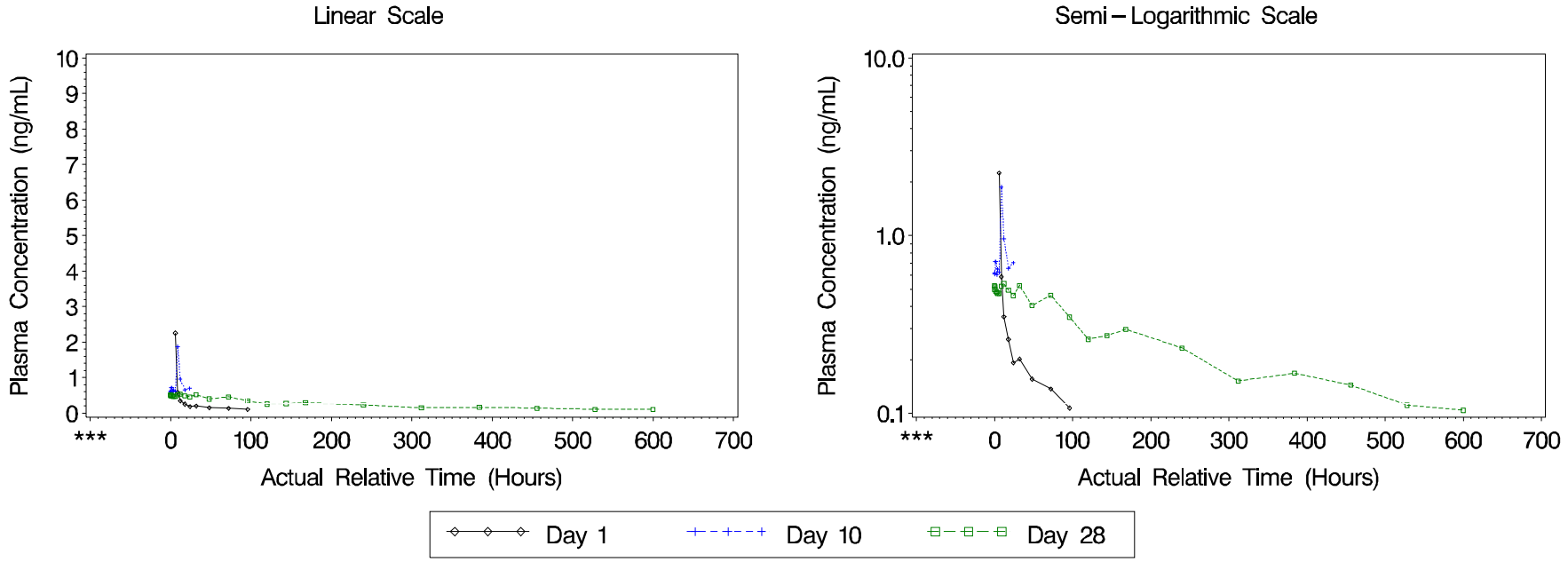
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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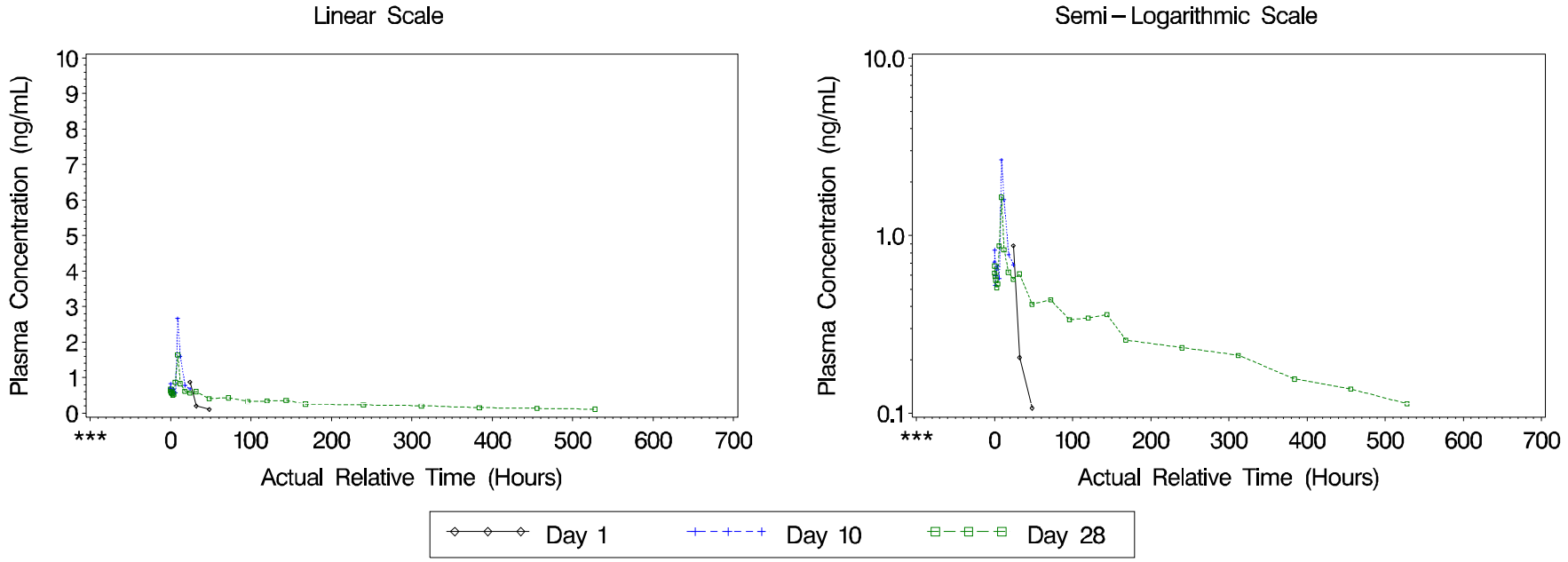
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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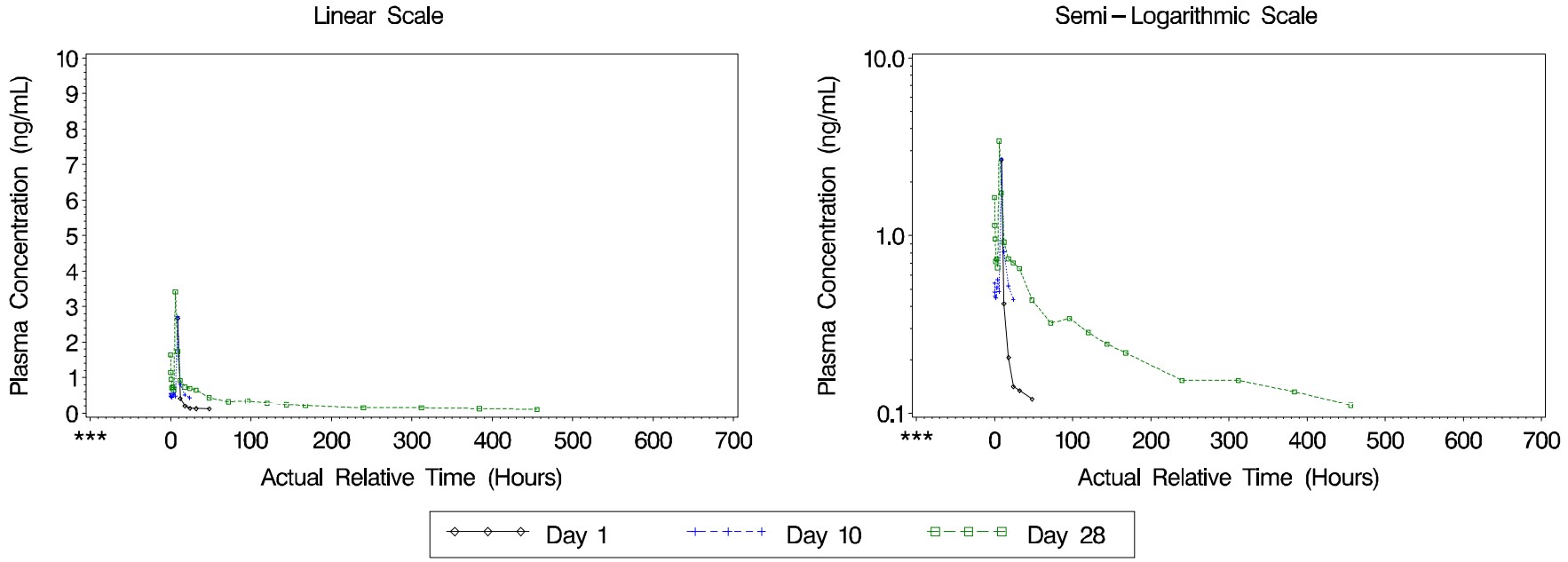
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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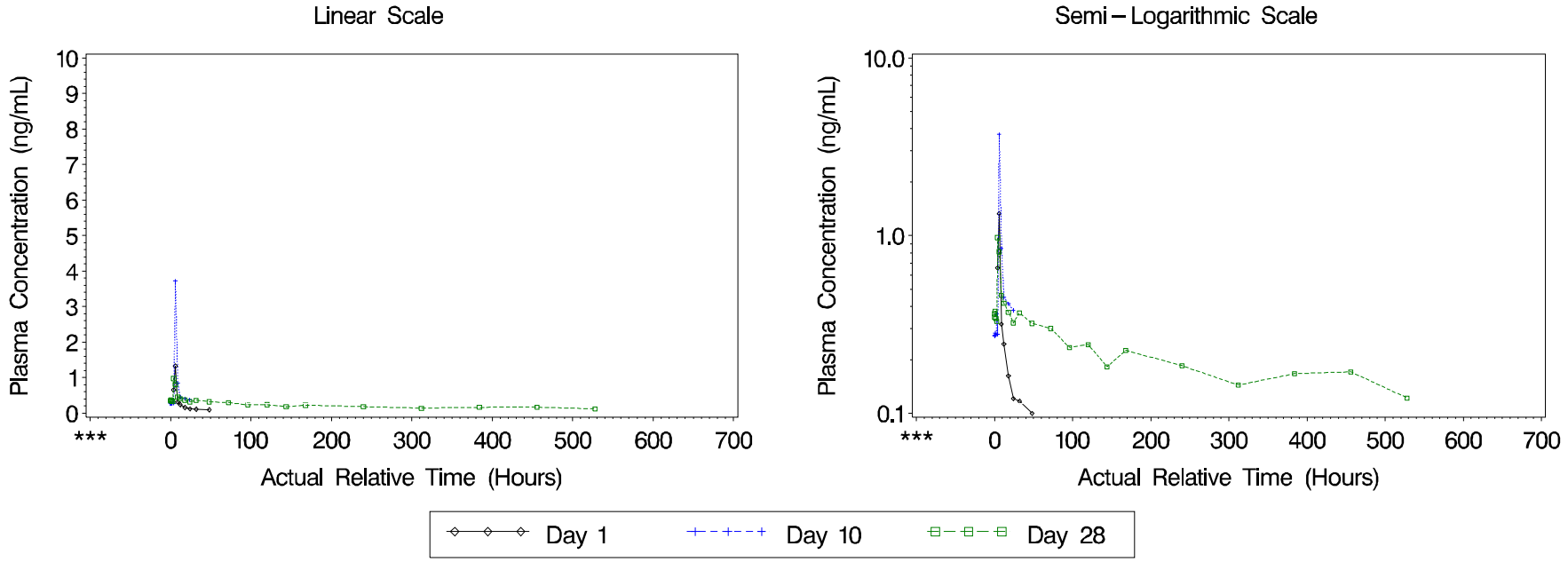
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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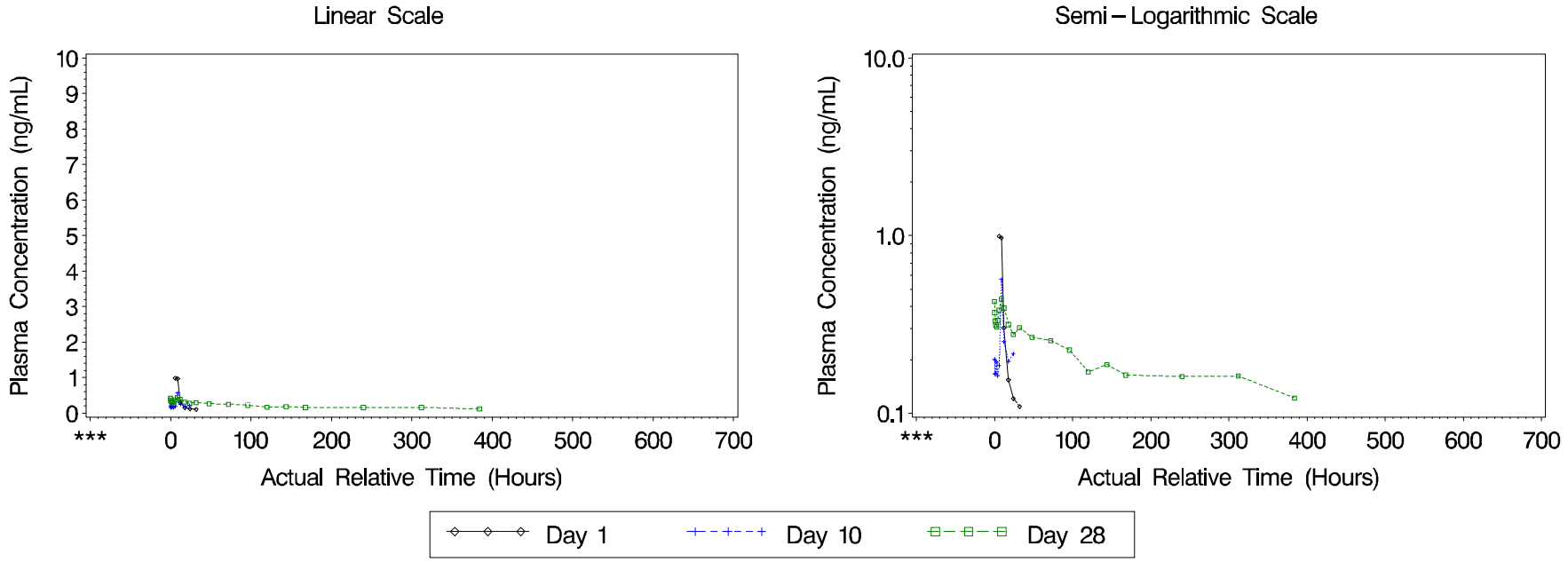
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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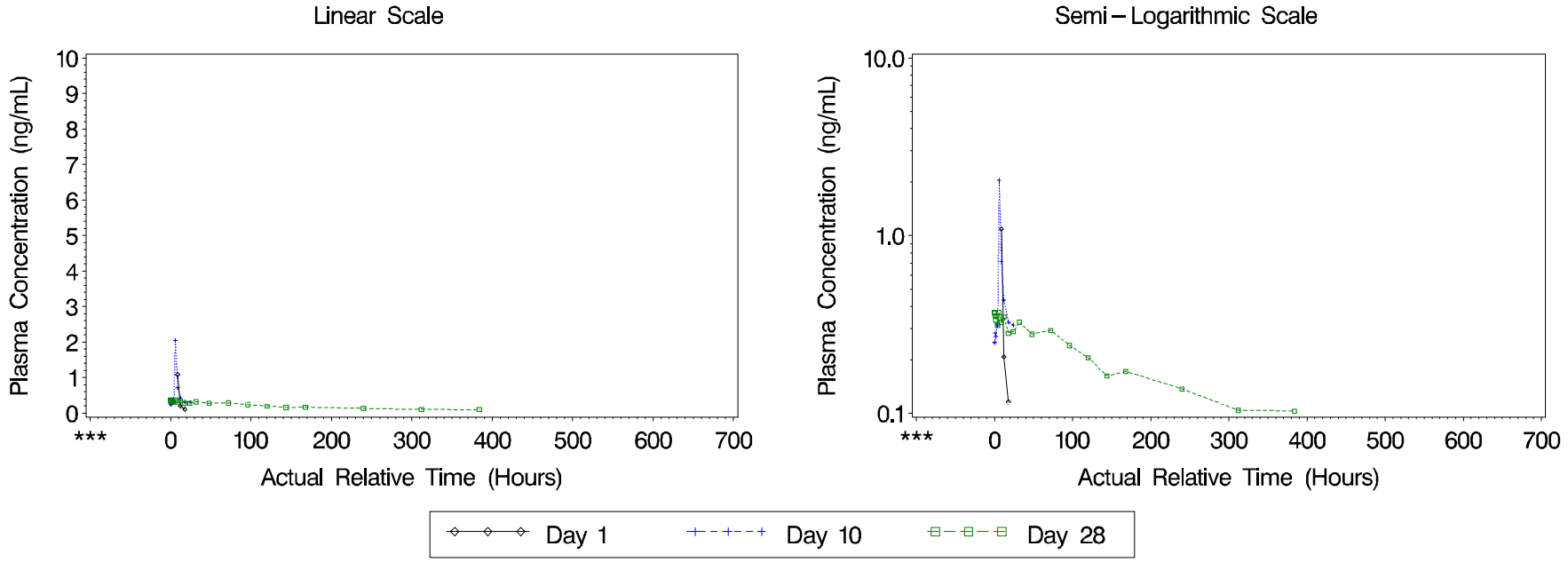
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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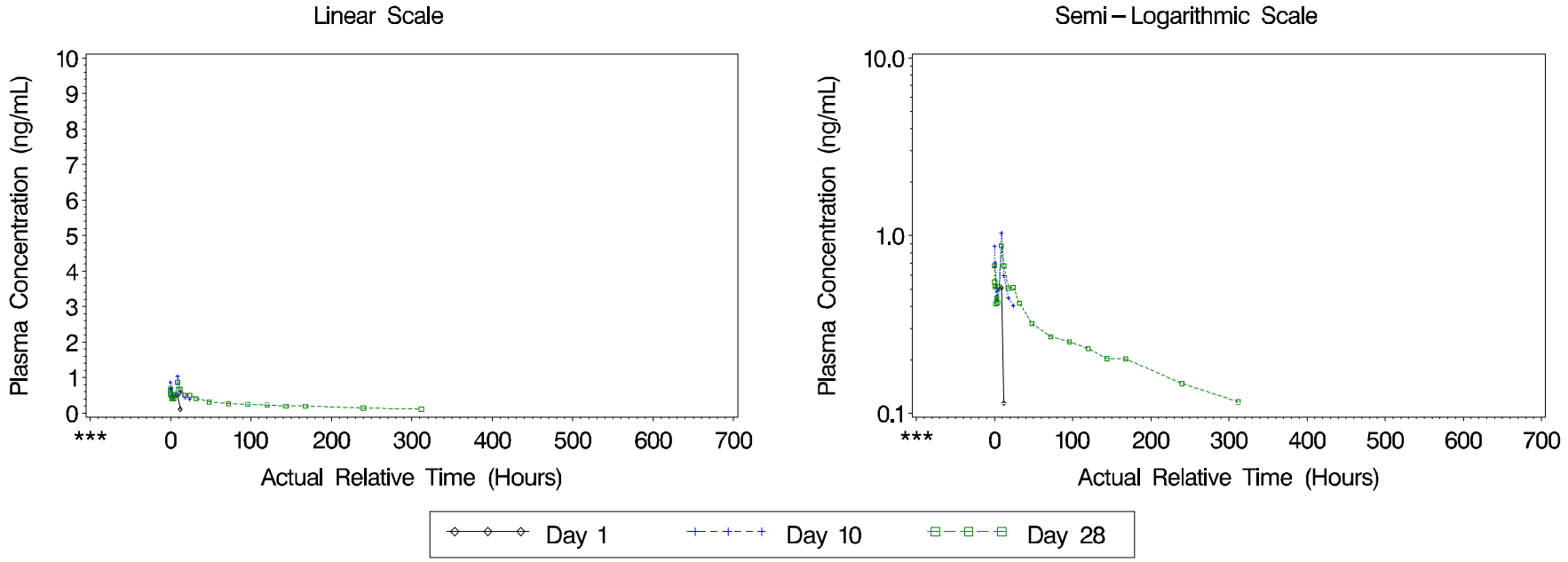
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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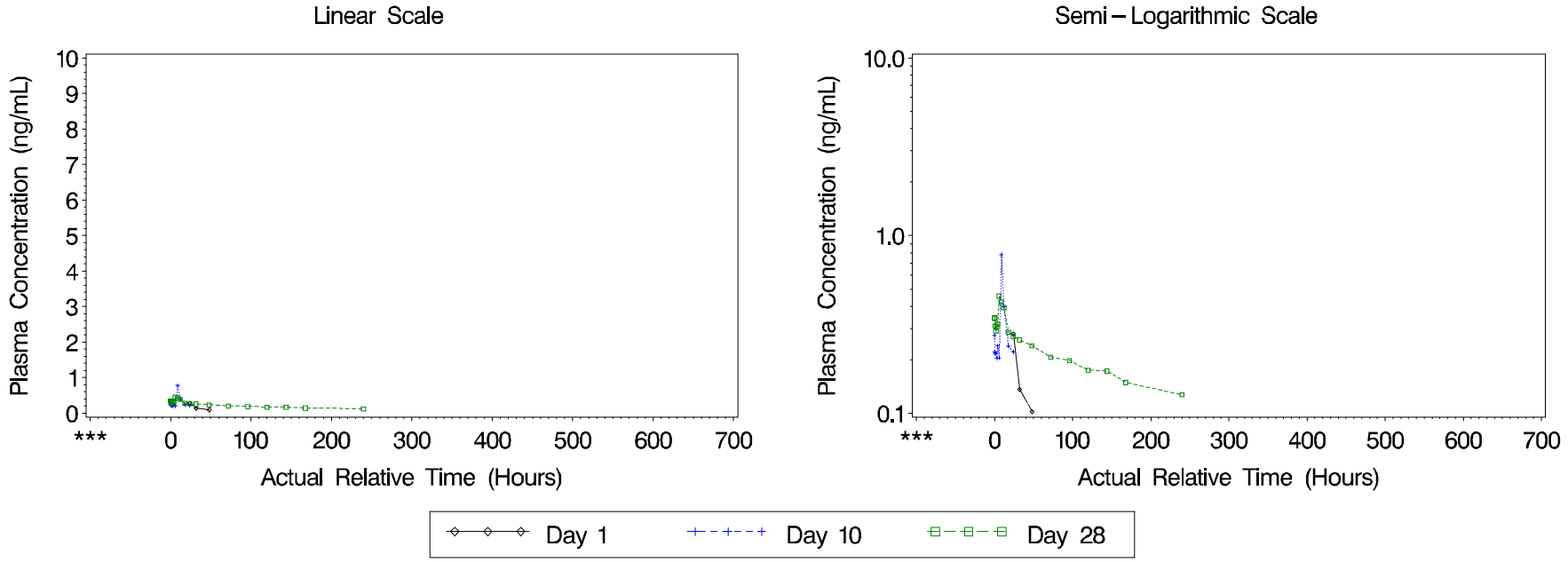
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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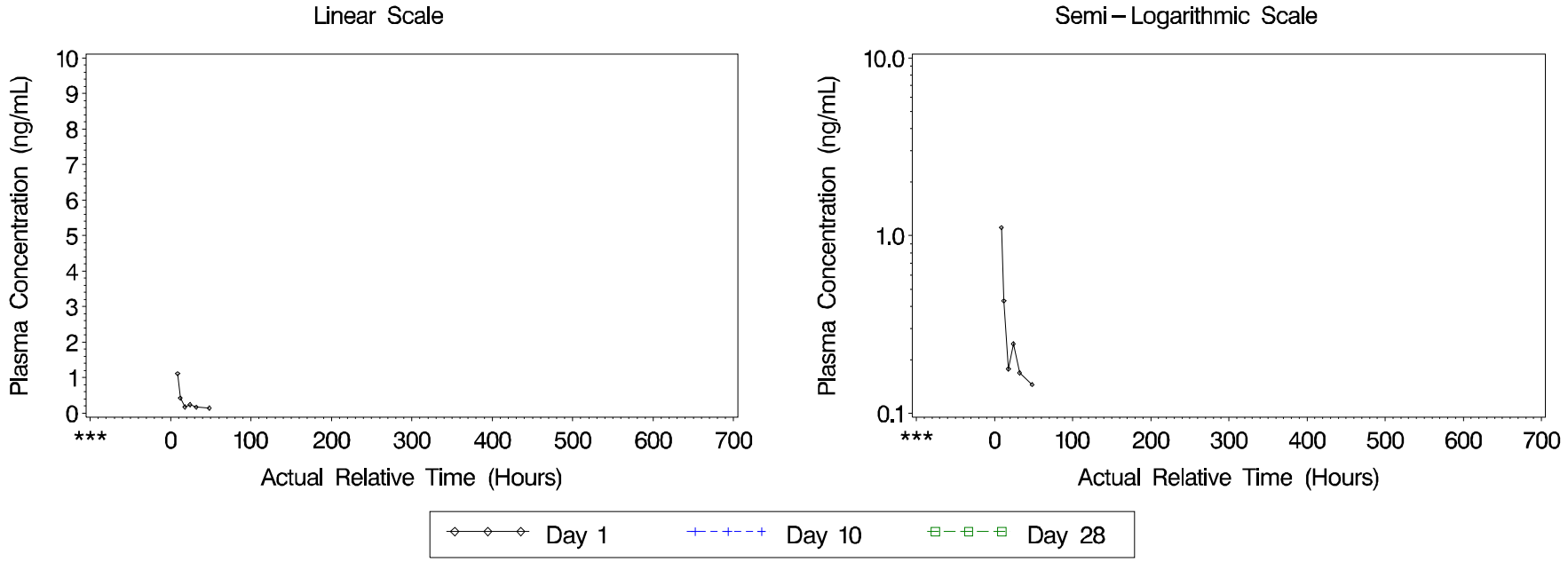
[redacted]

Figure 11.2
Individual Subject Plasma SB−553253 Concentration − Time Plot
Subject ID=[redacted]



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Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
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[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]

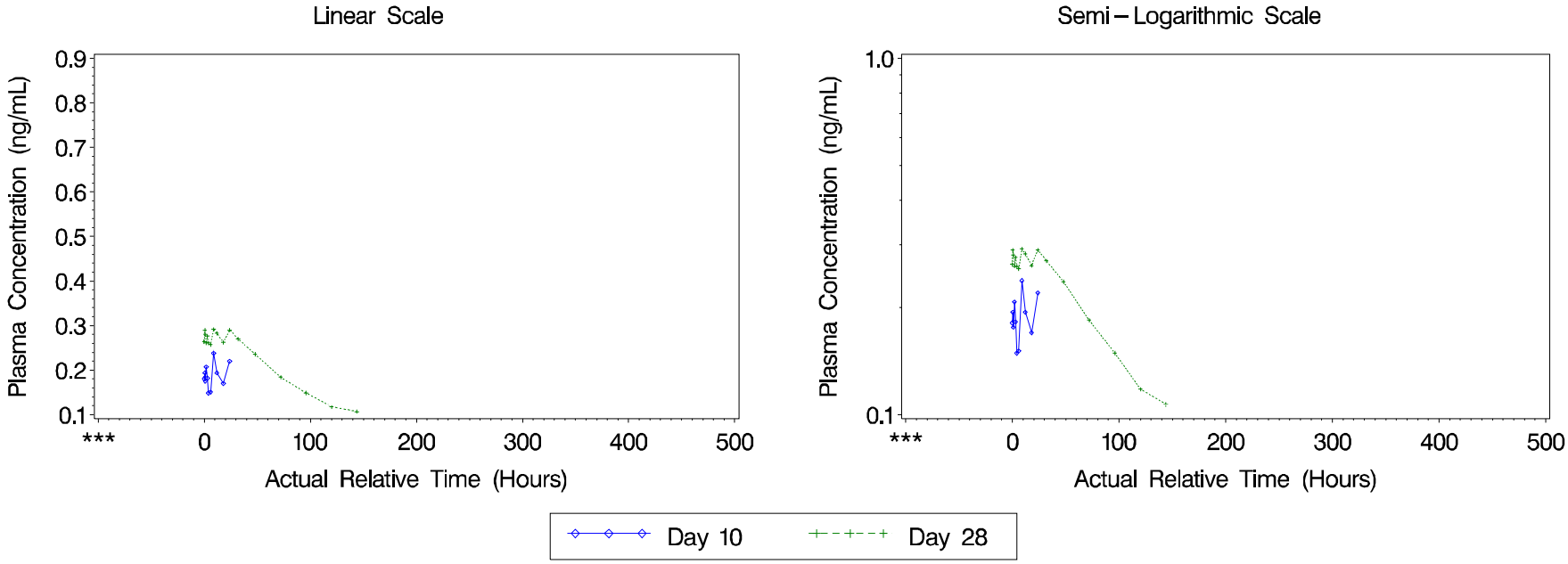

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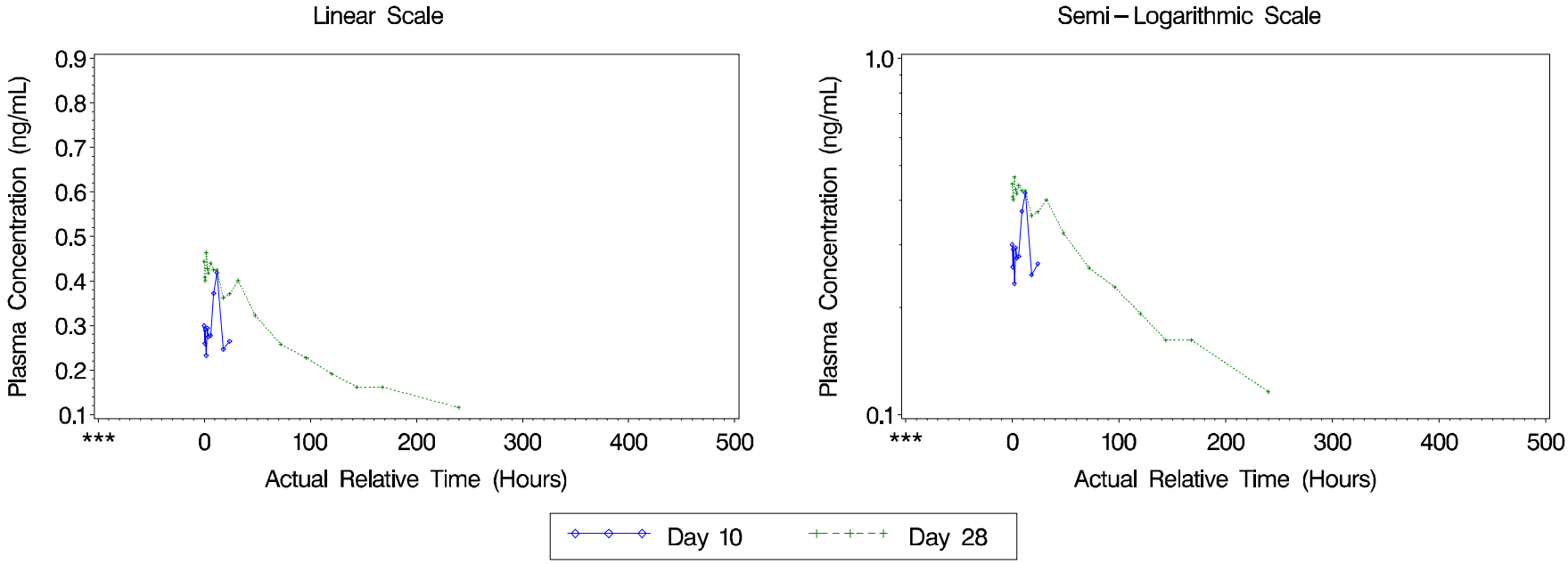
Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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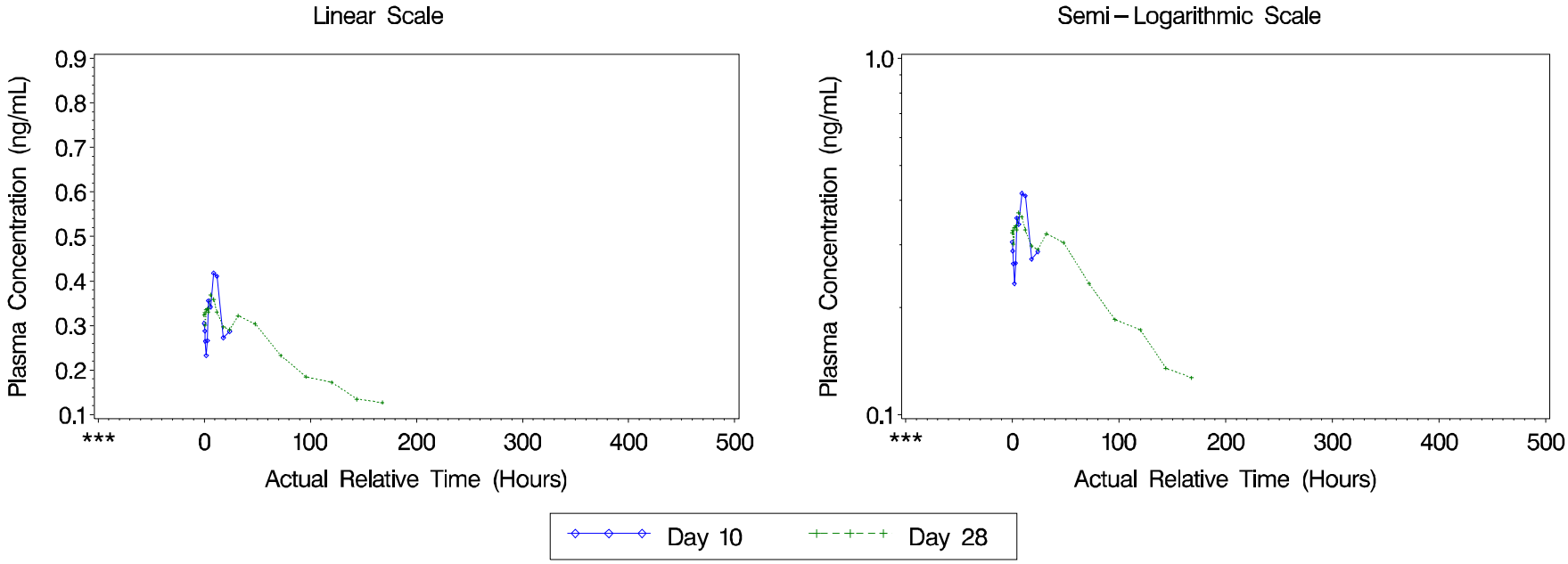
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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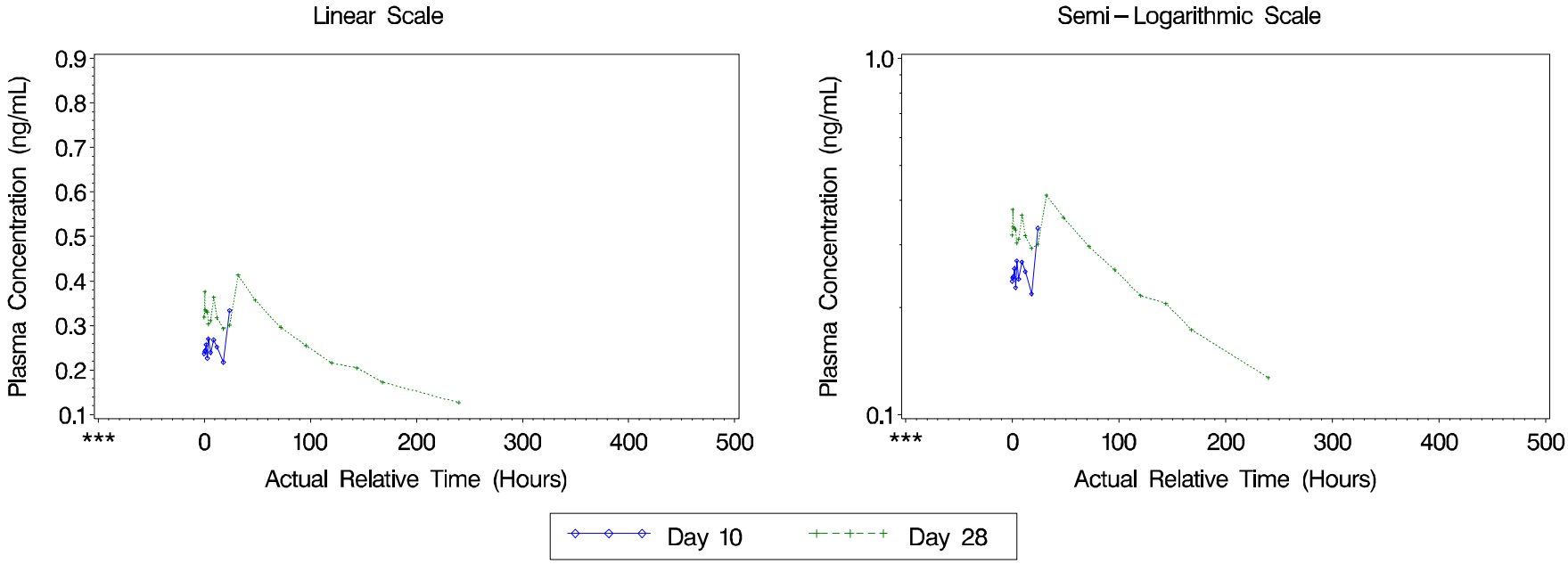
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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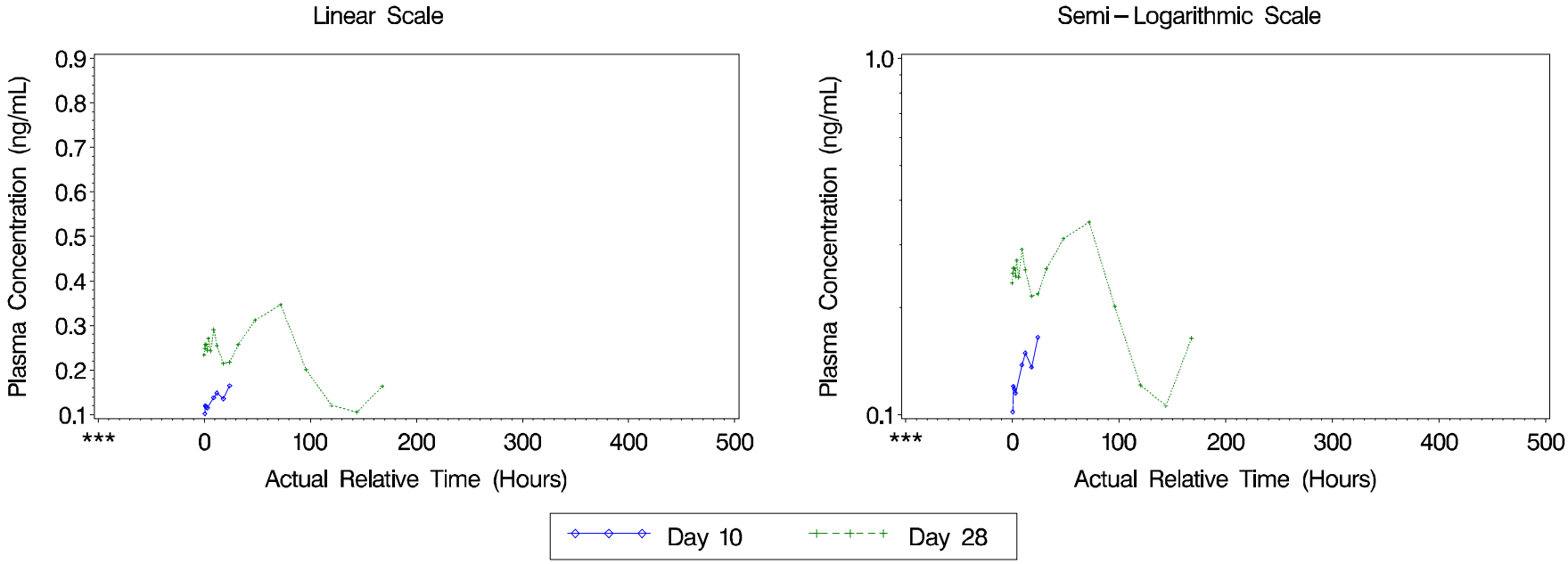
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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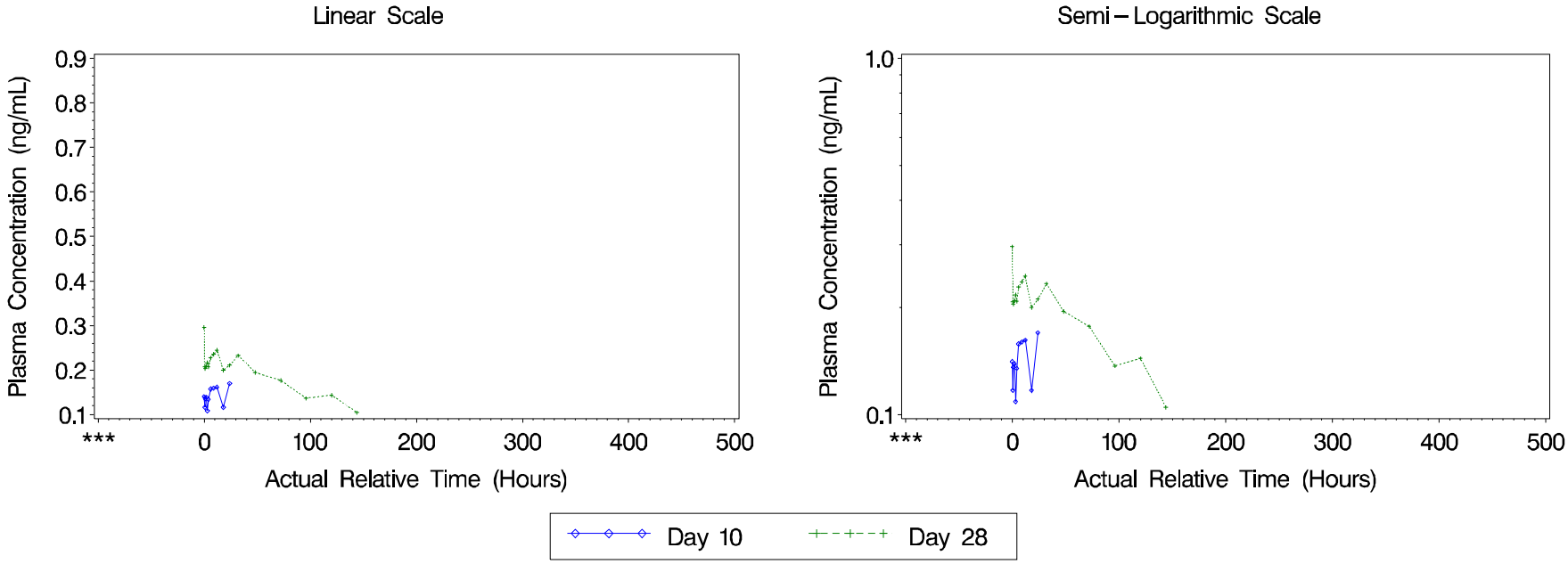
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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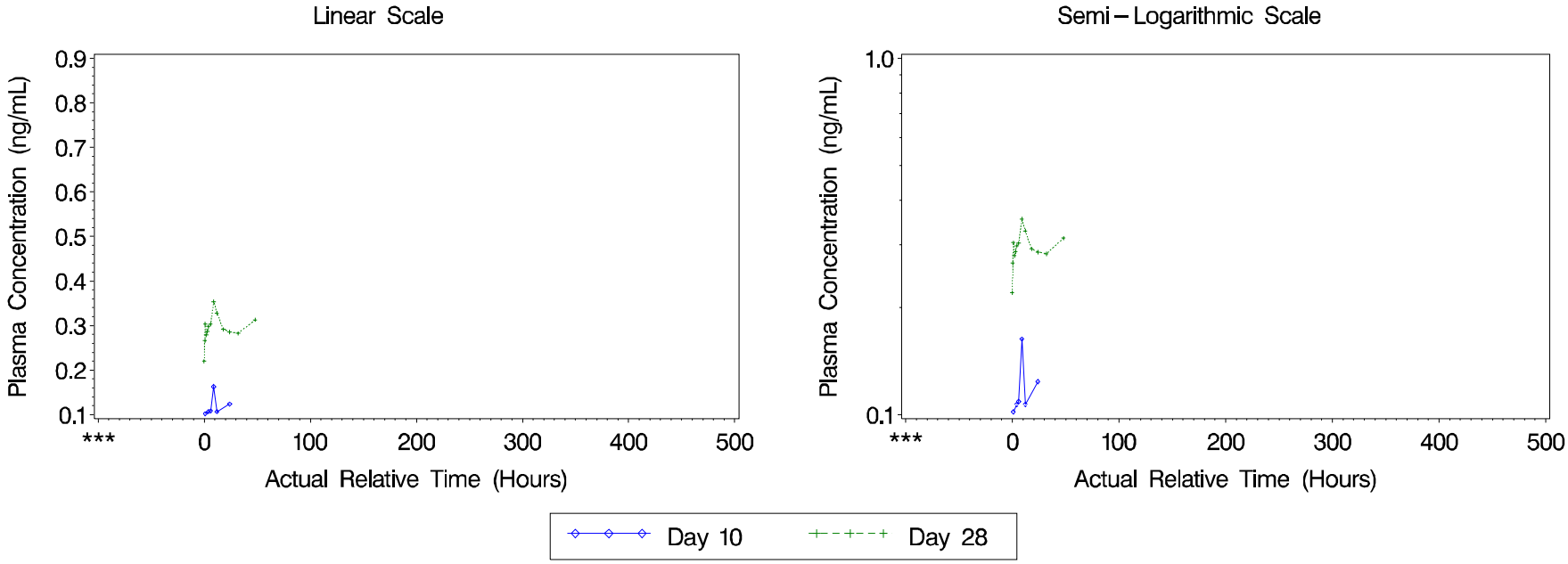
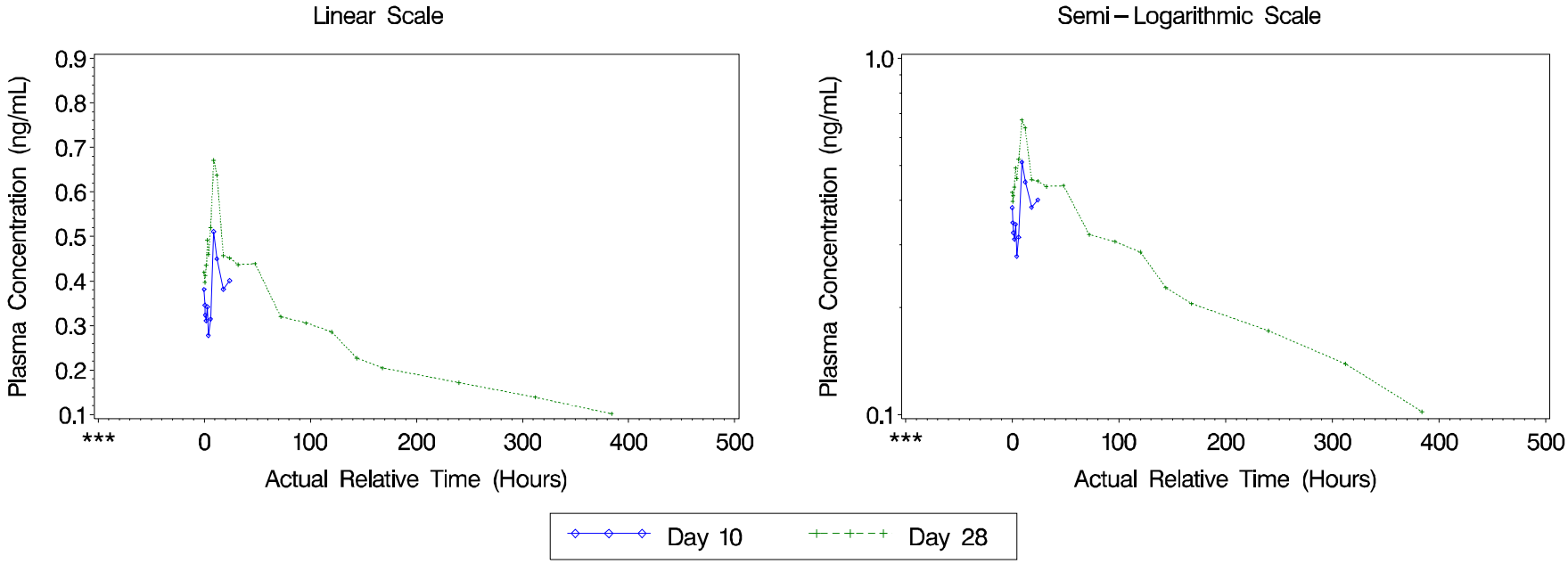
[redacted]

Figure 11.3
Individual Subject Plasma SB-554008 Concentration – Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free-base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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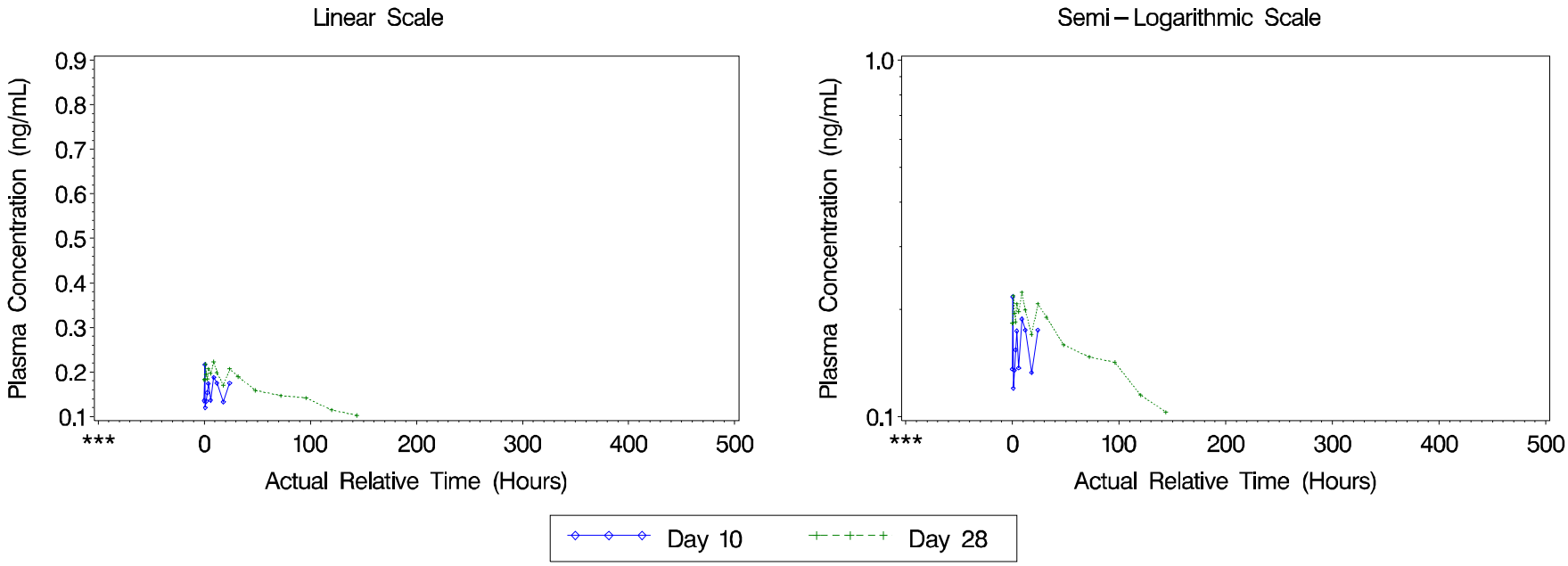
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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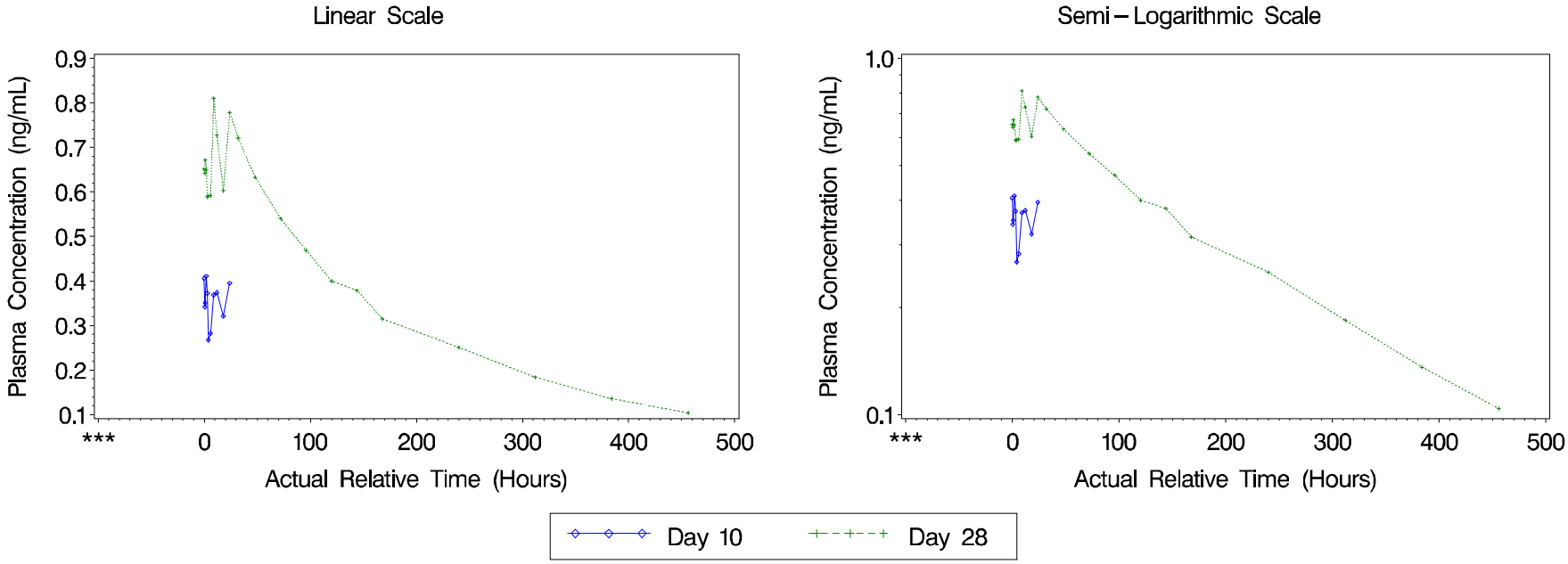
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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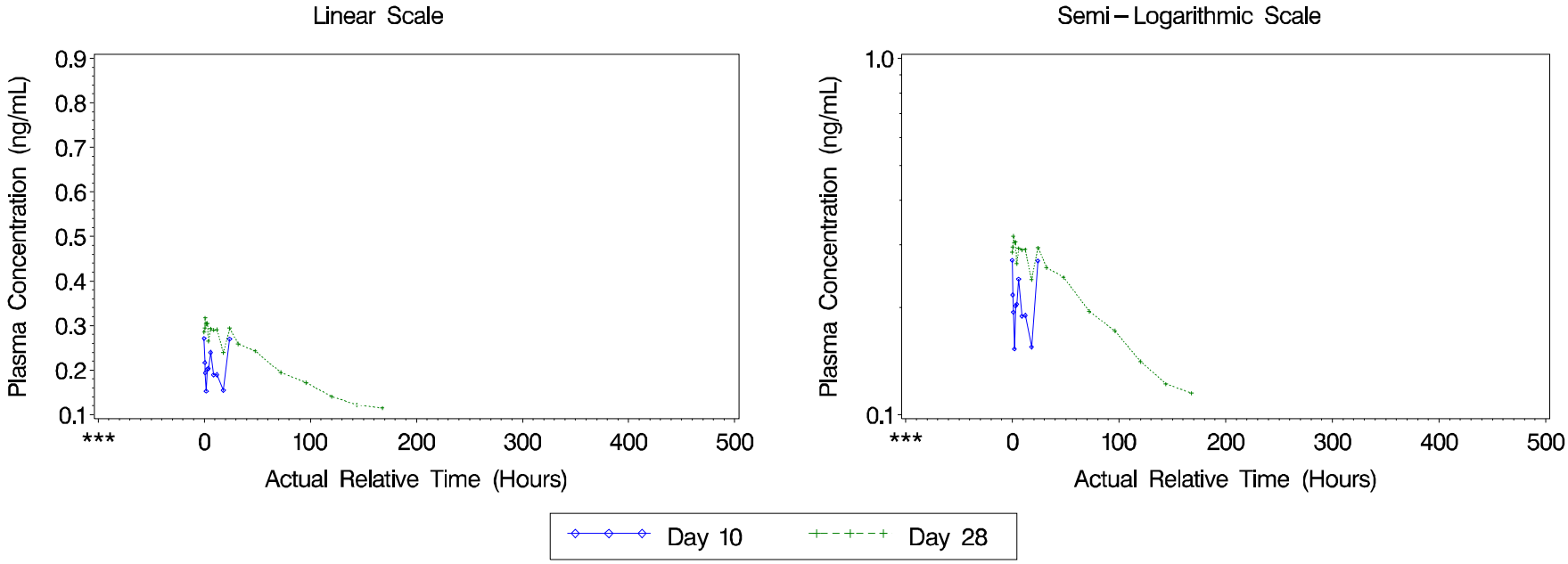
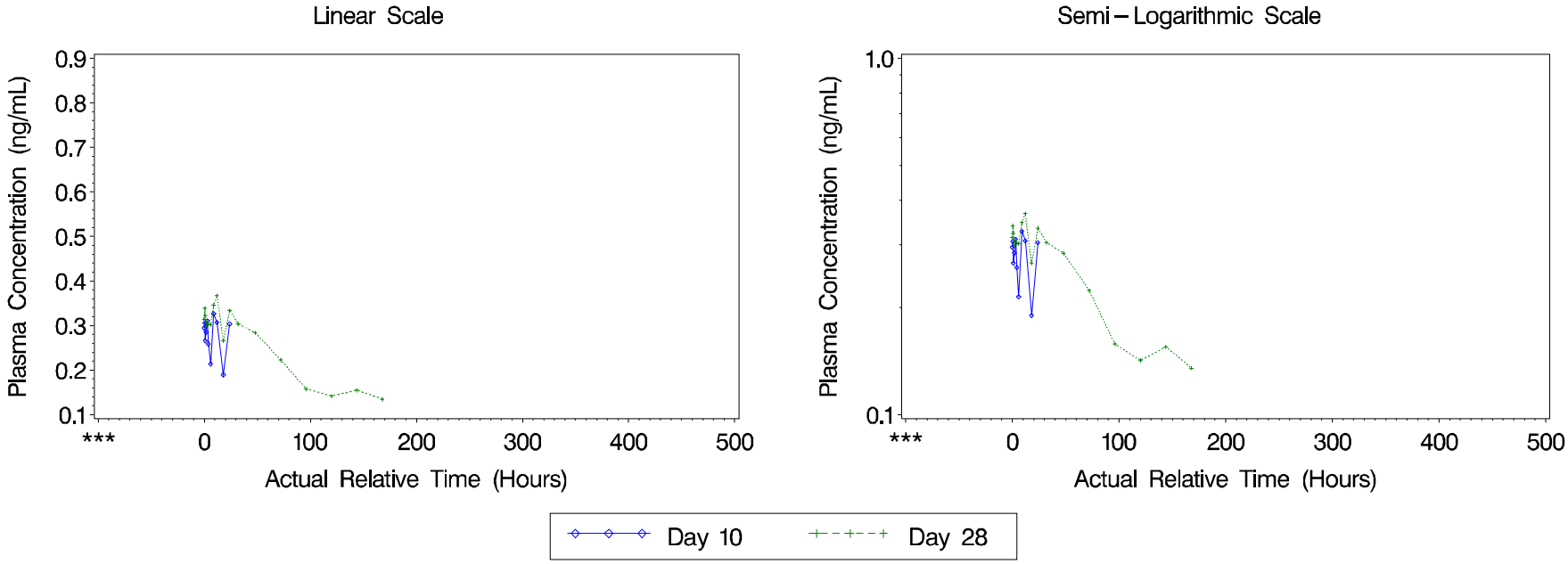
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB-554008 Concentration – Time Plot
Subject ID = [redacted]



Note:
Day 1: 160 mg of EC micronized free-base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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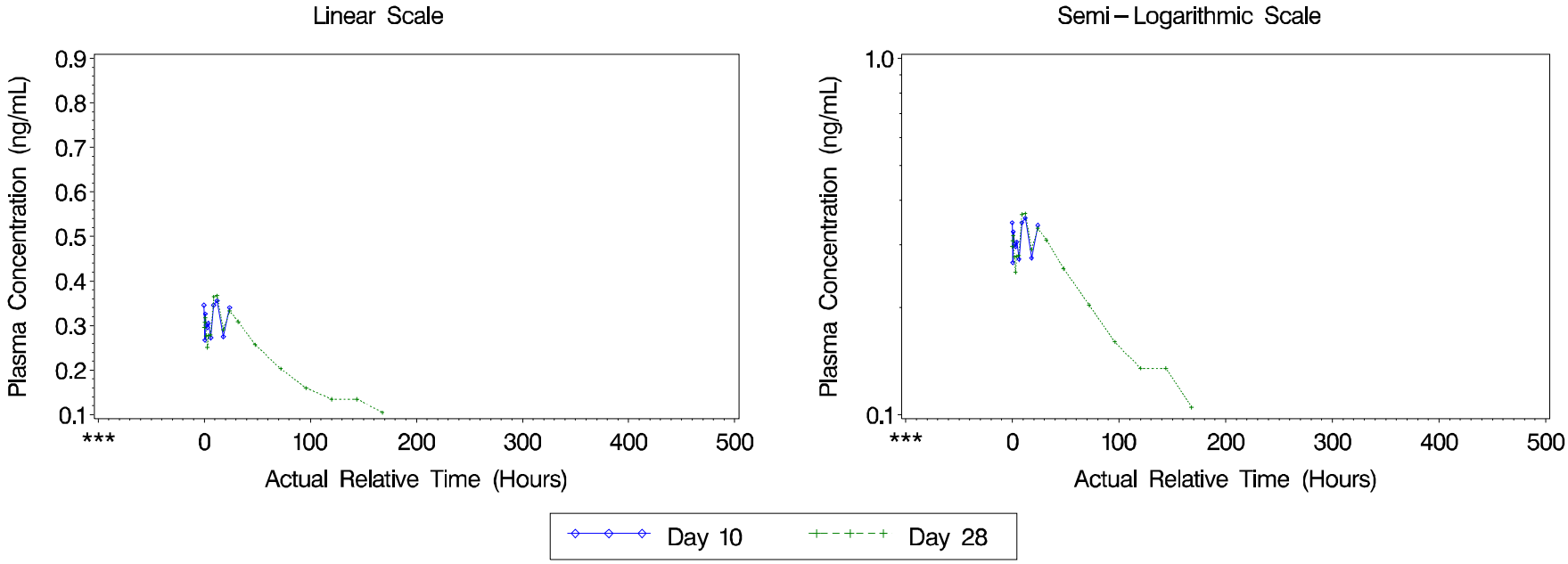
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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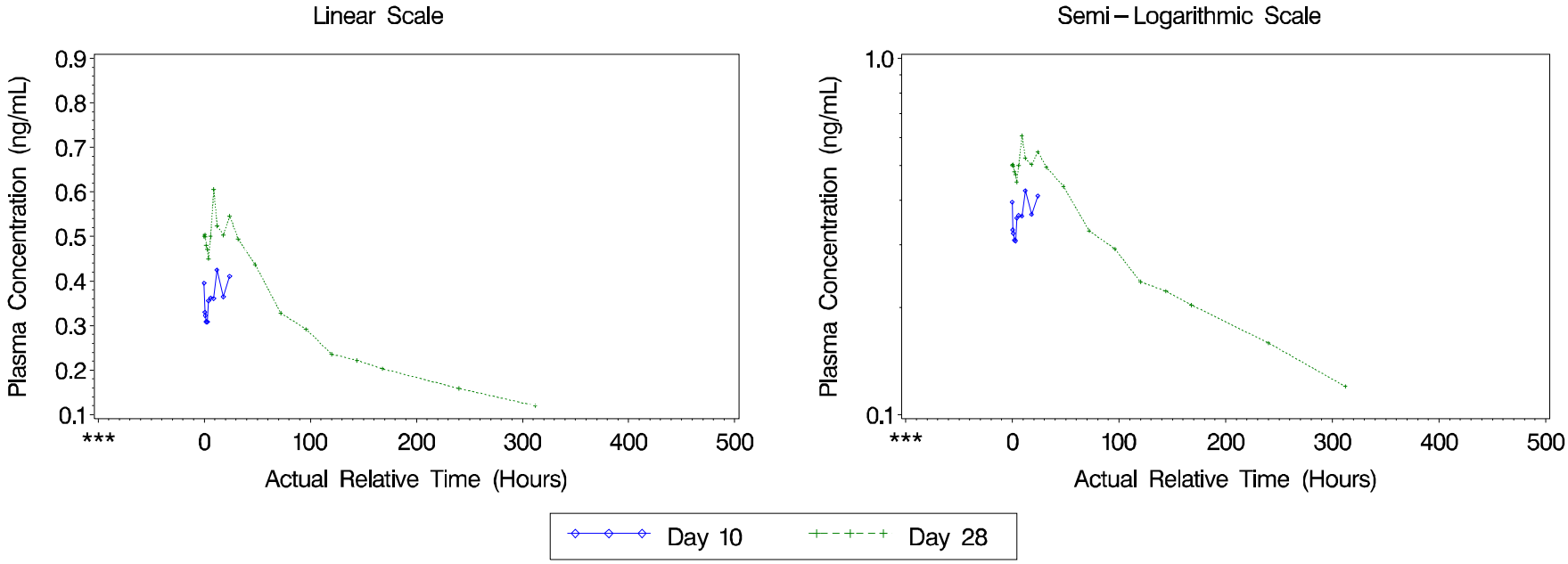
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



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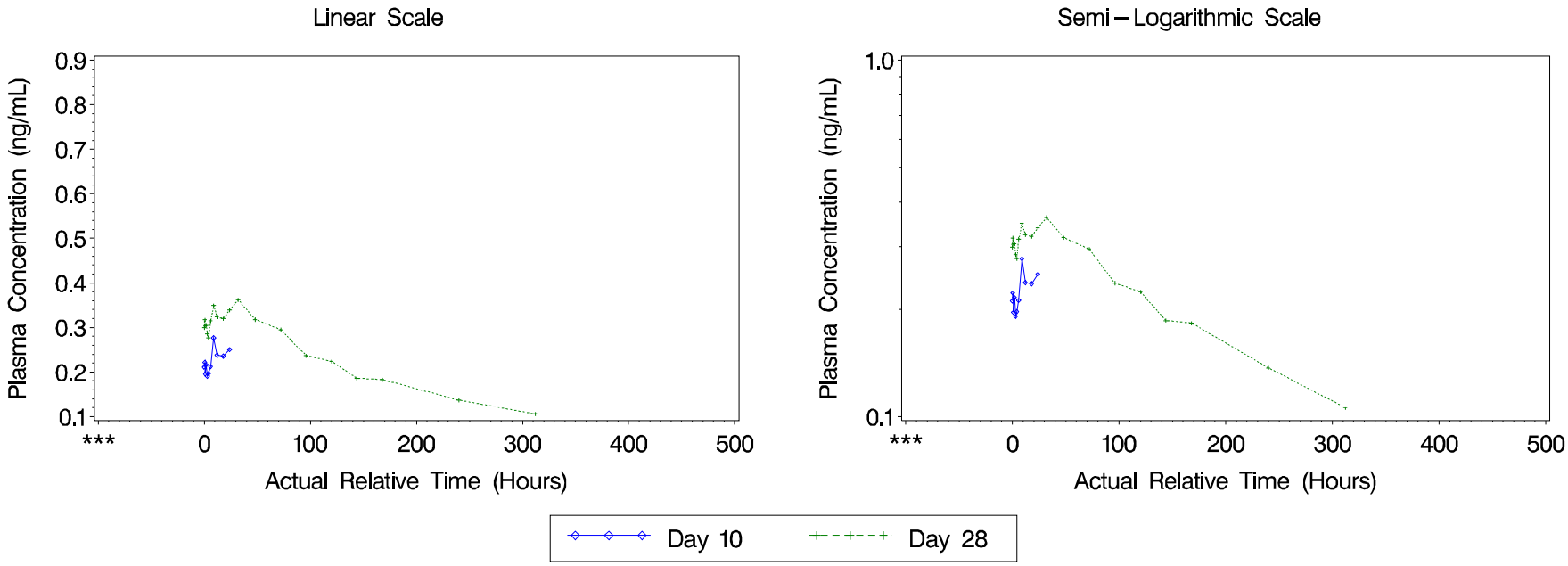
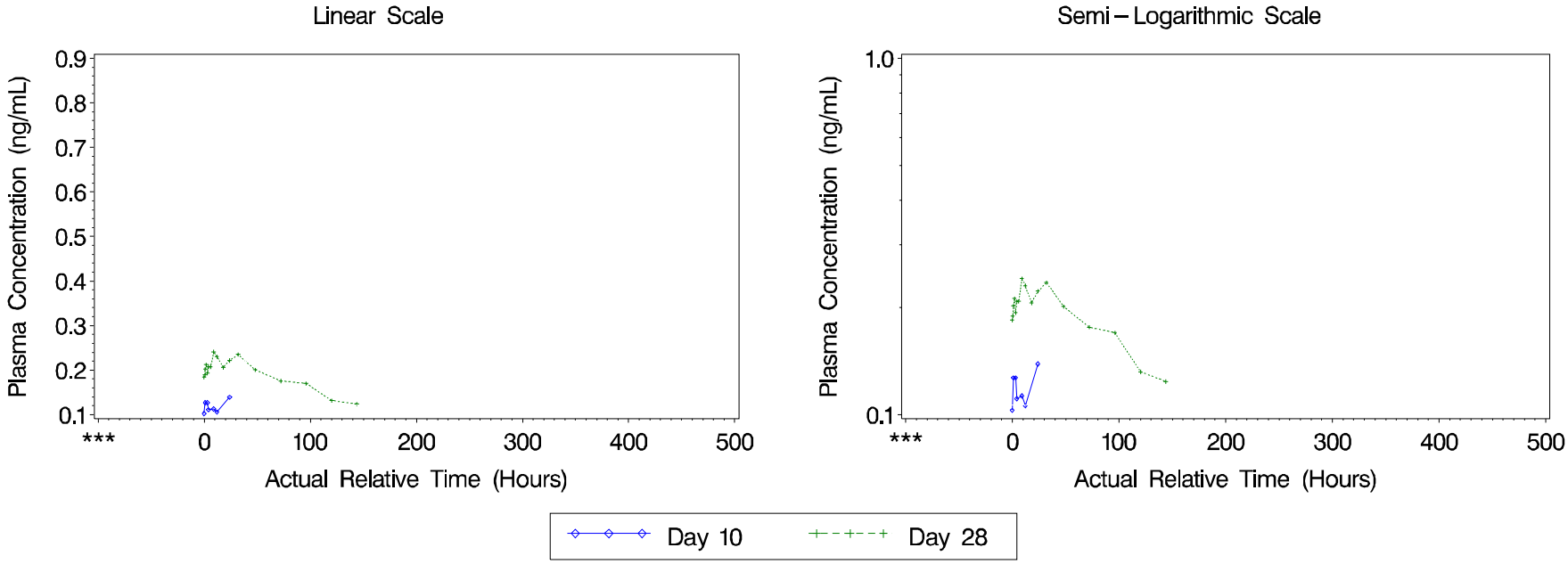
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



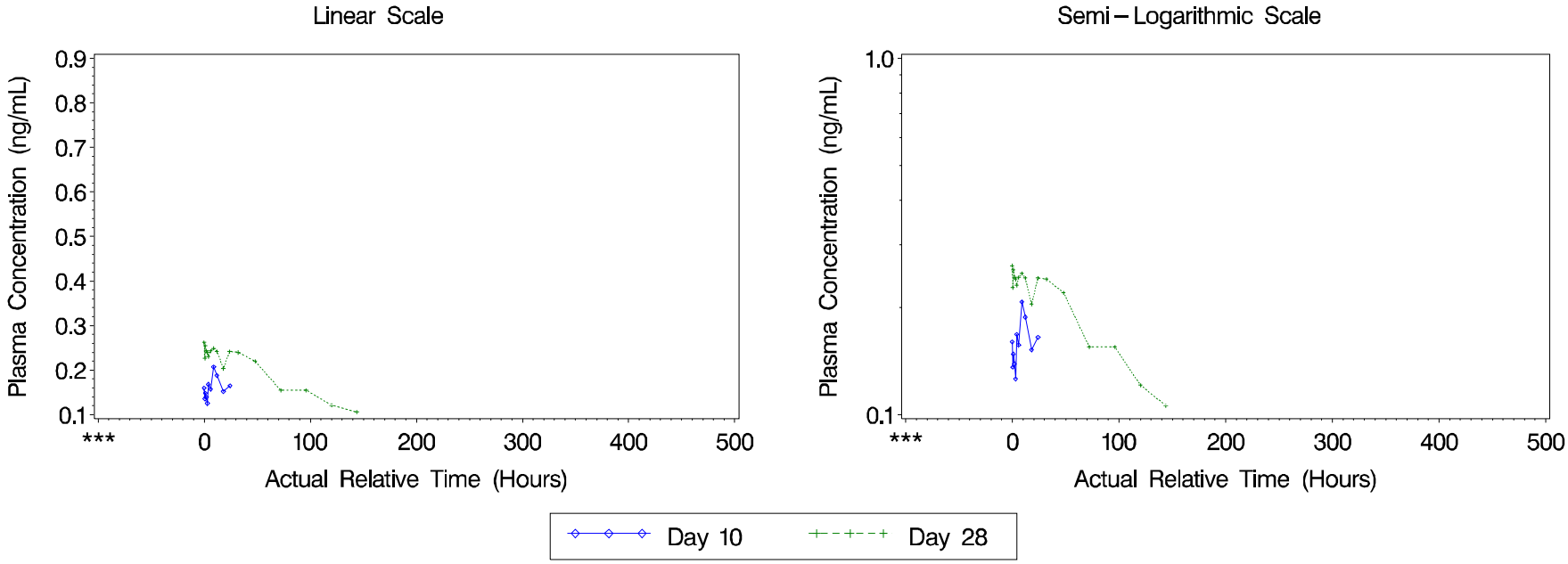
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



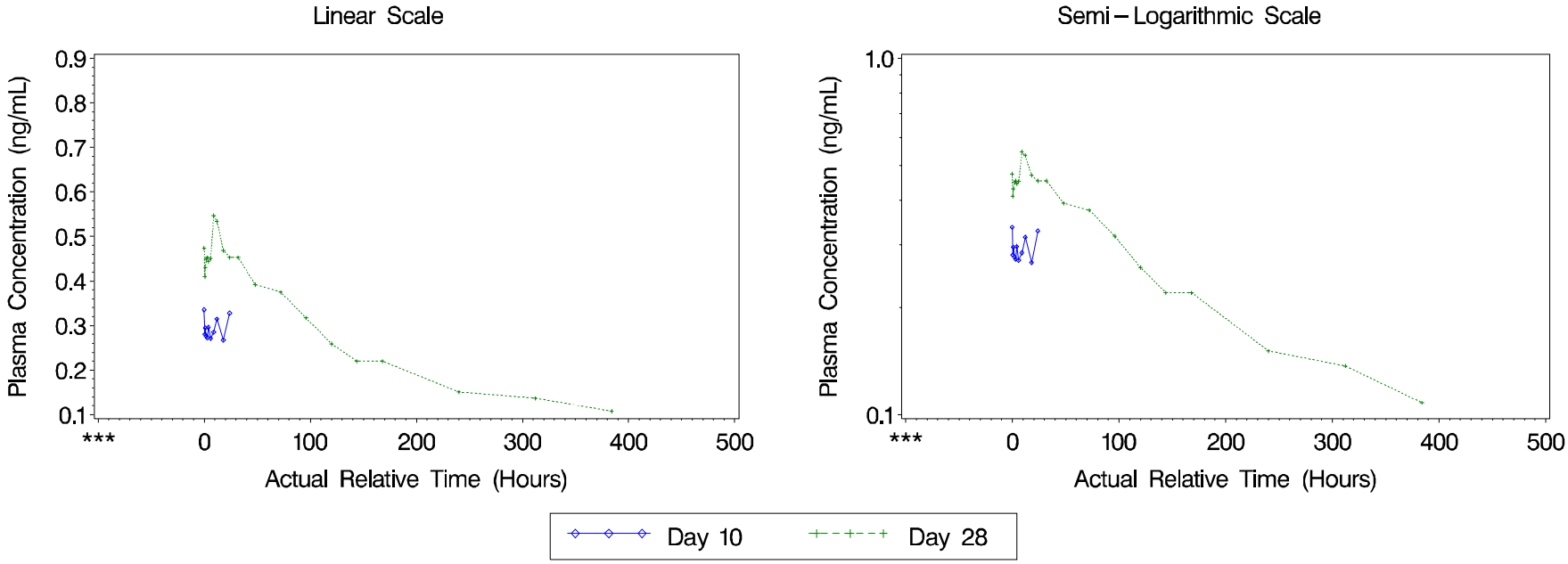
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



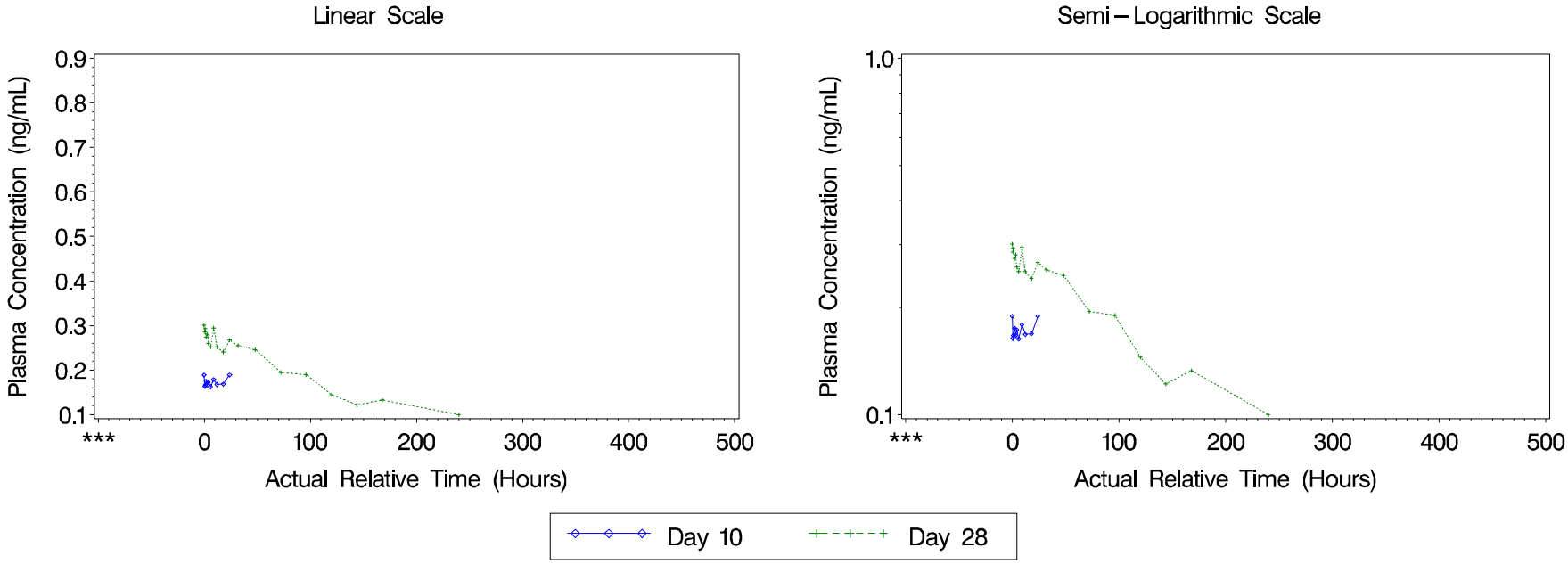
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



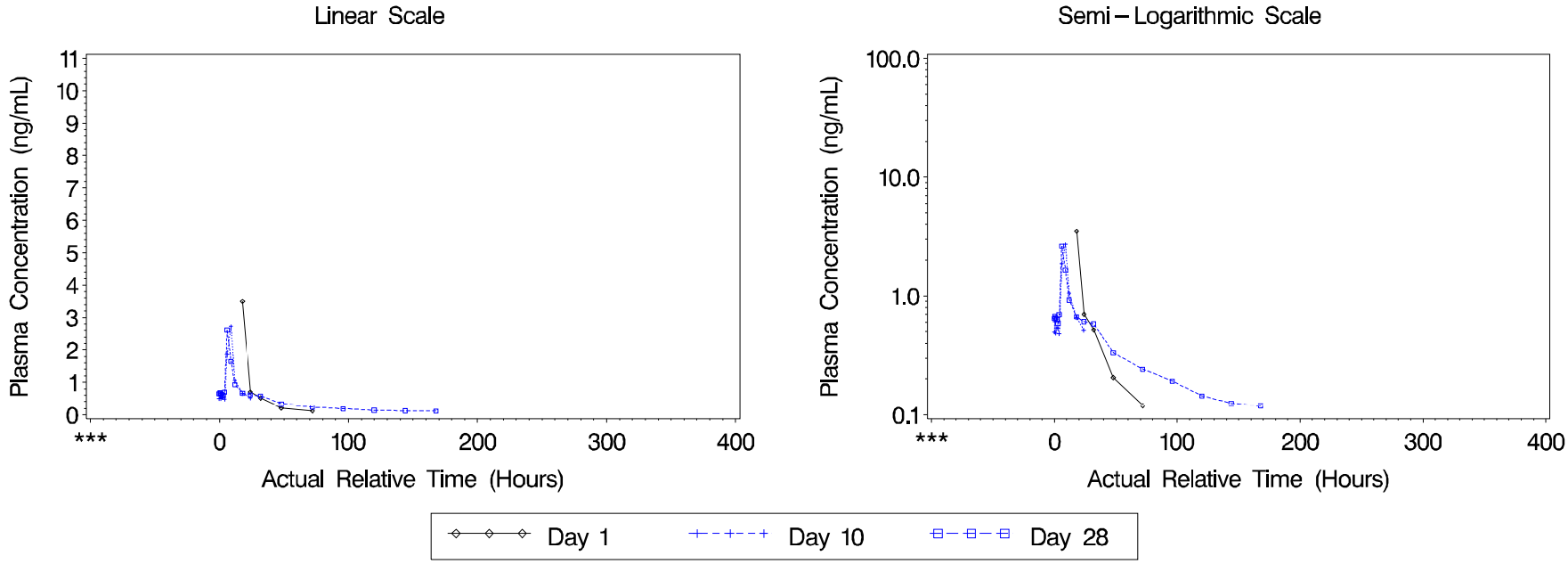
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.3
Individual Subject Plasma SB−554008 Concentration − Time Plot
Subject ID=[redacted]



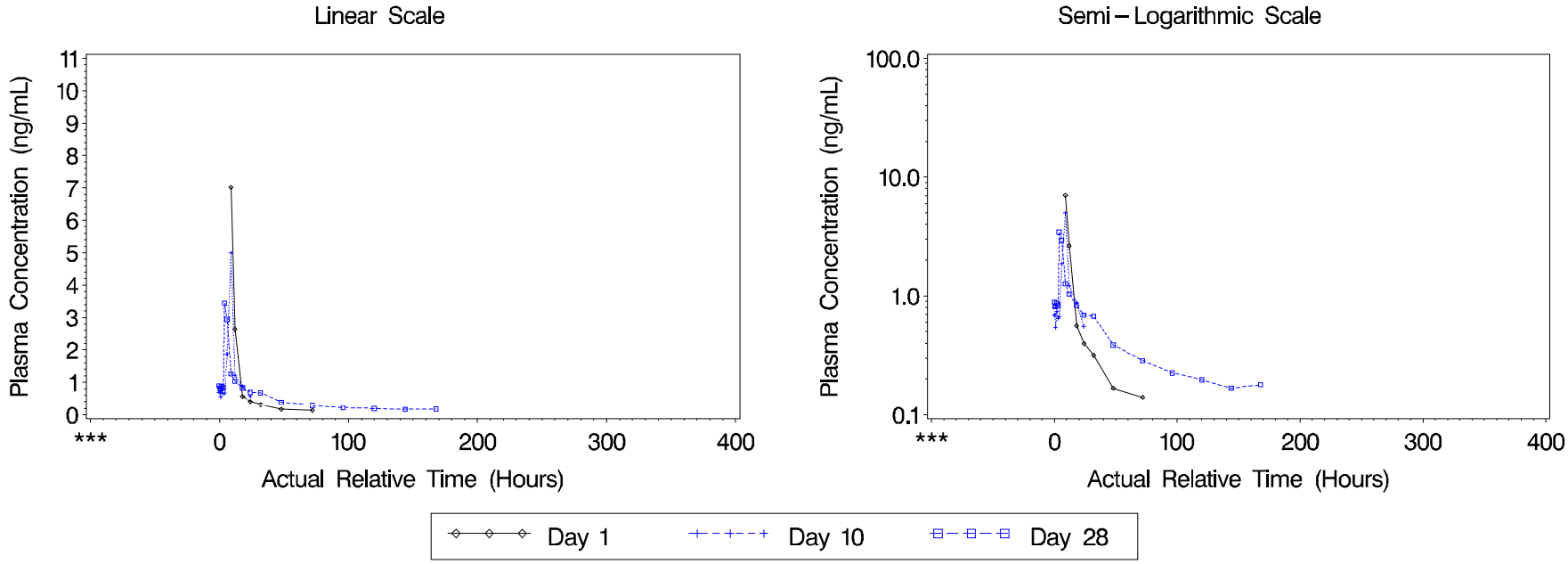
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



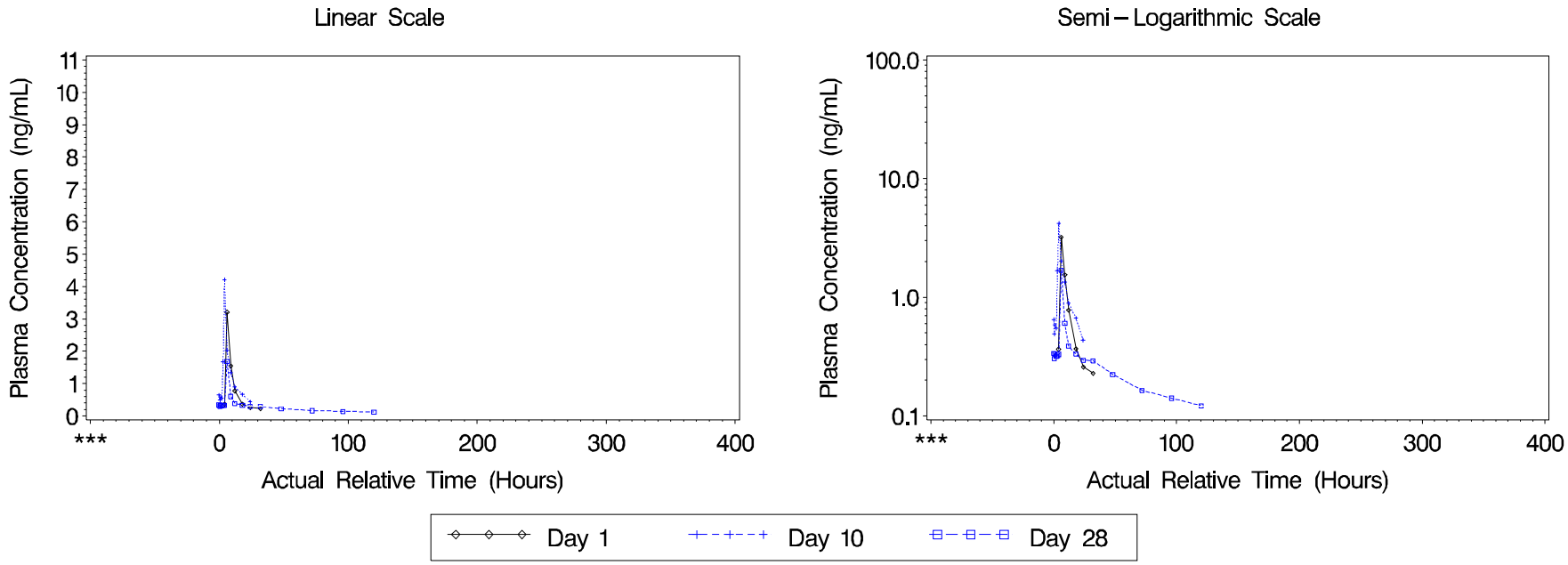
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



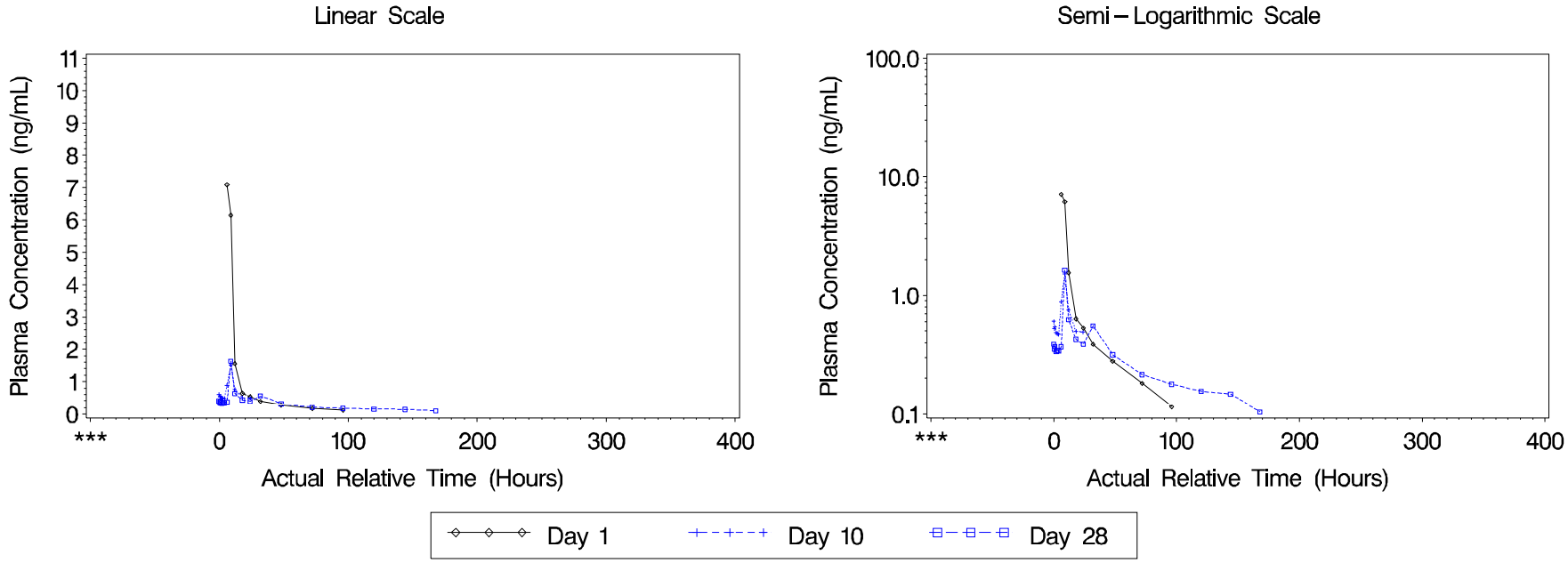
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



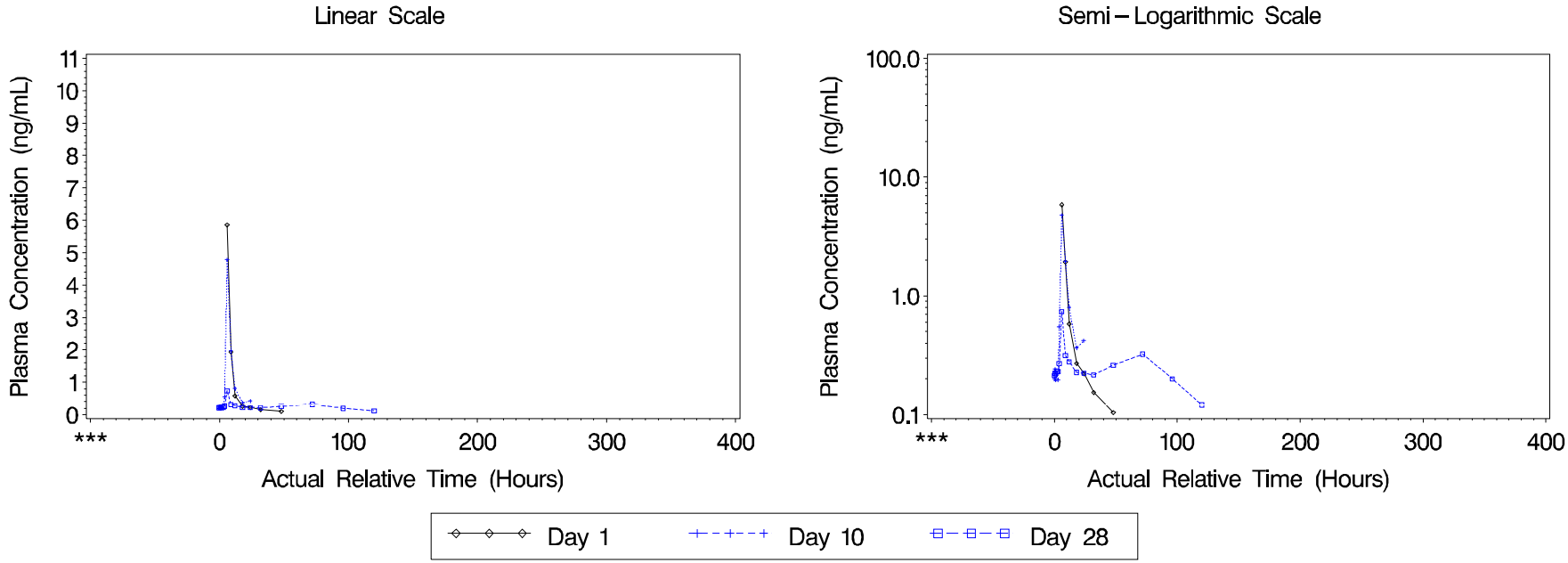
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



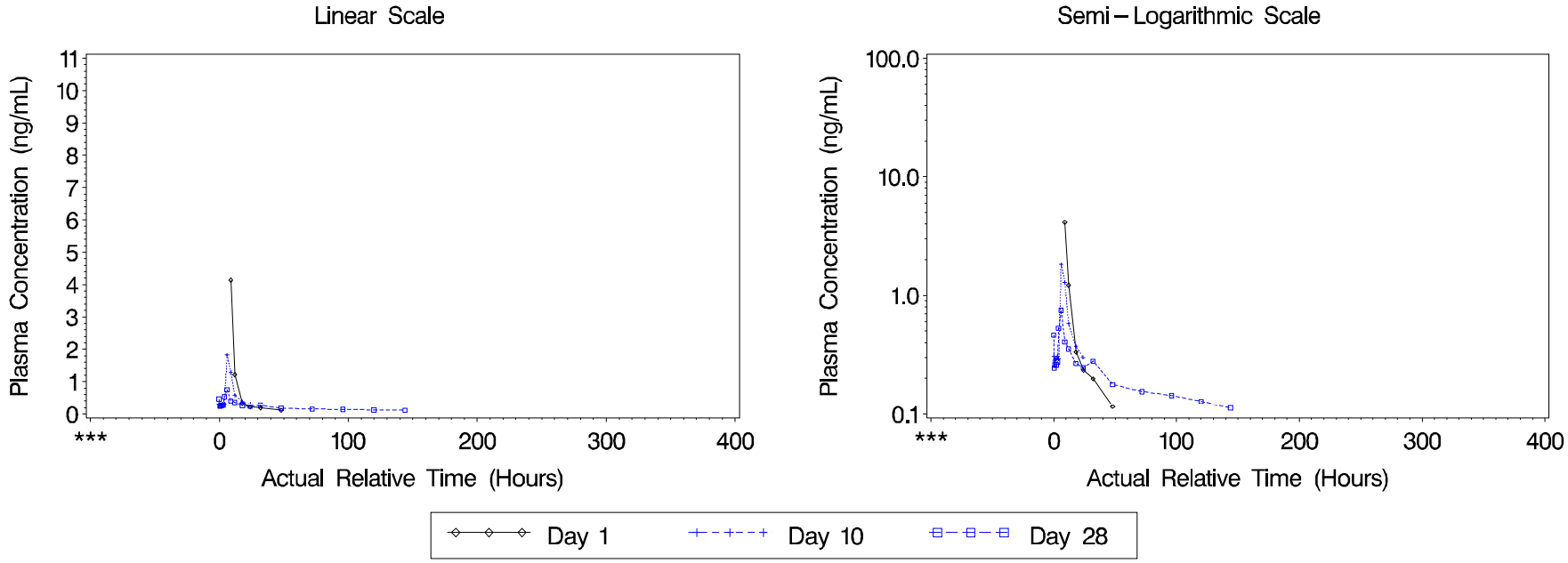
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



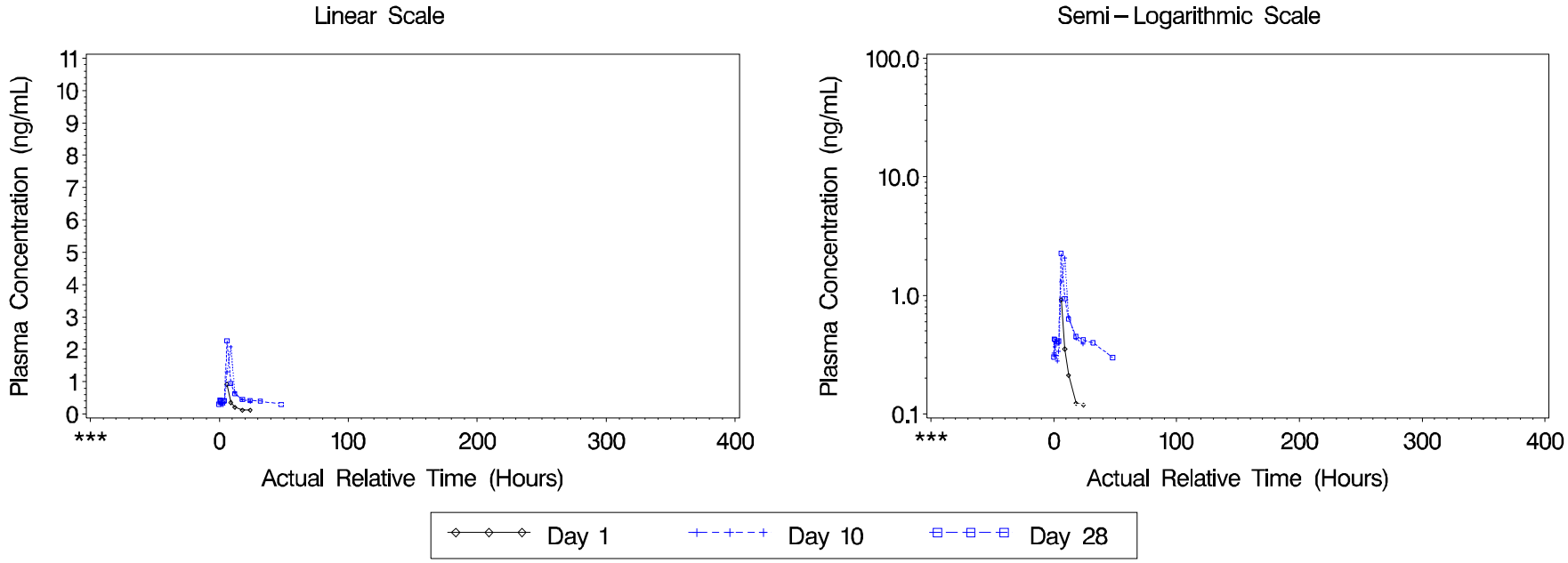
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



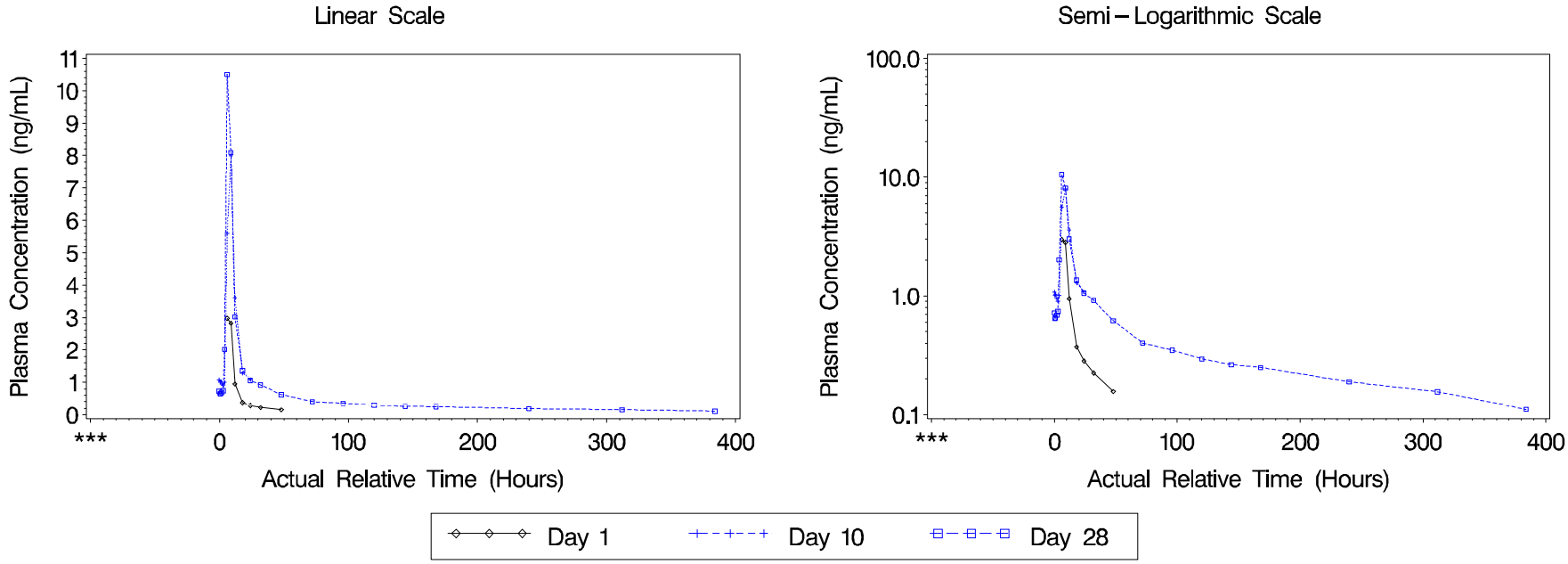
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



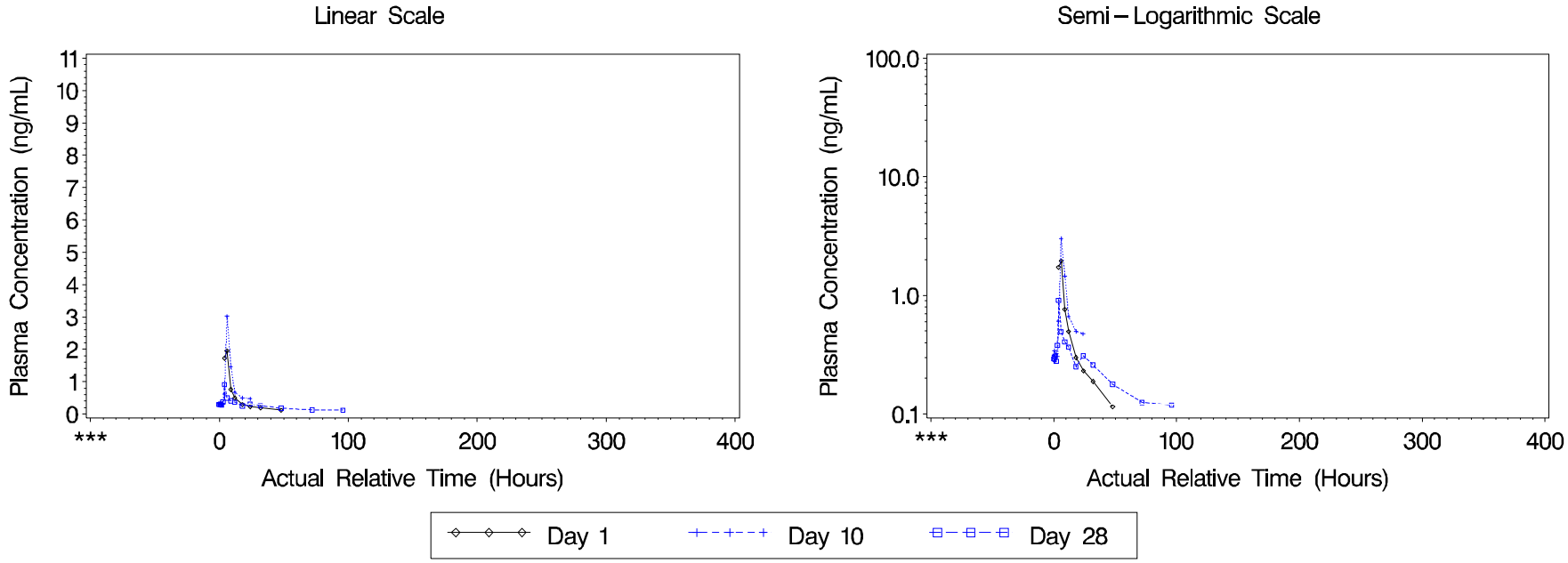
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



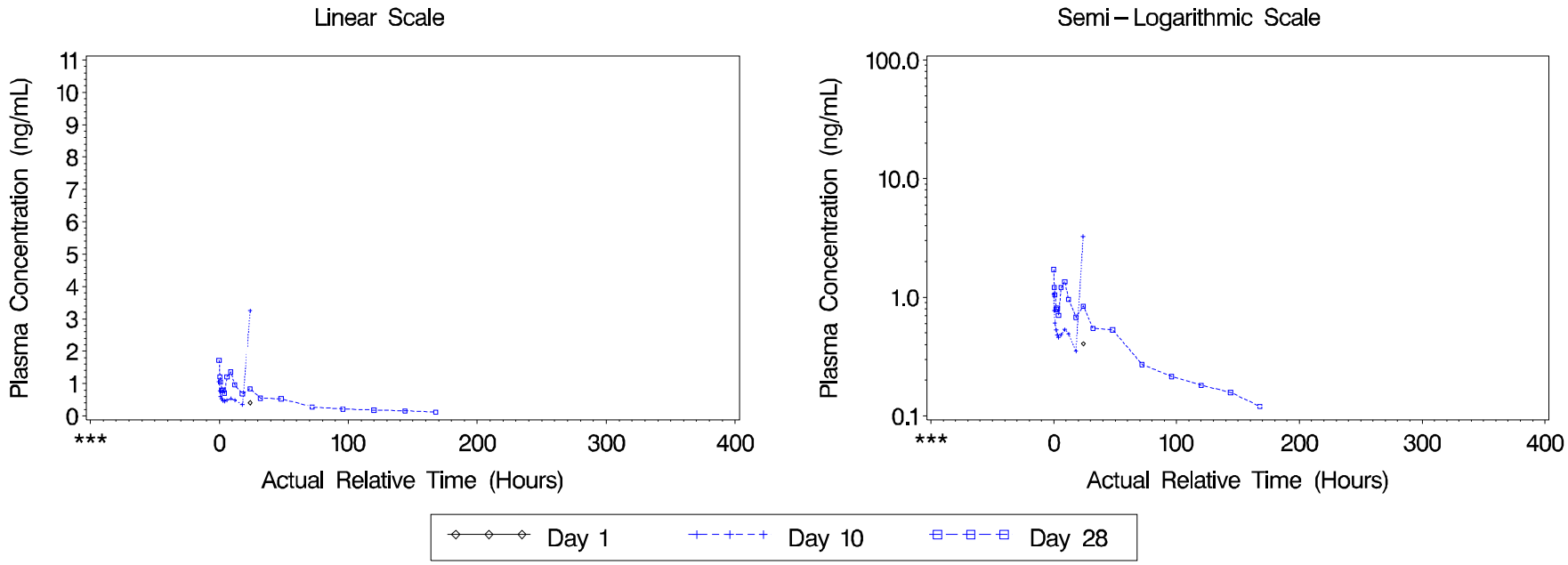
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



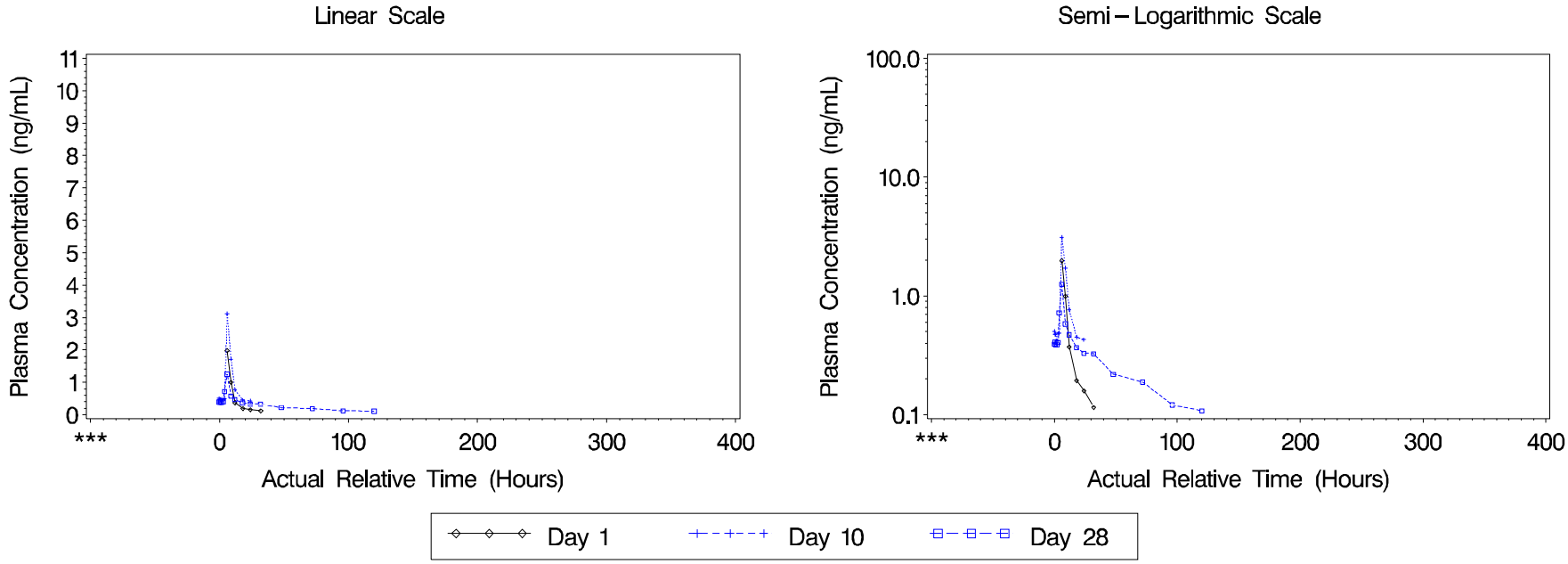
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



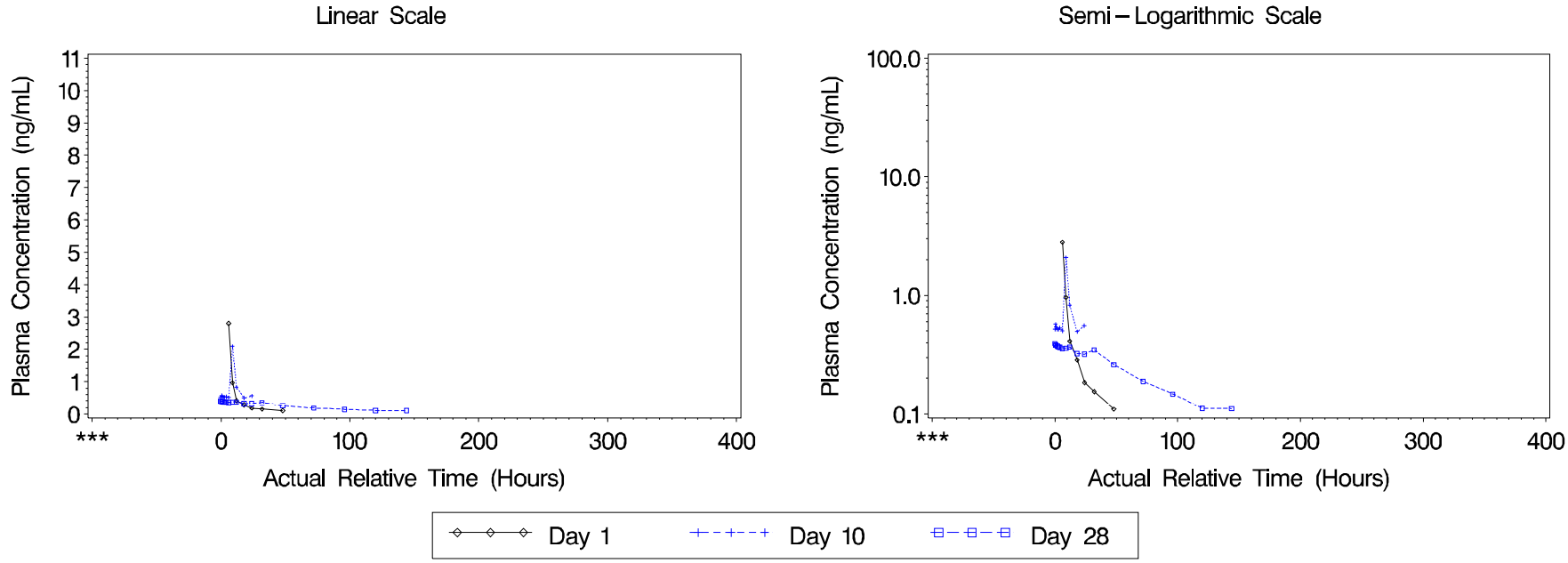
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



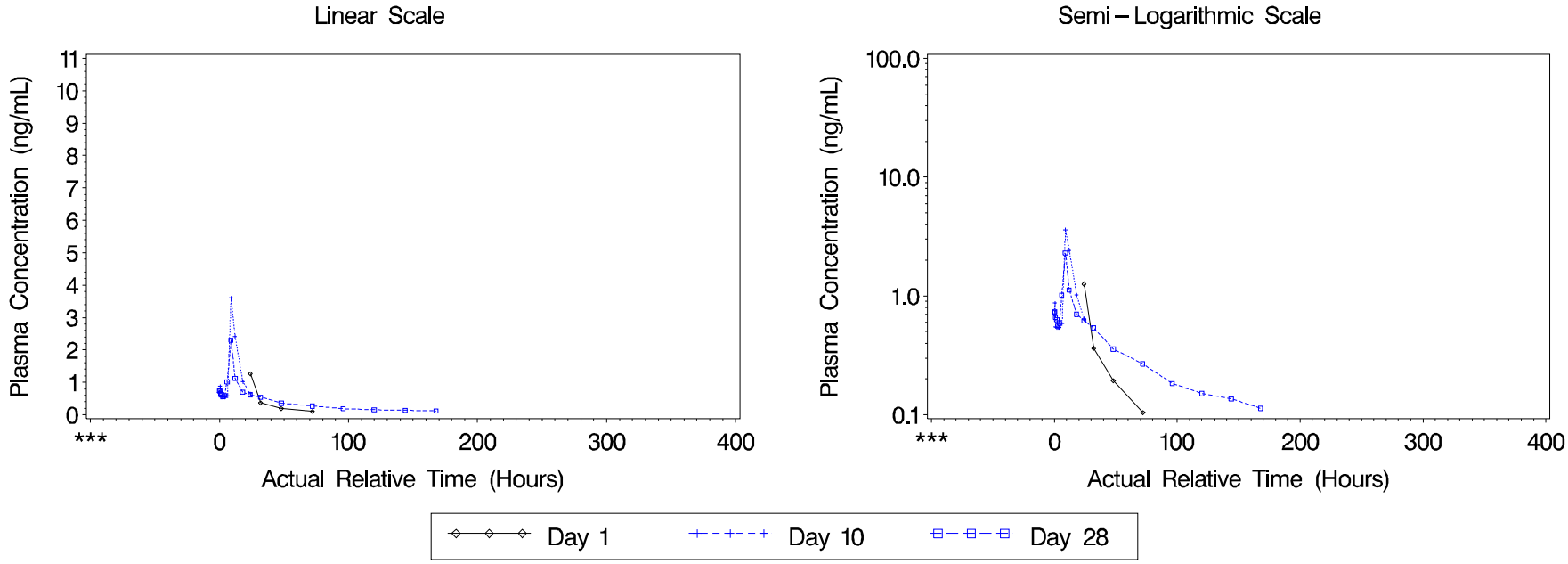
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



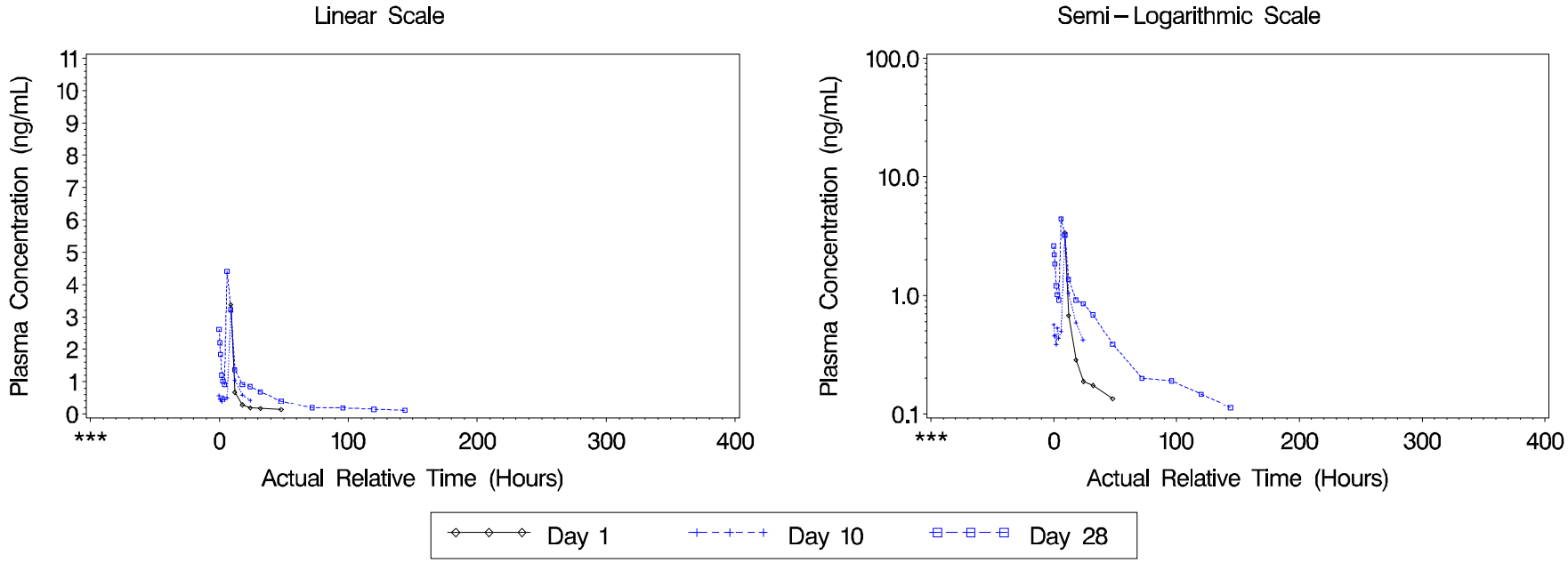
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



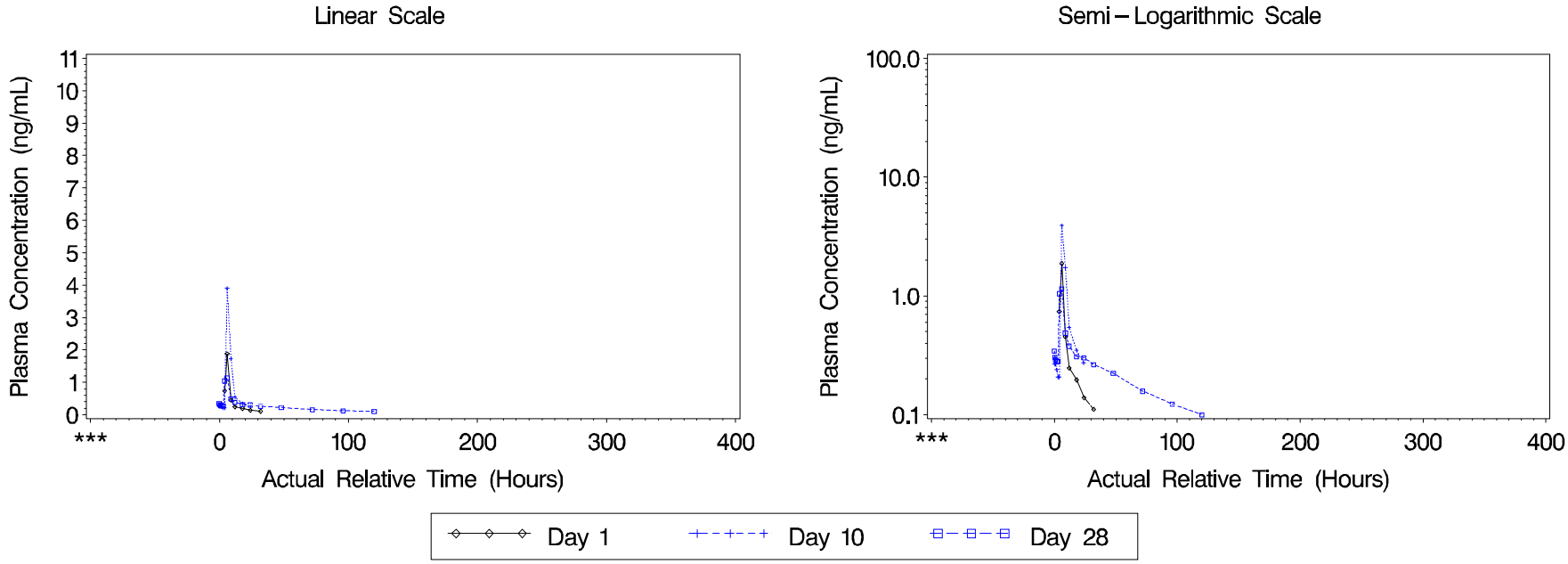
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



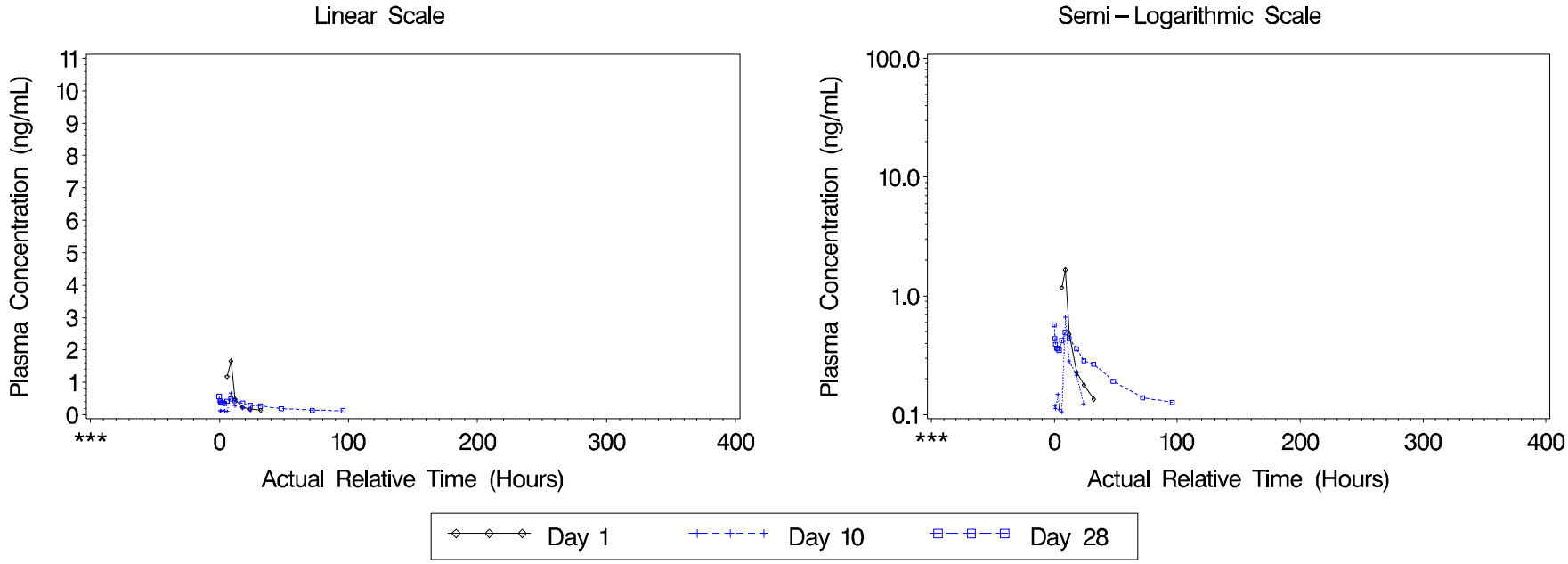
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



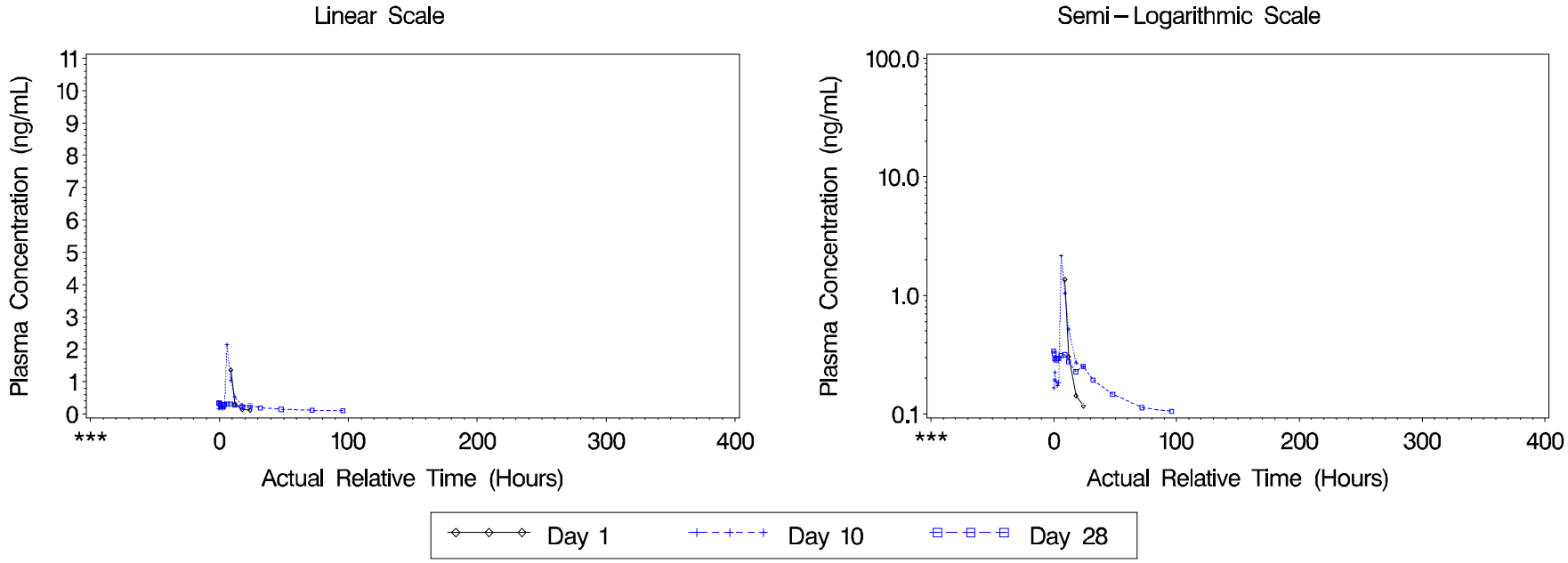
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



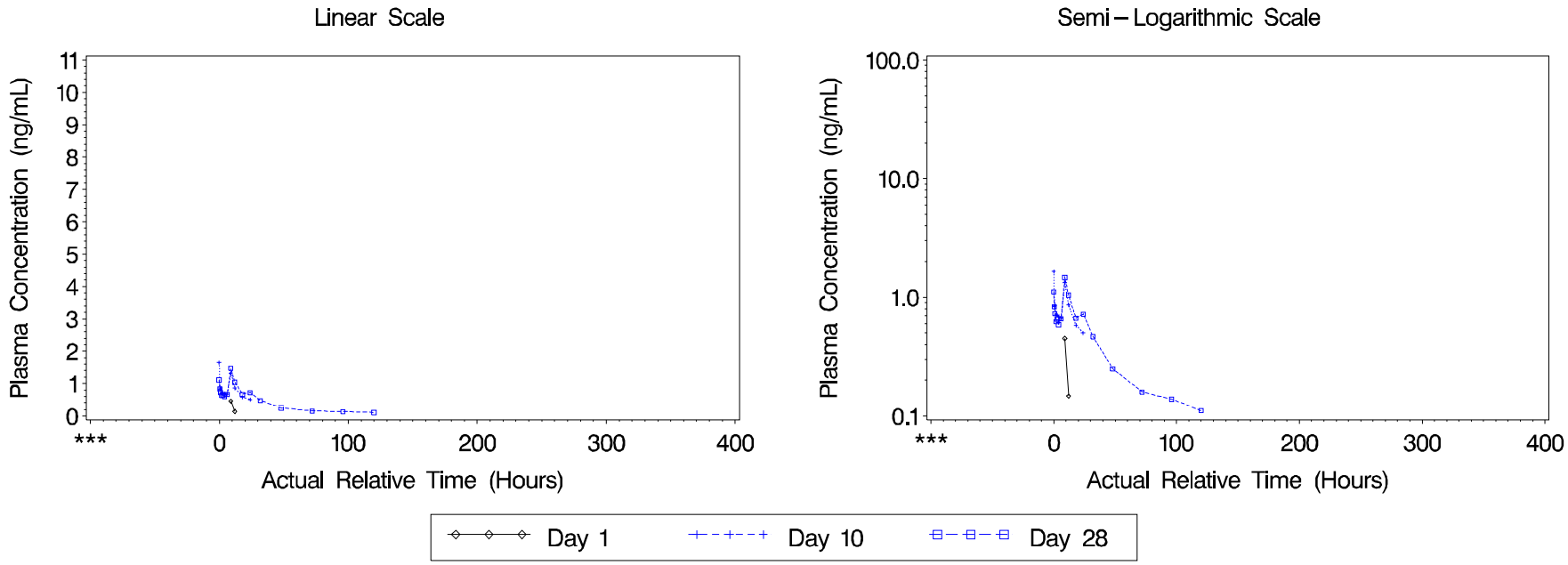
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



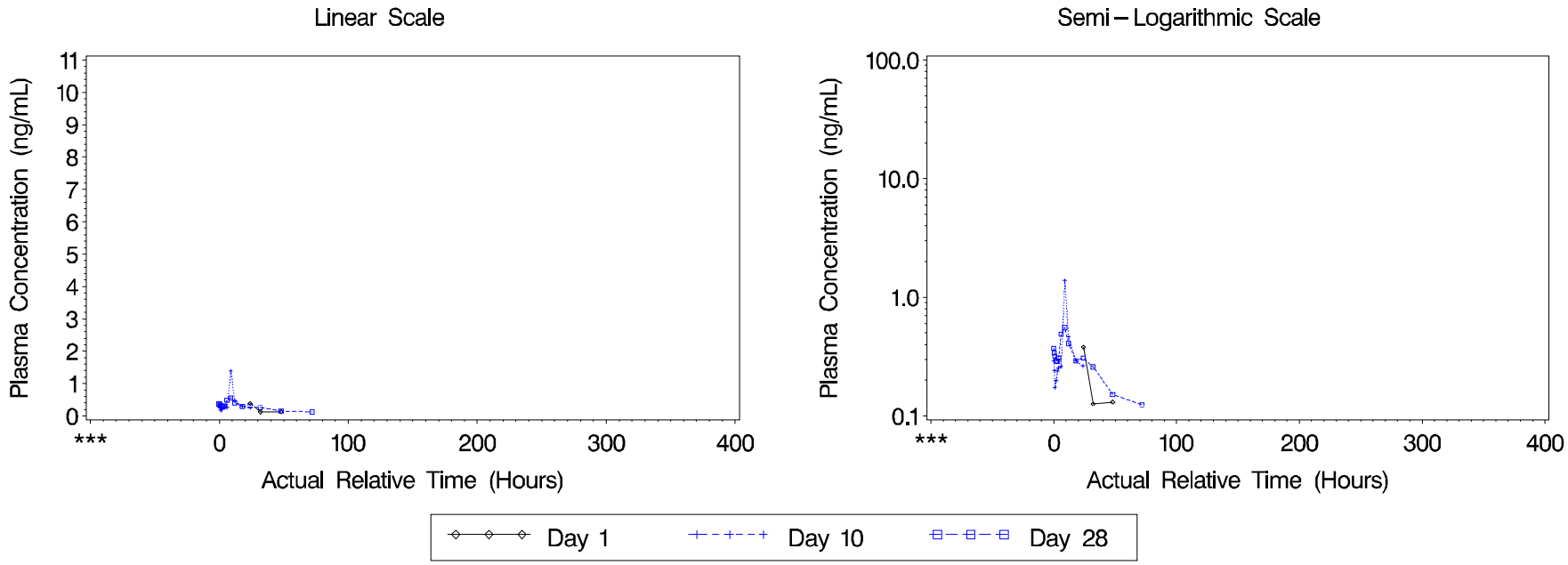
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



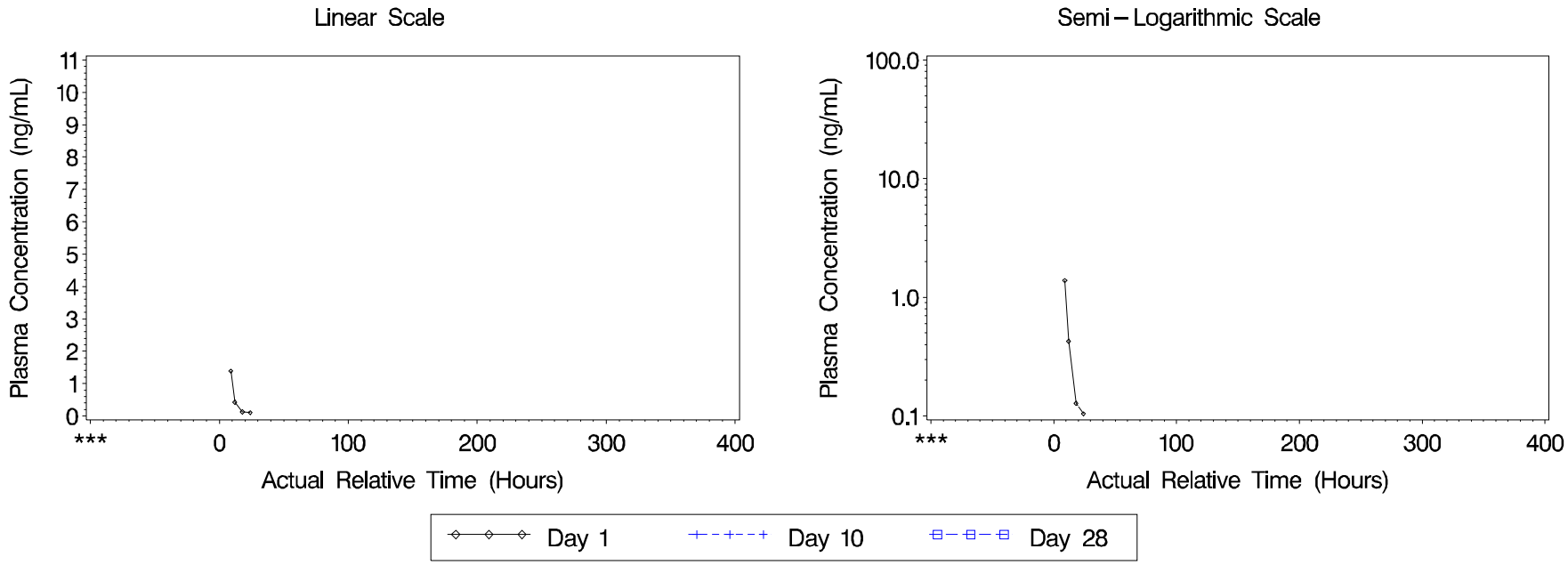
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



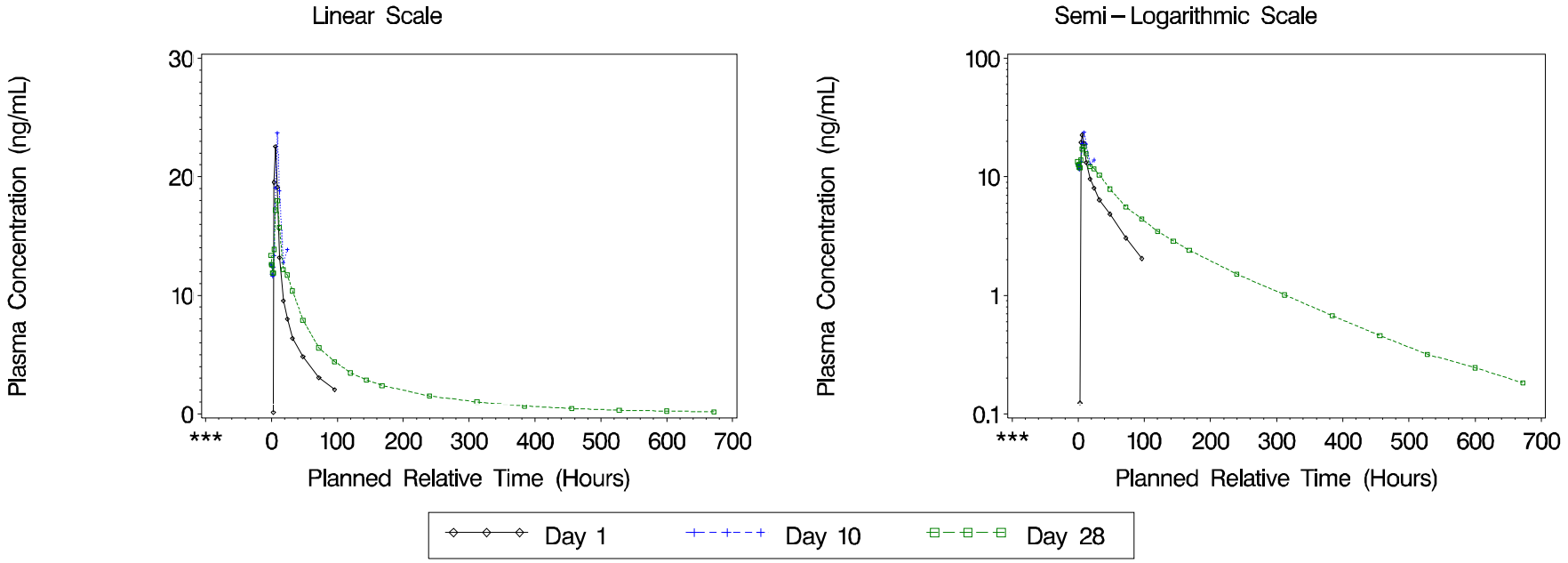
Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

Figure 11.4
Individual Subject Plasma SB−823094 Concentration − Time Plot
Subject ID=[redacted]



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28
[redacted]

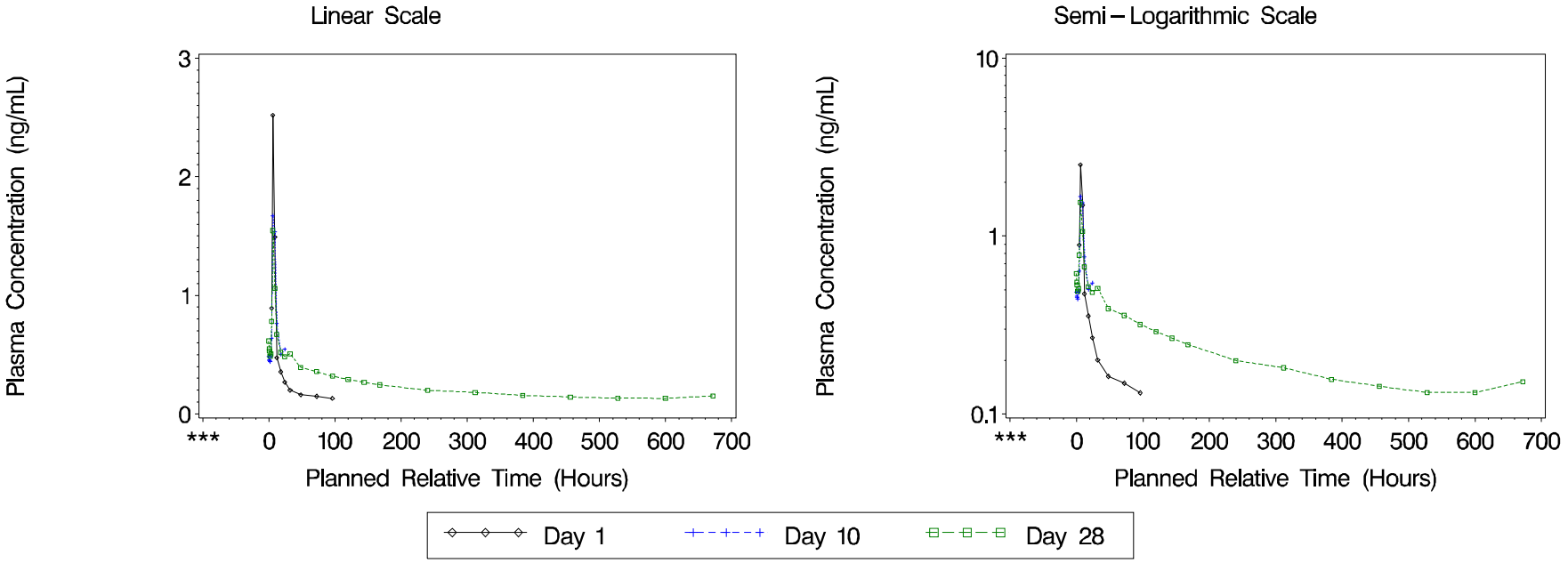
Figure 11.5
Mean Plasma SB−480848 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

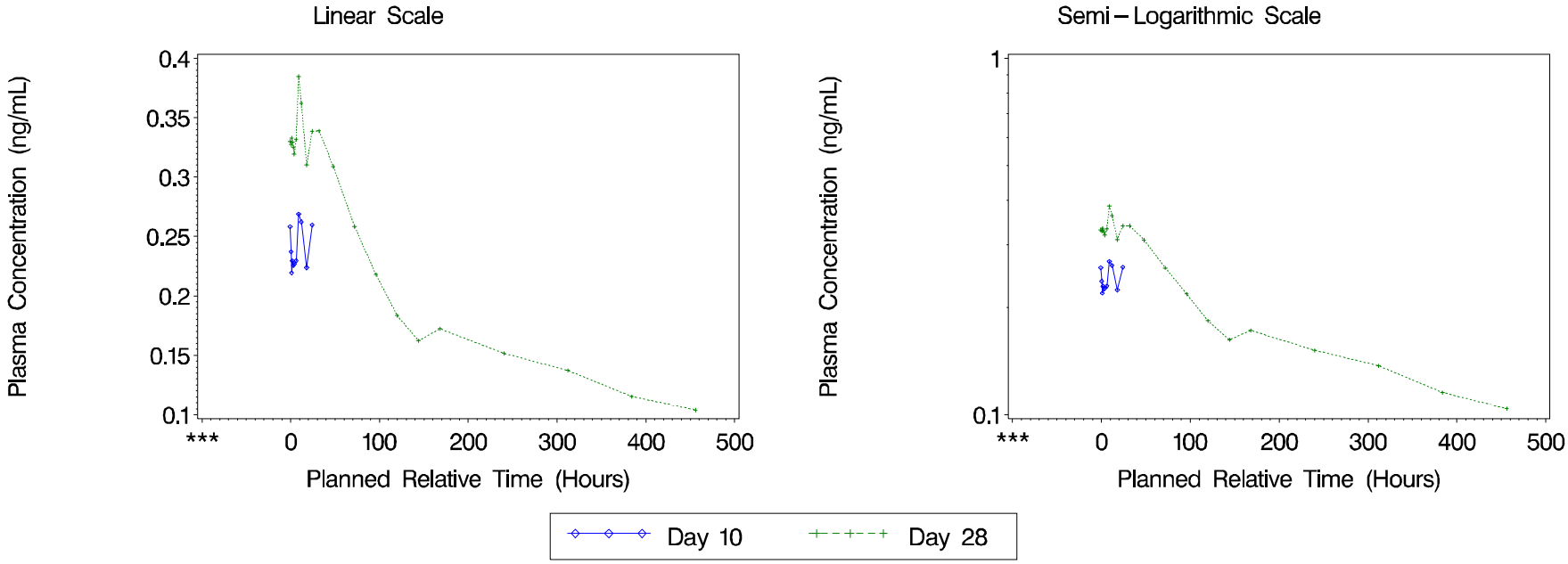
Figure 11.6
Mean Plasma SB−553253 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

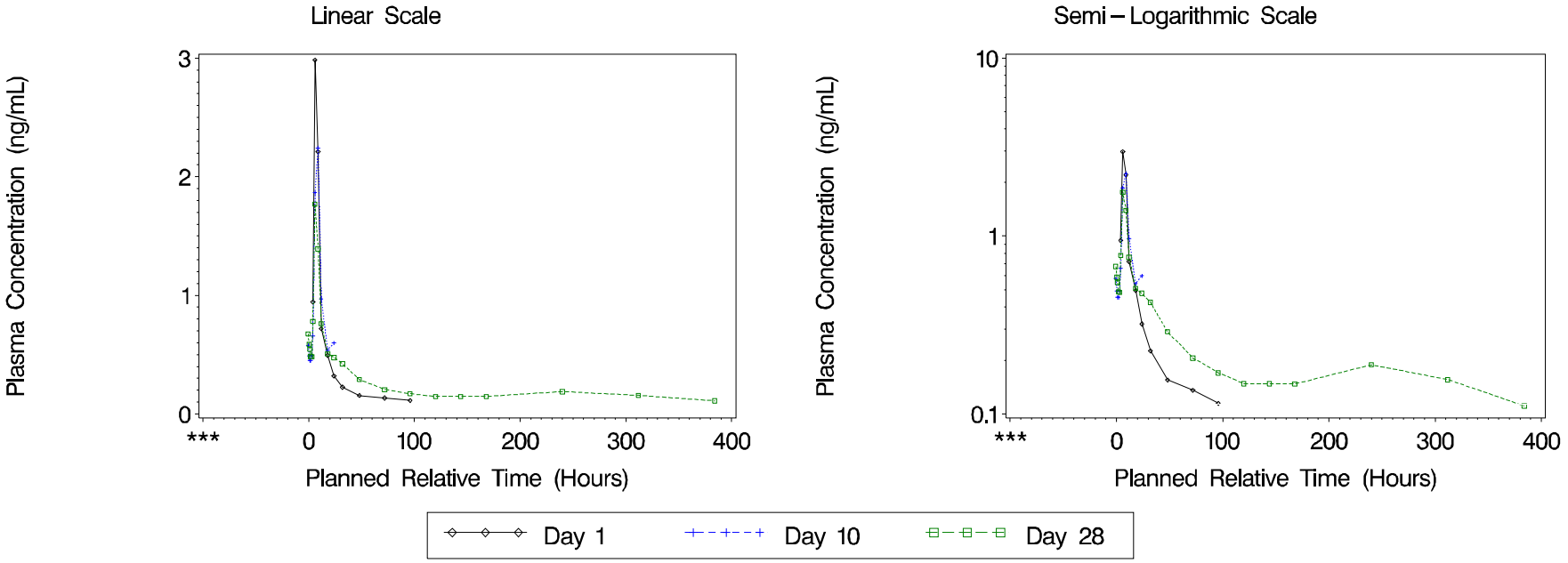
Figure 11.7
Mean Plasma SB−554008 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

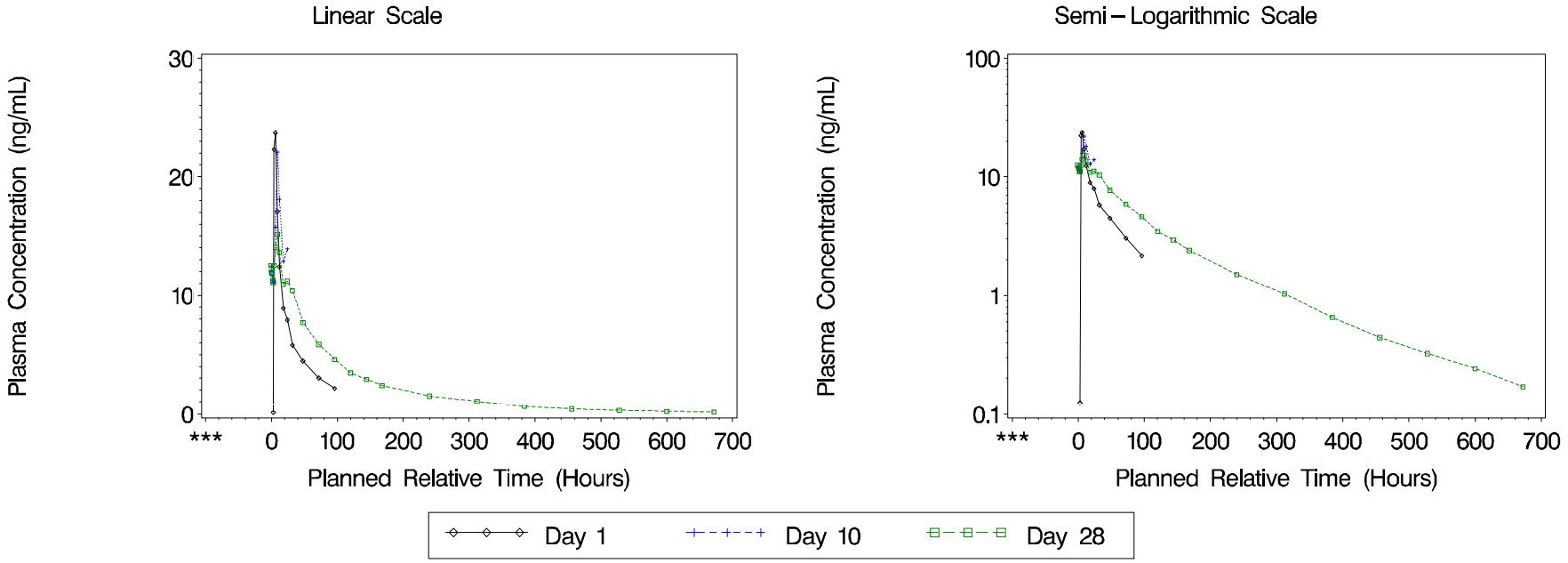
Figure 11.8
Mean Plasma SB−823094 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

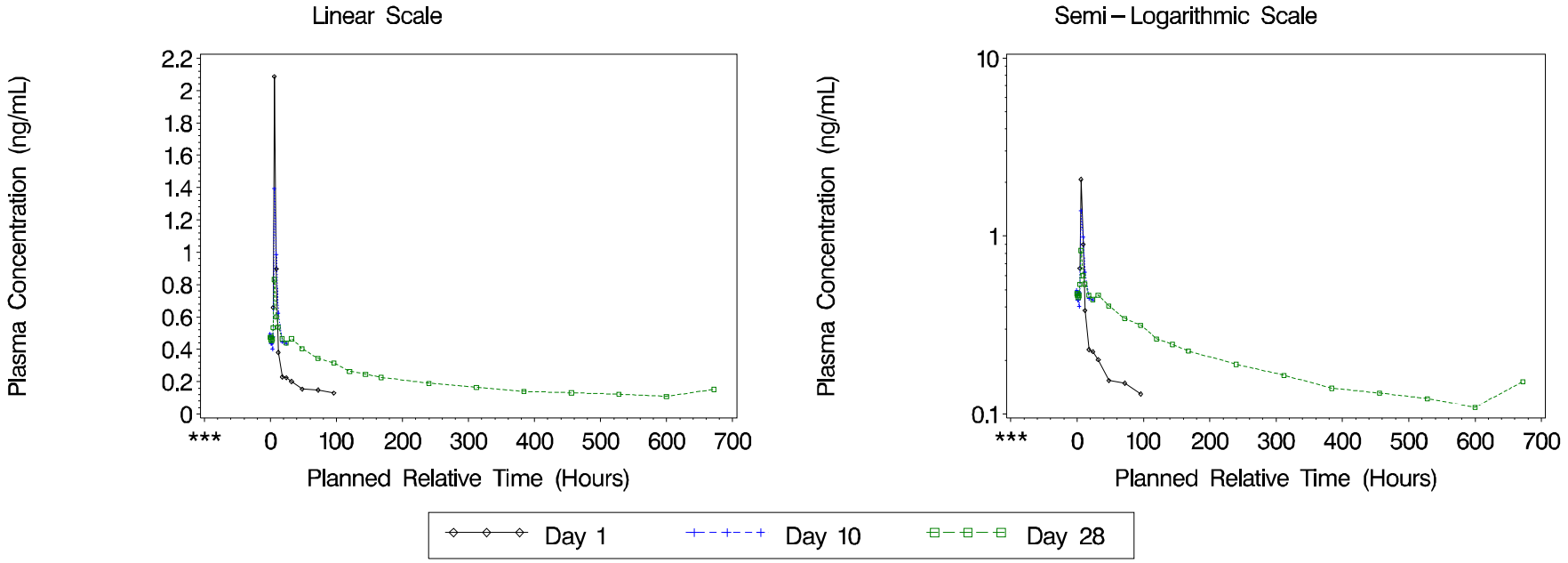
Figure 11.9
Median Plasma SB−480848 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

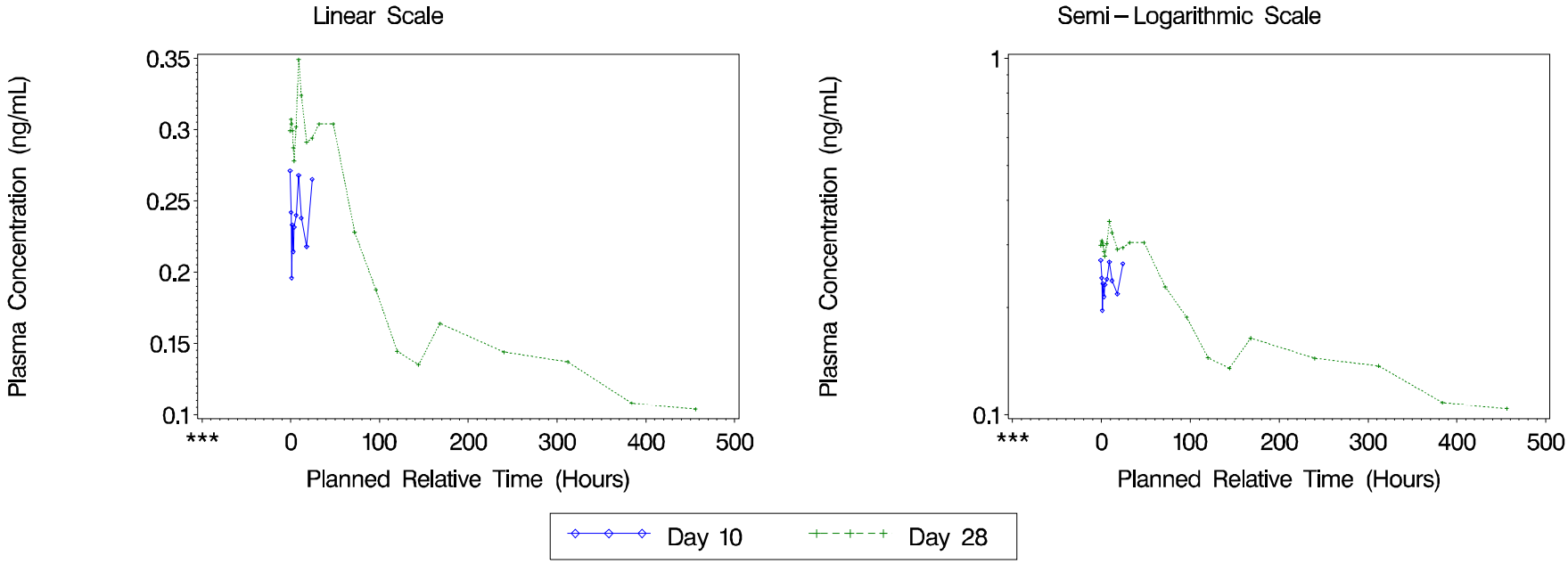
Figure 11.10
Median Plasma SB−553253 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

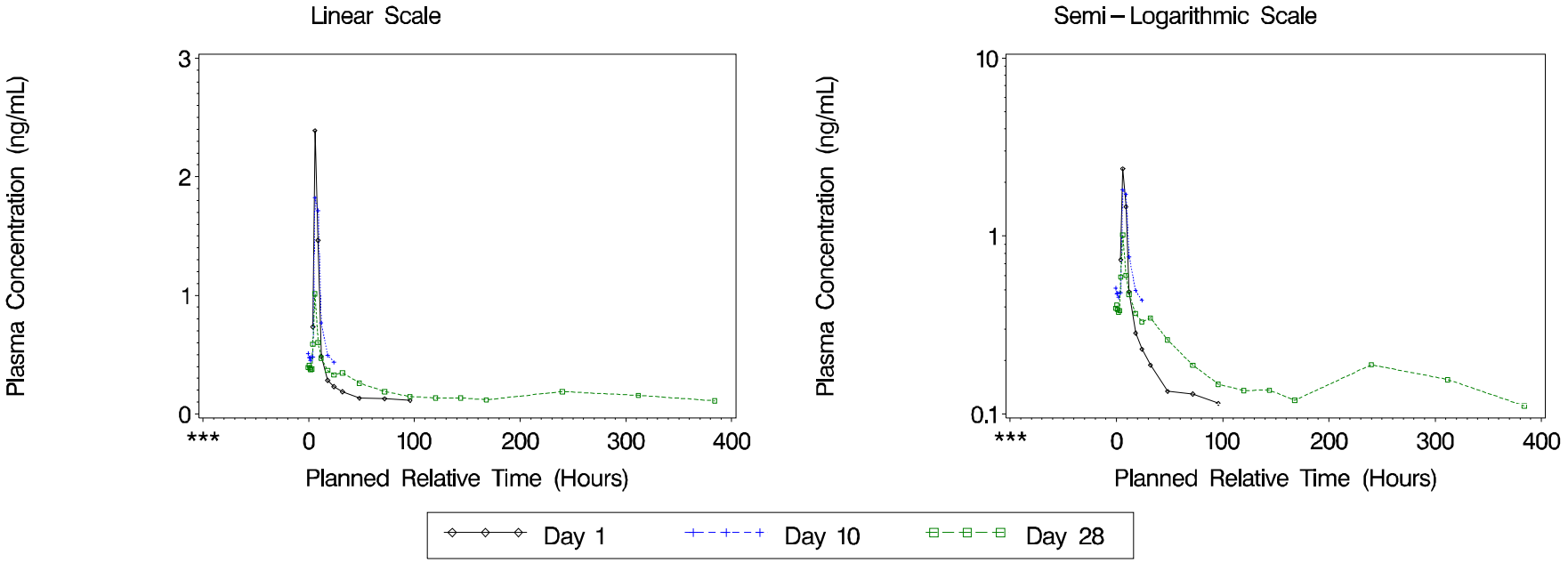
Figure 11.11
Median Plasma SB−554008 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

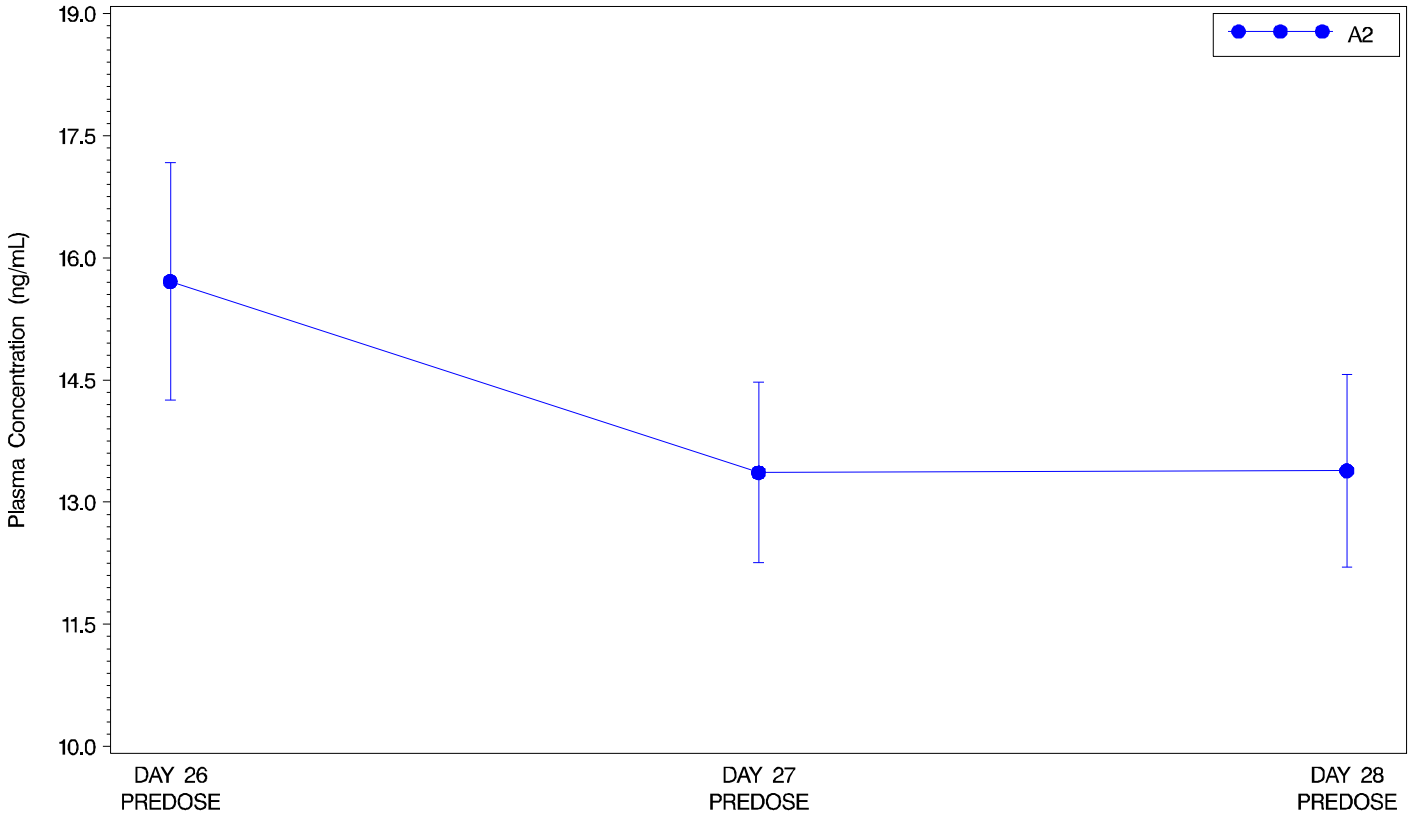
Figure 11.12
Median Plasma SB−823094 Concentration − Time Plot



Note:
Day 1: 160 mg of EC micronized free−base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 10
Day 28: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

Figure 11.13
Mean (+/− SE) Plasma SB−480848 Ctau Plot (Day 26, 27, 28)



Regimen Key:
A2: 160 mg of EC micronized free−base darapladib as repeat dose for 28 days

[redacted]

Table 11.1
Summary of Plasma SB-480848 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S1D1	20	PREDOSE	20	20	0.0000			0.0000	0.000	0.000
		0.5 H	20	20	0.0000			0.0000	0.000	0.000
		1 H	20	20	0.0000			0.0000	0.000	0.000
		2 H	20	20	0.0000			0.0000	0.000	0.000
		3 H	20	19	0.0062	(-0.0068, 0.0192)		0.0000	0.000	0.124
		4 H	20	17	2.9308	(-0.6123, 6.4739)		0.0000	0.000	25.369
		6 H	20	9	12.3944	(5.8860, 18.9028)		6.3755	0.000	40.344
		9 H	20	4	15.2990	(10.2216, 20.3764)	10.84888	14.5390	0.000	39.390
		12 H	20	4	10.5426	(7.1422, 13.9430)	7.26552	9.5110	0.000	25.437
		18 H	20	3	8.1155	(5.4462, 10.7848)	5.70345	7.5780	0.000	24.519
		24 H	20	0	7.9990	(6.6325, 9.3655)	2.91980	7.9345	3.155	13.071
		32 H	20	0	6.3846	(5.2830, 7.4861)	2.35366	5.7970	2.493	11.426
		48 H	20	0	4.8431	(3.9998, 5.6864)	1.80196	4.4750	1.856	7.783
		72 H	20	0	3.0481	(2.4874, 3.6088)	1.19795	3.0350	0.959	5.093
		96 H	20	0	2.0509	(1.6705, 2.4313)	0.81289	2.1595	0.728	3.342
S2D10	20	PREDOSE	19	0	12.6398	(10.4678, 14.8119)	4.50640	11.9860	5.351	23.686
		0.5 H	19	0	12.4846	(10.4860, 14.4833)	4.14668	12.4400	5.167	21.400
		1 H	19	0	11.7484	(10.0336, 13.4631)	3.55766	11.6590	5.745	19.604
		2 H	19	0	11.6106	(9.9152, 13.3061)	3.51770	11.3000	5.352	18.755
		3 H	19	0	12.3602	(9.4442, 15.2761)	6.04987	11.0790	5.652	33.511
		4 H	19	0	13.3271	(9.8830, 16.7712)	7.14566	11.0980	5.332	38.558
		6 H	19	0	19.0765	(14.6416, 23.5115)	9.20145	15.7280	4.825	41.389
		9 H	19	0	23.6910	(18.6392, 28.7428)	10.48132	22.0980	9.602	54.741
		12 H	19	0	18.8289	(14.8334, 22.8245)	8.28987	18.0700	9.040	44.652
		18 H	19	0	12.7806	(10.9433, 14.6180)	3.81199	12.8400	6.420	21.355
		24 H	19	0	13.8557	(11.4182, 16.2932)	5.05721	13.9150	6.298	26.244
S2D26	20	PREDOSE	19	0	15.7090	(12.6501, 18.7679)	6.34638	13.6820	8.321	35.645

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 11.1
Summary of Plasma SB-480848 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S2D27	20	PREDOSE	19	0	13.3635	(11.0355, 15.6915)	4.83007	12.2630	7.831	29.827
S2D28	20	PREDOSE	19	0	13.3859	(10.8972, 15.8747)	5.16359	12.5290	6.381	27.885
		0.5 H	19	0	12.6160	(10.4917, 14.7403)	4.40732	11.9650	6.424	25.603
		1 H	19	0	12.5755	(10.6214, 14.5296)	4.05428	11.8740	6.377	22.933
		2 H	19	0	11.8974	(10.1933, 13.6015)	3.53557	11.2420	6.543	20.290
		3 H	19	0	11.9050	(10.1790, 13.6310)	3.58096	11.1020	6.492	18.286
		4 H	19	0	13.8806	(10.4760, 17.2852)	7.06372	12.5090	6.218	33.824
		6 H	19	0	17.1866	(12.4462, 21.9269)	9.83509	14.0720	6.891	47.055
		9 H	19	0	17.9772	(13.8970, 22.0574)	8.46535	15.1600	6.457	40.537
		12 H	19	0	15.7437	(12.0778, 19.4096)	7.60582	13.6030	6.161	40.195
		18 H	19	0	12.1781	(9.9897, 14.3665)	4.54046	10.9320	5.222	24.429
		24 H	19	0	11.7142	(9.8482, 13.5802)	3.87149	11.1940	5.289	20.817
		32 H	19	0	10.3715	(8.9427, 11.8002)	2.96433	10.4020	4.903	16.310
		48 H	19	0	7.8948	(6.7497, 9.0400)	2.37594	7.7110	3.431	13.760
		72 H	18	0	5.5701	(4.8653, 6.2748)	1.41713	5.8670	2.666	8.831
		96 H	18	0	4.4052	(3.7789, 5.0314)	1.25930	4.6015	2.172	7.319
		120 H	18	0	3.4725	(2.8932, 4.0518)	1.16499	3.4710	1.524	6.126
		144 H	18	0	2.8768	(2.3988, 3.3548)	0.96121	2.9285	1.310	4.794
		168 H	18	0	2.3976	(1.9865, 2.8086)	0.82656	2.3940	1.130	4.512
		240 H	18	0	1.5093	(1.2083, 1.8104)	0.60544	1.4930	0.609	3.155
		312 H	18	0	1.0111	(0.7803, 1.2418)	0.46409	1.0325	0.392	2.323
		384 H	18	0	0.6739	(0.5102, 0.8377)	0.32926	0.6540	0.212	1.630
		456 H	18	0	0.4574	(0.3333, 0.5814)	0.24943	0.4415	0.141	1.164
		528 H	18	1	0.2997	(0.2147, 0.3847)	0.17096	0.3000	0.000	0.745
		600 H	17	2	0.2167	(0.1465, 0.2870)	0.13664	0.2370	0.000	0.569
		672 H	18	3	0.1522	(0.1010, 0.2033)	0.10282	0.1330	0.000	0.393

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days
[redacted]

Table 11.2
Summary of Plasma SB-553253 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S1D1	20	PREDOSE	20	20	0.0000			0.0000	0.000	0.000
		0.5 H	20	20	0.0000			0.0000	0.000	0.000
		1 H	20	20	0.0000			0.0000	0.000	0.000
		2 H	20	20	0.0000			0.0000	0.000	0.000
		3 H	20	20	0.0000			0.0000	0.000	0.000
		4 H	20	17	0.1338	(-0.0530, 0.3206)		0.0000	0.000	1.686
		6 H	20	10	1.2589	(0.4530, 2.0647)		0.4490	0.000	6.142
		9 H	20	4	1.1931	(0.5256, 1.8606)	1.42620	0.6770	0.000	5.485
		12 H	20	4	0.3796	(0.2071, 0.5520)	0.36851	0.3270	0.000	1.608
		18 H	20	4	0.2846	(0.0771, 0.4921)	0.44326	0.1885	0.000	2.090
		24 H	20	2	0.2409	(0.1501, 0.3317)	0.19409	0.2115	0.000	0.878
		32 H	20	3	0.1707	(0.1175, 0.2238)	0.11358	0.1525	0.000	0.445
		48 H	20	7	0.1058	(0.0634, 0.1482)		0.1135	0.000	0.254
		72 H	20	12	0.0597	(0.0236, 0.0958)		0.0000	0.000	0.195
		96 H	20	14	0.0395	(0.0101, 0.0689)		0.0000	0.000	0.162
S2D10	20	PREDOSE	19	0	0.4844	(0.3833, 0.5855)	0.20976	0.4960	0.175	0.871
		0.5 H	19	0	0.4582	(0.3586, 0.5578)	0.20665	0.4800	0.159	0.829
		1 H	19	0	0.4526	(0.3591, 0.5460)	0.19387	0.4350	0.159	0.799
		2 H	19	0	0.4419	(0.3446, 0.5392)	0.20184	0.4350	0.159	0.865
		3 H	19	0	0.4852	(0.3348, 0.6355)	0.31200	0.4020	0.164	1.575
		4 H	19	0	0.6364	(0.2741, 0.9987)	0.75167	0.4800	0.162	3.645
		6 H	19	0	1.6707	(0.9986, 2.3428)	1.39444	1.3920	0.185	5.049
		9 H	19	0	1.5372	(0.9079, 2.1664)	1.30547	0.9870	0.403	5.673
		12 H	19	0	0.7651	(0.5447, 0.9854)	0.45717	0.6240	0.253	2.047
		18 H	19	0	0.5031	(0.3890, 0.6172)	0.23668	0.4450	0.196	1.001
		24 H	19	0	0.5456	(0.3418, 0.7495)	0.42289	0.4370	0.216	2.131
S2D26	20	PREDOSE	19	0	0.8199	(0.4128, 1.2270)	0.84456	0.5180	0.279	3.234

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 11.2
Summary of Plasma SB-553253 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S2D27	20	PREDOSE	19	0	0.5931	(0.4177, 0.7685)	0.36398	0.5070	0.269	1.926
S2D28	20	PREDOSE	19	0	0.6151	(0.4407, 0.7895)	0.36192	0.4740	0.229	1.641
		0.5 H	19	0	0.5504	(0.4287, 0.6721)	0.25247	0.4620	0.221	1.145
		1 H	19	0	0.5327	(0.4301, 0.6352)	0.21279	0.4750	0.240	1.046
		2 H	19	0	0.4897	(0.4013, 0.5782)	0.18353	0.4540	0.242	1.009
		3 H	19	0	0.5067	(0.4082, 0.6052)	0.20434	0.4640	0.265	1.119
		4 H	19	0	0.7821	(0.4114, 1.1527)	0.76896	0.5350	0.271	3.512
		6 H	19	0	1.5474	(0.5039, 2.5910)	2.16514	0.8310	0.369	9.768
		9 H	19	0	1.0608	(0.4758, 1.6459)	1.21392	0.6000	0.323	5.722
		12 H	19	0	0.6719	(0.4818, 0.8621)	0.39450	0.5380	0.282	1.972
		18 H	19	0	0.5191	(0.4064, 0.6317)	0.23378	0.4660	0.230	1.144
		24 H	19	0	0.4838	(0.3890, 0.5787)	0.19670	0.4400	0.223	0.899
		32 H	19	0	0.5085	(0.4207, 0.5962)	0.18211	0.4660	0.259	0.878
		48 H	19	0	0.3917	(0.3425, 0.4408)	0.10198	0.4040	0.240	0.580
		72 H	18	0	0.3583	(0.3160, 0.4005)	0.08493	0.3435	0.207	0.525
		96 H	18	0	0.3189	(0.2768, 0.3610)	0.08472	0.3155	0.198	0.505
		120 H	18	0	0.2902	(0.2450, 0.3354)	0.09085	0.2640	0.171	0.476
		144 H	18	0	0.2669	(0.2203, 0.3136)	0.09383	0.2460	0.137	0.488
		168 H	18	0	0.2455	(0.2025, 0.2885)	0.08646	0.2260	0.129	0.457
		240 H	18	0	0.1995	(0.1647, 0.2343)	0.06991	0.1900	0.110	0.397
		312 H	18	3	0.1515	(0.1068, 0.1962)	0.08997	0.1575	0.000	0.330
		384 H	18	4	0.1218	(0.0832, 0.1605)	0.07778	0.1365	0.000	0.268
		456 H	18	6	0.0954	(0.0571, 0.1337)		0.1160	0.000	0.255
		528 H	18	11	0.0513	(0.0169, 0.0858)		0.0000	0.000	0.207
		600 H	18	13	0.0366	(0.0050, 0.0683)		0.0000	0.000	0.193
		672 H	18	16	0.0169	(-0.0078, 0.0416)		0.0000	0.000	0.172

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 11.3
Summary of Plasma SB-554008 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S1D1	20	PREDOSE	20	20	0.0000			0.0000	0.000	0.000
		0.5 H	20	20	0.0000			0.0000	0.000	0.000
		1 H	20	20	0.0000			0.0000	0.000	0.000
		2 H	20	20	0.0000			0.0000	0.000	0.000
		3 H	20	20	0.0000			0.0000	0.000	0.000
		4 H	20	20	0.0000			0.0000	0.000	0.000
		6 H	20	20	0.0000			0.0000	0.000	0.000
		9 H	20	20	0.0000			0.0000	0.000	0.000
		12 H	20	20	0.0000			0.0000	0.000	0.000
		18 H	20	20	0.0000			0.0000	0.000	0.000
		24 H	20	20	0.0000			0.0000	0.000	0.000
		32 H	20	20	0.0000			0.0000	0.000	0.000
		48 H	20	20	0.0000			0.0000	0.000	0.000
		72 H	20	20	0.0000			0.0000	0.000	0.000
		96 H	20	20	0.0000			0.0000	0.000	0.000
S2D10	20	PREDOSE	19	2	0.2312	(0.1722, 0.2903)	0.12251	0.2370	0.000	0.406
		0.5 H	18	1	0.2239	(0.1778, 0.2701)	0.09281	0.2320	0.000	0.346
		1 H	19	0	0.2195	(0.1792, 0.2599)	0.08367	0.1960	0.102	0.351
		2 H	18	1	0.2166	(0.1693, 0.2640)	0.09520	0.2245	0.000	0.411
		3 H	19	1	0.2138	(0.1672, 0.2605)	0.09685	0.2020	0.000	0.373
		4 H	19	1	0.2148	(0.1700, 0.2596)	0.09289	0.2040	0.000	0.356
		6 H	18	1	0.2169	(0.1717, 0.2622)	0.09107	0.2270	0.000	0.362
		9 H	19	0	0.2689	(0.2168, 0.3209)	0.10799	0.2680	0.113	0.511
		12 H	19	0	0.2624	(0.2069, 0.3179)	0.11510	0.2380	0.106	0.450
		18 H	17	0	0.2239	(0.1820, 0.2658)	0.08152	0.2180	0.117	0.382
		24 H	19	0	0.2596	(0.2151, 0.3041)	0.09232	0.2650	0.124	0.411
S2D26	20	PREDOSE	19	0	0.3367	(0.2737, 0.3997)	0.13073	0.3080	0.211	0.783

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 11.3
Summary of Plasma SB-554008 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S2D27	20	PREDOSE	19	0	0.3258	(0.2711, 0.3806)	0.11361	0.2960	0.208	0.711
S2D28	20	PREDOSE	19	0	0.3301	(0.2729, 0.3873)	0.11874	0.2990	0.183	0.651
		0.5 H	19	0	0.3274	(0.2730, 0.3818)	0.11289	0.3070	0.183	0.641
		1 H	19	0	0.3330	(0.2786, 0.3874)	0.11284	0.3040	0.202	0.672
		2 H	19	0	0.3295	(0.2735, 0.3854)	0.11612	0.2990	0.195	0.649
		3 H	19	0	0.3249	(0.2714, 0.3785)	0.11110	0.2870	0.184	0.589
		4 H	19	0	0.3191	(0.2686, 0.3697)	0.10487	0.2780	0.207	0.591
		6 H	19	0	0.3317	(0.2764, 0.3871)	0.11485	0.3020	0.197	0.592
		9 H	19	0	0.3848	(0.3072, 0.4625)	0.16103	0.3490	0.223	0.810
		12 H	19	0	0.3620	(0.2919, 0.4321)	0.14552	0.3240	0.199	0.727
		18 H	19	0	0.3100	(0.2531, 0.3669)	0.11803	0.2910	0.170	0.603
		24 H	19	0	0.3387	(0.2715, 0.4059)	0.13947	0.2940	0.207	0.778
		32 H	19	0	0.3388	(0.2780, 0.3997)	0.12626	0.3040	0.190	0.721
		48 H	19	0	0.3089	(0.2556, 0.3622)	0.11051	0.3040	0.159	0.633
		72 H	18	0	0.2582	(0.2088, 0.3075)	0.09917	0.2280	0.147	0.540
		96 H	18	0	0.2179	(0.1757, 0.2602)	0.08488	0.1875	0.137	0.469
		120 H	18	0	0.1833	(0.1458, 0.2209)	0.07557	0.1445	0.115	0.400
		144 H	18	0	0.1623	(0.1276, 0.1970)	0.06982	0.1350	0.103	0.379
		168 H	18	5	0.1244	(0.0785, 0.1704)	0.09234	0.1340	0.000	0.315
		240 H	18	10	0.0674	(0.0261, 0.1087)		0.0000	0.000	0.251
		312 H	18	13	0.0381	(0.0059, 0.0703)		0.0000	0.000	0.184
		384 H	18	15	0.0192	(-0.0030, 0.0414)		0.0000	0.000	0.136
		456 H	18	17	0.0058	(-0.0064, 0.0180)		0.0000	0.000	0.104
		528 H	18	18	0.0000			0.0000	0.000	0.000
		600 H	18	18	0.0000			0.0000	0.000	0.000
		672 H	18	18	0.0000			0.0000	0.000	0.000

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 11.4
Summary of Plasma SB-823094 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S1D1	20	PREDOSE	20	20	0.0000			0.0000	0.000	0.000
		0.5 H	20	20	0.0000			0.0000	0.000	0.000
		1 H	20	20	0.0000			0.0000	0.000	0.000
		2 H	20	20	0.0000			0.0000	0.000	0.000
		3 H	20	20	0.0000			0.0000	0.000	0.000
		4 H	20	17	0.1416	(-0.0525, 0.3356)		0.0000	0.000	1.730
		6 H	20	10	1.4916	(0.5279, 2.4553)		0.4610	0.000	7.092
		9 H	20	4	1.7683	(0.8281, 2.7085)	2.00891	1.1785	0.000	7.019
		12 H	20	4	0.5743	(0.2752, 0.8733)	0.63887	0.4180	0.000	2.640
		18 H	20	4	0.3959	(0.0447, 0.7471)	0.75036	0.2485	0.000	3.496
		24 H	20	1	0.3044	(0.1746, 0.4342)	0.27730	0.2260	0.000	1.260
		32 H	20	5	0.1695	(0.1026, 0.2363)	0.14288	0.1535	0.000	0.517
		48 H	20	9	0.0856	(0.0443, 0.1269)		0.1070	0.000	0.278
		72 H	20	16	0.0272	(0.0003, 0.0541)		0.0000	0.000	0.181
		96 H	20	19	0.0058	(-0.0063, 0.0178)		0.0000	0.000	0.115
S2D10	20	PREDOSE	19	1	0.5461	(0.3594, 0.7328)	0.38742	0.5040	0.000	1.654
		0.5 H	19	0	0.4911	(0.3686, 0.6137)	0.25426	0.4740	0.119	1.010
		1 H	19	0	0.4517	(0.3389, 0.5646)	0.23408	0.4770	0.113	1.032
		2 H	18	0	0.4518	(0.3481, 0.5555)	0.20849	0.4515	0.187	0.953
		3 H	19	0	0.4923	(0.3232, 0.6613)	0.35080	0.4820	0.148	1.676
		4 H	19	0	0.6586	(0.2319, 1.0853)	0.88530	0.4800	0.111	4.212
		6 H	19	0	1.8661	(1.1015, 2.6307)	1.58644	1.8230	0.106	5.602
		9 H	19	0	2.2427	(1.3969, 3.0886)	1.75494	1.7150	0.535	7.981
		12 H	19	0	0.9702	(0.5942, 1.3462)	0.78018	0.7660	0.282	3.607
		18 H	19	0	0.5395	(0.4088, 0.6701)	0.27112	0.4940	0.215	1.284
		24 H	19	0	0.5987	(0.2740, 0.9234)	0.67368	0.4360	0.123	3.256
S2D26	20	PREDOSE	19	0	1.0108	(0.3420, 1.6797)	1.38773	0.4630	0.201	5.161

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 11.4
Summary of Plasma SB-823094 Pharmacokinetic Concentration (ng/mL) - Time (Hours) Data

Visit	N	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.
S2D27	20	PREDOSE	19	0	0.6464	(0.3331, 0.9597)	0.64998	0.4770	0.262	3.211
S2D28	20	PREDOSE	19	0	0.6758	(0.3902, 0.9614)	0.59254	0.3920	0.213	2.614
		0.5 H	19	0	0.5867	(0.3612, 0.8122)	0.46786	0.4100	0.222	2.202
		1 H	19	0	0.5468	(0.3610, 0.7326)	0.38547	0.3880	0.222	1.841
		2 H	19	0	0.4865	(0.3605, 0.6126)	0.26153	0.3740	0.232	1.203
		3 H	19	0	0.4822	(0.3721, 0.5922)	0.22839	0.3810	0.231	1.016
		4 H	19	0	0.7809	(0.4132, 1.1486)	0.76283	0.5880	0.269	3.441
		6 H	19	0	1.7703	(0.6247, 2.9159)	2.37686	1.0140	0.312	10.503
		9 H	19	0	1.3925	(0.5243, 2.2607)	1.80127	0.6030	0.315	8.095
		12 H	19	0	0.7604	(0.4516, 1.0692)	0.64070	0.4710	0.275	3.017
		18 H	19	0	0.5078	(0.3641, 0.6516)	0.29820	0.3670	0.227	1.361
		24 H	19	0	0.4770	(0.3560, 0.5980)	0.25107	0.3300	0.223	1.057
		32 H	19	0	0.4242	(0.3291, 0.5192)	0.19722	0.3470	0.193	0.917
		48 H	19	0	0.2901	(0.2296, 0.3505)	0.12547	0.2610	0.147	0.618
		72 H	18	0	0.2064	(0.1677, 0.2452)	0.07787	0.1880	0.113	0.400
		96 H	18	1	0.1609	(0.1262, 0.1956)	0.06984	0.1450	0.000	0.349
		120 H	18	4	0.1151	(0.0766, 0.1535)	0.07733	0.1215	0.000	0.295
		144 H	18	9	0.0741	(0.0328, 0.1153)		0.0555	0.000	0.264
		168 H	18	12	0.0492	(0.0104, 0.0879)		0.0000	0.000	0.250
		240 H	18	17	0.0105	(-0.0117, 0.0327)		0.0000	0.000	0.189
		312 H	18	17	0.0087	(-0.0096, 0.0270)		0.0000	0.000	0.156
		384 H	18	17	0.0062	(-0.0068, 0.0192)		0.0000	0.000	0.111
		456 H	18	18	0.0000			0.0000	0.000	0.000
		528 H	18	18	0.0000			0.0000	0.000	0.000
		600 H	18	18	0.0000			0.0000	0.000	0.000
		672 H	18	18	0.0000			0.0000	0.000	0.000

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

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Table 11.5
Summary Statistics of Metabolite/Parent Ratio of Derived Pharmacokinetic Parameters

Analyte	Metabolite	Parameter	Visit	N	n	Mean	95% CI (Lower,Upper)	SD	% CVb	Median	Min.	Max.
SB-553253	M4	AUC(0-t) (ng*hr/mL)	S1D1	20	18	3.154	(2.544,3.764)	1.2262	38.88	3.007	1.15	5.40
		AUC(0-tau) (ng*hr/mL)	S1D1	20	14	5.031	(4.182,5.880)	1.4701	29.22	4.997	2.72	7.66
			S2D10	20	19	4.870	(4.251,5.490)	1.2861	26.41	4.827	2.55	6.66
			S2D28	20	19	4.844	(4.155,5.532)	1.4280	29.48	4.372	2.90	8.66
		Cmax (ng/mL)	S1D1	20	20	9.000	(7.424,10.576)	3.3668	37.41	8.229	3.33	15.22
			S2D10	20	19	8.790	(7.037,10.544)	3.6379	41.38	8.120	3.62	16.74
			S2D28	20	19	7.541	(5.614,9.468)	3.9977	53.01	6.392	3.09	20.76
SB-554008	M10	AUC(0-tau) (ng*hr/mL)	S2D10	20	19	1.519	(1.298,1.739)	0.4567	30.08	1.576	0.79	2.69
			S2D28	20	19	2.516	(2.177,2.855)	0.7040	27.98	2.209	1.65	4.02
		Cmax (ng/mL)	S2D10	20	19	1.131	(0.987,1.274)	0.2977	26.32	1.093	0.65	1.57
			S2D28	20	19	2.231	(1.853,2.608)	0.7830	35.10	2.038	1.43	3.84
SB-823094	M3	AUC(0-t) (ng*hr/mL)	S1D1	20	18	3.624	(2.803,4.444)	1.6499	45.53	3.691	1.15	7.55
		AUC(0-tau) (ng*hr/mL)	S1D1	20	15	6.716	(5.328,8.103)	2.5055	37.31	6.686	2.72	12.07
			S2D10	20	19	5.796	(5.013,6.579)	1.6240	28.02	5.476	3.12	9.05

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.5
Summary Statistics of Metabolite/Parent Ratio of Derived Pharmacokinetic Parameters

Analyte	Metabolite	Parameter	Visit	N	n	Mean	95% CI (Lower,Upper)	SD	% CVb	Median	Min.	Max.
SB-823094	M3	AUC(0-tau) (ng*hr/mL)	S2D28	20	19	5.079	(4.160,5.998)	1.9072	37.55	4.399	3.13	10.73
		Cmax (ng/mL)	S1D1	20	20	11.313	(9.395,13.231)	4.0982	36.23	11.751	4.52	17.82
			S2D10	20	19	11.106	(9.422,12.791)	3.4942	31.46	11.085	6.53	19.64
			S2D28	20	19	8.743	(6.630,10.856)	4.3845	50.15	7.803	3.67	22.32

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.6
Summary Statistics of Log-Transformed Plasma SB-480848 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
AUC(0-inf) (ng*hr/mL)	S1D1	20	20	560.824 (448.232,701.699)	0.4788	617.485 (499.328,735.643)	252.4646	50.76	617.843	184.20	1060.71
AUC(0-t) (ng*hr/mL)	S1D1	20	20	456.078 (367.280,566.346)	0.4627	499.053 (406.089,592.016)	198.6337	48.86	479.380	147.49	853.67
AUC(0-tau) (ng*hr/mL)	S1D1	20	20	151.723 (98.009,234.877)	0.9337	199.372 (148.095,250.649)	109.5631	117.96	205.786	12.74	386.14
	S2D10	20	19	362.212 (309.239,424.260)	0.3281	381.102 (319.050,443.154)	128.7430	33.71	354.084	180.00	750.60
	S2D28	20	19	315.080 (261.113,380.202)	0.3898	338.963 (271.557,406.370)	139.8517	40.51	294.838	143.57	734.58
Cmax (ng/mL)	S1D1	20	20	18.641 (14.103,24.640)	0.5962	21.501 (16.652,26.351)	10.3620	65.33	23.545	4.25	40.34
	S2D10	20	19	25.060 (20.917,30.025)	0.3750	26.730 (21.896,31.565)	10.0308	38.86	24.032	9.60	54.74
	S2D28	20	19	17.513 (13.960,21.970)	0.4704	19.477 (14.777,24.178)	9.7516	49.77	18.952	6.89	47.06

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.6
Summary Statistics of Log-Transformed Plasma SB-480848 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
Ctau (ng/mL)	S2D26	20	19	14.734 (12.412,17.492)	0.3559	15.709 (12.650,18.768)	6.3464	36.75	13.682	8.32	35.65
	S2D27	20	19	12.735 (10.999,14.746)	0.3041	13.364 (11.036,15.692)	4.8301	31.13	12.263	7.83	29.83
	S2D28	20	19	12.554 (10.530,14.966)	0.3647	13.386 (10.897,15.875)	5.1636	37.71	12.529	6.38	27.89
t1/2 (hr)	S1D1	20	20	37.953 (34.704,41.506)	0.1912	38.621 (35.133,42.109)	7.4533	19.30	39.790	29.02	54.37
	S2D28	20	19	126.272 (109.765,145.261)	0.2907	131.201 (113.638,148.763)	36.4375	29.69	131.204	61.70	216.85

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.7
Summary Statistics of Derived Plasma SB-480848 Pharmacokinetic Parameter Tmax

Parameter	Visit	N	n	Geo.mean (95% CI)	Arith.mean (95% CI)	SD	% CVb	Median	Min.	Max.
tmax (hr)	S1D1	20	20	8.813 (6.878,11.293)	10.250 (7.172,13.328)	6.5765	64.16	9.000	4.00	24.00
	S2D10	20	19	7.941 (6.614,9.533)	8.104 (5.928,10.279)	4.5138	55.70	9.000	0.00	23.92
	S2D28	20	19	6.078 (4.424,8.349)	6.873 (5.680,8.066)	2.4752	36.01	6.000	0.50	12.00

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.8
Summary Statistics of Log-Transformed Plasma SB-553253 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
AUC(0-t) (ng*hr/mL)	S1D1	20	18	14.596 (10.195,20.898)	0.7216	18.332 (12.222,24.443)	12.2880	82.66	14.891	4.18	46.06
AUC(0-tau) (ng*hr/mL)	S1D1	20	14	11.756 (8.840,15.635)	0.4938	13.211 (9.166,17.257)	7.0069	52.54	11.360	5.23	29.58
	S2D10	20	19	17.010 (13.491,21.447)	0.4809	18.979 (14.264,23.694)	9.7830	51.01	17.795	5.92	49.96
	S2D28	20	19	14.712 (11.294,19.164)	0.5485	17.437 (11.109,23.764)	13.1277	59.24	13.446	6.91	63.63
Cmax (ng/mL)	S1D1	20	20	1.562 (1.030,2.367)	0.8889	2.153 (1.373,2.934)	1.6679	109.71	1.861	0.26	6.14
	S2D10	20	19	2.027 (1.500,2.738)	0.6243	2.388 (1.759,3.016)	1.3035	69.04	2.131	0.57	5.67
	S2D28	20	19	1.193 (0.800,1.778)	0.8285	1.762 (0.729,2.795)	2.1432	99.33	0.994	0.37	9.77
Ctau (ng/mL)	S2D26	20	19	0.621 (0.451,0.854)	0.6623	0.820 (0.413,1.227)	0.8446	74.21	0.518	0.28	3.23
	S2D27	20	19	0.532 (0.432,0.656)	0.4339	0.593 (0.418,0.769)	0.3640	45.52	0.507	0.27	1.93
	S2D28	20	19	0.542 (0.429,0.686)	0.4886	0.615 (0.441,0.790)	0.3619	51.93	0.474	0.23	1.64

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.8
Summary Statistics of Log-Transformed Plasma SB-553253 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
t1/2 (hr)	S2D28	20	15	285.166 (248.587,327.126)	0.2479	293.271 (254.145,332.397)	70.6521	25.17	296.519	179.95	412.08

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.9
Summary Statistics of Derived Plasma SB-553253 Pharmacokinetic Parameter Tmax

Parameter	Visit	N	n	Geo.mean (95% CI)	Arith.mean (95% CI)	SD	% CVb	Median	Min.	Max.
tmax (hr)	S1D1	20	20	8.813 (6.932,11.205)	10.200 (7.131,13.269)	6.5582	64.30	7.500	6.00	24.00
	S2D10	20	19	7.993 (6.725,9.500)	8.577 (6.617,10.537)	4.0662	47.41	9.000	4.05	23.92
	S2D28	20	19	6.406 (5.457,7.521)	6.005 (4.585,7.425)	2.9465	49.06	6.000	0.00	12.00

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.10
Summary Statistics of Log-Transformed Plasma SB-554008 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
AUC(0-tau) (ng*hr/mL)	S2D10	20	19	5.268 (4.349,6.381)	0.3976	5.662 (4.630,6.695)	2.1425	41.38	5.592	2.74	9.38
	S2D28	20	19	7.658 (6.508,9.011)	0.3376	8.112 (6.642,9.583)	3.0509	34.75	7.579	4.68	16.23
Cmax (ng/mL)	S2D10	20	19	0.273 (0.226,0.330)	0.3938	0.293 (0.240,0.346)	0.1103	40.96	0.277	0.14	0.51
	S2D28	20	19	0.371 (0.313,0.439)	0.3505	0.395 (0.319,0.471)	0.1571	36.15	0.354	0.22	0.81
Ctau (ng/mL)	S2D26	20	19	0.319 (0.274,0.372)	0.3168	0.337 (0.274,0.400)	0.1307	32.49	0.308	0.21	0.78
	S2D27	20	19	0.312 (0.271,0.359)	0.2913	0.326 (0.271,0.381)	0.1136	29.76	0.296	0.21	0.71
	S2D28	20	19	0.313 (0.266,0.367)	0.3332	0.330 (0.273,0.387)	0.1187	34.26	0.299	0.18	0.65
t1/2 (hr)	S2D28	20	16	148.152 (122.640,178.971)	0.3547	157.402 (126.044,188.761)	58.8495	36.61	137.616	87.56	297.82

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

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Table 11.11
Summary Statistics of Derived Plasma SB-554008 Pharmacokinetic Parameter Tmax

Parameter	Visit	N	n	Geo.mean (95% CI)	Arith.mean (95% CI)	SD	% CVb	Median	Min.	Max.
tmax (hr)	S2D10	20	19	9.222 (5.443,15.624)	10.385 (6.375,14.395)	8.3192	80.11	9.000	0.00	23.92
	S2D28	20	19	6.031 (3.657,9.946)	6.511 (4.420,8.601)	4.3374	66.62	9.000	0.00	12.18

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

[redacted]

Table 11.12
Summary Statistics of Log-Transformed Plasma SB-823094 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
AUC(0-t) (ng*hr/mL)	S1D1	20	18	16.243 (11.306,23.334)	0.7285	20.682 (13.068,28.296)	15.3112	83.67	17.719	5.04	64.42
AUC(0-tau) (ng*hr/mL)	S1D1	20	15	14.309 (10.142,20.189)	0.6216	17.164 (10.891,23.436)	11.3267	68.68	14.100	5.23	46.59
	S2D10	20	19	20.205 (15.843,25.768)	0.5046	22.806 (16.568,29.045)	12.9426	53.85	20.549	5.62	67.90
	S2D28	20	19	15.125 (11.017,20.764)	0.6575	19.241 (11.004,27.478)	17.0898	73.54	12.512	6.57	78.83
Cmax (ng/mL)	S1D1	20	20	1.960 (1.301,2.953)	0.8761	2.680 (1.727,3.632)	2.0355	107.45	1.962	0.38	7.09
	S2D10	20	19	2.659 (2.026,3.489)	0.5638	3.059 (2.251,3.868)	1.6773	61.17	3.018	0.66	7.98
	S2D28	20	19	1.381 (0.910,2.096)	0.8652	2.037 (0.922,3.153)	2.3147	105.55	1.469	0.34	10.50
Ctau (ng/mL)	S2D26	20	19	0.633 (0.421,0.950)	0.8435	1.011 (0.342,1.680)	1.3877	101.84	0.463	0.20	5.16
	S2D27	20	19	0.519 (0.392,0.687)	0.5828	0.646 (0.333,0.960)	0.6500	63.60	0.477	0.26	3.21
	S2D28	20	19	0.534 (0.391,0.729)	0.6458	0.676 (0.390,0.961)	0.5925	71.94	0.392	0.21	2.61

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

[redacted]

Table 11.12
Summary Statistics of Log-Transformed Plasma SB-823094 Pharmacokinetic Parameters

Parameter	Visit	N	n	Geo. mean (95% CI)	SD log	Arith. mean (95% CI)	SD	% CVb	Median	Min.	Max.
t1/2 (hr)	S2D28	20	16	96.367 (83.289,111.499)	0.2737	100.027 (83.781,116.274)	30.4890	27.89	95.731	64.05	187.54

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

[redacted]

Table 11.13
Summary Statistics of Derived Plasma SB-823094 Pharmacokinetic Parameter Tmax

Parameter	Visit	N	n	Geo.mean (95% CI)	Arith.mean (95% CI)	SD	% CVb	Median	Min.	Max.
tmax (hr)	S1D1	20	20	8.994 (7.101,11.392)	10.350 (7.312,13.388)	6.4911	62.72	9.000	6.00	24.00
	S2D10	20	19	7.941 (6.614,9.533)	8.104 (5.928,10.279)	4.5138	55.70	9.000	0.00	23.92
	S2D28	20	19	6.336 (5.486,7.318)	5.161 (3.658,6.664)	3.1184	60.42	6.000	0.00	9.03

Note:
S1: 160 mg of EC micronized free-base darapladib as a single dose.
S2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days.

[redacted]

Table 11.14
Analysis of PK Parameter of SB-480848

Regimen	Compound	Parameter	Comparison	Ratio	90% CI	%CVw
A	SB-480848	Rcmax	Day 10 : Day 1	1.35	(1.08, 1.67)	41.76
			Day 28 : Day 1	0.94	(0.76, 1.17)	
		Ro	Day 10 : Day 1	2.39	(1.76, 3.25)	61.09
			Day 28 : Day 1	2.08	(1.53, 2.82)	
		Rp	AUCINF :AUCTAU	3.70	(2.89, 4.72)	47.11
		Rs	Day 10 : Day 1	0.64	(0.55, 0.76)	30.40
			Day 28 : Day 1	0.56	(0.48, 0.66)	

A: 160 mg of enteric-coat free base (micronised) darapladib
Comparison of AUCINF vs AUCTAU is on day 1

[redacted]

Table 11.15
Analysis of PK Parameter of Metabolite of SB-480848

Regimen	Compound	Parameter	Comparison	Ratio	90% CI	%CVw
A	SB-553253	Rcmax	Day 10 : Day 1	1.29	(0.92, 1.80)	68.19
			Day 28 : Day 1	0.76	(0.54, 1.06)	
		Ro	Day 10 : Day 1	1.46	(1.17, 1.82)	36.22
			Day 28 : Day 1	1.27	(1.02, 1.58)	
	SB-823094	Rcmax	Day 10 : Day 1	1.35	(0.95, 1.91)	71.71
			Day 28 : Day 1	0.70	(0.49, 0.99)	
		Ro	Day 10 : Day 1	1.35	(1.03, 1.77)	46.85
			Day 28 : Day 1	1.01	(0.77, 1.33)	

A: 160mg of enteric-coated free base (micronised) darapladib

[redacted]

Table 11.16
Analysis of PK Parameter of SB-480848 without outlier

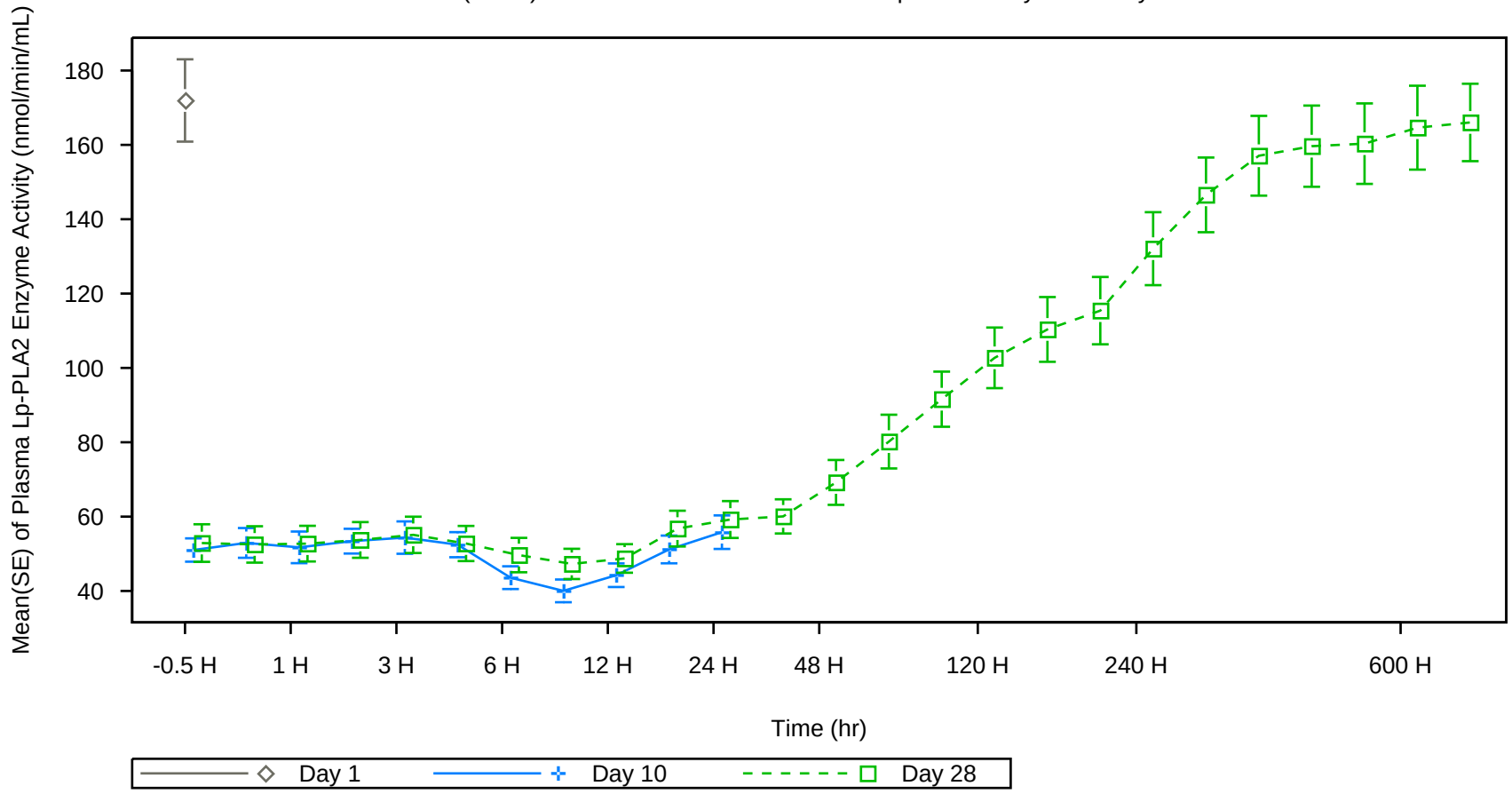
Regimen	Compound	Parameter	Comparison	Ratio	90% CI	%CVw
A	SB-480848	Rcmax	Day 10 : Day 1	1.24	(1.02, 1.50)	35.43
			Day 28 : Day 1	0.86	(0.71, 1.04)	
		Ro	Day 10 : Day 1	1.70	(1.46, 2.00)	26.99
			Day 28 : Day 1	1.44	(1.23, 1.69)	
		Rp	AUCINF :AUCTAU	2.87	(2.73, 3.01)	8.34
		Rs	Day 10 : Day 1	0.64	(0.55, 0.76)	30.40
			Day 28 : Day 1	0.56	(0.48, 0.66)	

A: 160 mg enteric-coat free base (micronised) darapladib
Comparison of AUCinf vs AUCtau is on day 1

[redacted]

Pharmacodynamic Data Source Figures and Tables

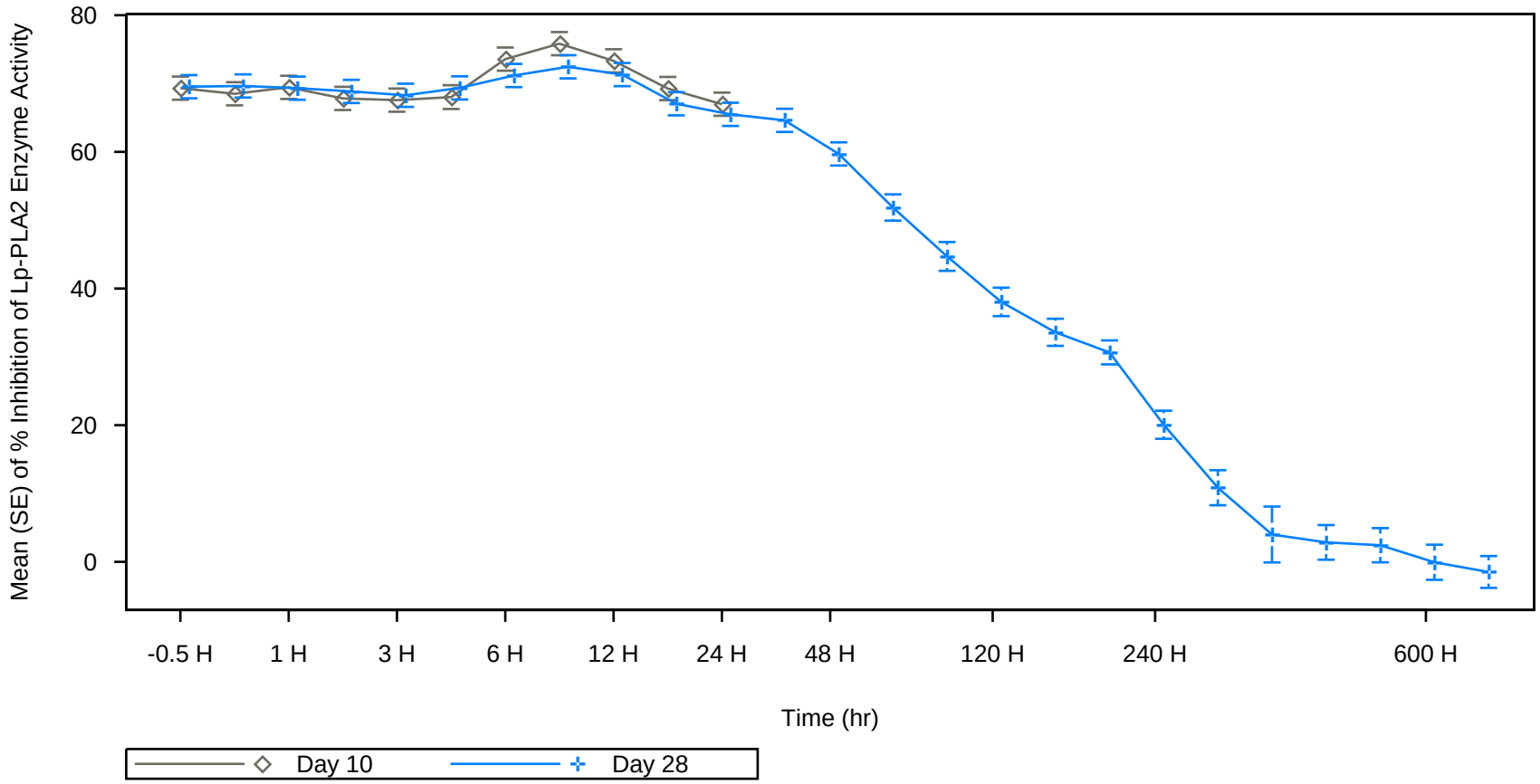
Figure 12.1
Mean (+/-SE) Plots of Time Course of Plasma Lp-PLA2 Enzyme Activity



Note: X-axis is a representative scale.
Day 1: 160 mg of EC micronized free-base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 10
Day28: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

Figure 12.2
Mean (+/-SE) Plots of Time Course of % Inhibition of Plasma Lp-PLA2 Enzyme Activity



Note: X-axis is a representative scale. % Inhibition was calculated with Session1 Day1 as baseline.
Day 1: 160 mg of EC micronized free-base darapladib as a single dose at Session 1 Day1
Day 10: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 10
Day28: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days at Session 2 Day 28

[redacted]

Table 12.1
Summary of Lp-PLA2 Activity - Time Data (nmol/min/ml)

Trt.	N	Visit	Pl.Time	n	Mean	95% CI of Mean	SD	Median	Min.	Max.
A1	20	S1D1	PREDOSE	20	171.95	(148.771,195.119)	49.515	171.65	77.3	260.3
A2	20	S2D10	PREDOSE	19	51.02	(44.428,57.604)	13.669	50.20	20.8	79.5
			0.5 H	19	52.93	(44.515,61.338)	17.452	47.60	21.9	93.6
			1 H	19	51.73	(42.794,60.669)	18.543	47.70	22.2	107.3
			2 H	19	53.40	(46.407,60.393)	14.508	50.60	22.5	84.4
			3 H	19	54.36	(45.212,63.504)	18.975	48.30	21.8	99.1
			4 H	19	52.45	(45.355,59.540)	14.715	48.60	23.0	91.7
			6 H	19	43.58	(37.442,49.716)	12.734	43.30	23.1	68.3
			9 H	19	40.03	(34.468,45.584)	11.532	36.30	22.6	64.6
			12 H	19	44.24	(37.568,50.906)	13.836	41.10	23.6	79.8
			18 H	19	51.17	(43.337,58.999)	16.247	46.30	24.6	88.8
			24 H	19	55.82	(46.339,65.293)	19.662	53.10	19.6	102.6
		S2D28	PREDOSE	19	52.89	(42.271,63.508)	22.032	46.90	21.1	103.8
			0.5 H	19	52.52	(42.236,62.796)	21.329	46.60	21.6	99.8
			1 H	19	52.73	(42.658,62.805)	20.900	45.00	22.4	100.0
			2 H	19	53.73	(43.635,63.818)	20.937	47.50	21.9	101.7
			3 H	18	55.09	(44.791,65.397)	20.718	49.60	23.0	95.1
			4 H	19	52.77	(42.843,62.694)	20.593	46.90	23.4	92.2
			6 H	18	49.66	(39.894,59.417)	19.630	45.55	22.6	97.5
			9 H	18	47.28	(38.695,55.861)	17.259	43.10	21.3	86.2
			12 H	19	48.75	(40.674,56.821)	16.750	46.50	22.1	79.6
			18 H	18	56.78	(46.632,66.923)	20.402	50.30	24.4	91.2
			24 H	19	59.22	(48.805,69.637)	21.611	53.50	24.7	99.5
			32 H	19	60.06	(50.399,69.717)	20.040	57.10	27.1	98.0
			48 H	19	69.20	(56.523,81.877)	26.301	64.80	26.9	114.8
			72 H	18	80.18	(64.942,95.425)	30.650	73.00	34.1	153.0
			96 H	18	91.59	(75.943,107.235)	31.463	86.30	36.4	145.8
			120 H	18	102.71	(85.514,119.909)	34.583	94.50	40.7	164.6
			144 H	18	110.36	(91.981,128.730)	36.949	103.45	42.2	178.5

Regimen Key:
A1: 160 mg of EC micronized free-base darapladib as a single dose.
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 12.1
Summary of Lp-PLA2 Activity - Time Data (nmol/min/ml)

Trt.	N	Visit	Pl.Time	n	Mean	95% CI of Mean	SD	Median	Min.	Max.
A2	20	S2D28	168 H	18	115.41	(96.300,134.522)	38.431	110.35	45.9	184.5
			240 H	18	132.08	(111.372,152.784)	41.637	127.40	60.9	202.3
			312 H	18	146.55	(125.355,167.745)	42.622	141.40	65.2	219.2
			384 H	18	157.07	(134.435,179.709)	45.521	154.95	69.3	226.2
			456 H	18	159.65	(136.609,182.691)	46.333	151.05	76.4	261.4
			528 H	18	160.33	(137.483,183.173)	45.939	155.05	78.1	241.3
			600 H	18	164.63	(140.819,188.437)	47.878	159.55	76.0	260.3
			672 H	18	166.03	(144.064,188.003)	44.179	158.35	80.7	248.3

Regimen Key:
A1: 160 mg of EC micronized free-base darapladib as a single dose.
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days

[redacted]

Table 12.2
Summary of % Inhibition of Lp-PLA2 Activity - Time Data

Trt.	N	Visit	Pl.Time	n	Mean	95% CI of Mean	SD	Median	Min.	Max.
A2	20	S2D10	PREDOSE	19	69.329	(66.6528,72.0051)	5.5523	69.430	56.12	77.35
			0.5 H	19	68.502	(65.4711,71.5331)	6.2887	69.220	53.91	77.44
			1 H	19	69.444	(66.9322,71.9551)	5.2106	68.650	58.27	77.07
			2 H	19	67.825	(64.6972,70.9533)	6.4899	68.270	48.03	76.67
			3 H	19	67.572	(64.1980,70.9462)	7.0005	67.030	56.21	83.62
			4 H	19	68.019	(64.3674,71.6715)	7.5771	67.180	54.83	83.75
			6 H	19	73.578	(70.4770,76.6787)	6.4335	75.240	61.01	84.48
			9 H	19	75.840	(73.4912,78.1888)	4.8732	76.400	65.75	84.98
			12 H	19	73.325	(70.5645,76.0850)	5.7269	73.290	62.46	83.08
			18 H	19	69.274	(66.2081,72.3392)	6.3603	68.760	53.01	79.96
			24 H	19	66.978	(63.5627,70.3941)	7.0867	69.550	47.82	76.10
		S2D28	PREDOSE	19	69.537	(67.0522,72.0225)	5.1560	69.530	59.45	77.56
			0.5 H	19	69.649	(67.1781,72.1198)	5.1264	69.360	58.54	78.47
			1 H	19	69.324	(66.6723,71.9761)	5.5021	69.780	58.51	78.05
			2 H	19	68.849	(66.4828,71.2151)	4.9091	69.050	60.44	77.91
			3 H	18	68.282	(66.1986,70.3658)	4.1900	67.870	60.20	74.91
			4 H	19	69.361	(67.1067,71.6154)	4.6772	69.100	63.72	81.30
			6 H	18	71.179	(68.4740,73.8837)	5.4392	70.665	62.08	83.03
			9 H	18	72.453	(70.1057,74.7998)	4.7197	72.155	63.27	83.19
			12 H	19	71.317	(69.1617,73.4720)	4.4715	71.410	61.98	80.96
			18 H	18	67.041	(64.5301,69.5521)	5.0493	67.095	56.44	77.05
			24 H	19	65.493	(63.2623,67.7240)	4.6285	64.830	57.95	74.15
			32 H	19	64.615	(62.1022,67.1272)	5.2128	65.720	52.90	73.00
			48 H	19	59.701	(56.3226,63.0795)	7.0094	60.540	40.01	70.97
			72 H	18	51.862	(47.7995,55.9238)	8.1686	54.230	31.79	65.61
			96 H	18	44.700	(40.2454,49.1546)	8.9578	45.395	22.72	61.19
			120 H	18	38.041	(33.6466,42.4345)	8.8358	38.475	18.53	55.50
			144 H	18	33.591	(29.4085,37.7727)	8.4098	33.805	14.23	51.37
			168 H	18	30.653	(26.9562,34.3493)	7.4334	29.380	18.15	47.96

Regimen Key:
A1: 160 mg of EC micronized free-base darapladib as a single dose.
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days
Note: % Inhibition is calculated with baseline as Lp-PLA2 activity at visit S1D1.

[redacted]

Table 12.2
Summary of % Inhibition of Lp-PLA2 Activity - Time Data

Trt.	N	Visit	Pl.Time	n	Mean	95% CI of Mean	SD	Median	Min.	Max.
A2	20	S2D28	240 H	18	20.063	(15.7236,24.4031)	8.7268	21.285	0.27	37.58
			312 H	18	10.848	(5.4385,16.2570)	10.8775	9.820	-9.83	31.52
			384 H	18	4.002	(-4.6279,12.6313)	17.3533	5.120	-52.99	28.87
			456 H	18	2.846	(-2.5047,8.1958)	10.7588	4.220	-19.65	22.03
			528 H	18	2.429	(-2.8516,7.7105)	10.6197	2.155	-17.53	26.52
			600 H	18	-0.063	(-5.4829,5.3574)	10.8994	1.205	-19.86	21.72
			672 H	18	-1.484	(-6.3946,3.4257)	9.8738	-1.670	-17.69	16.75

Regimen Key:
A1: 160 mg of EC micronized free-base darapladib as a single dose.
A2: 160 mg of EC micronized free-base darapladib as repeat dose for 28 days
Note: % Inhibition is calculated with baseline as Lp-PLA2 activity at visit S1D1.

[redacted]

Attachment 1: Time and Events Table

Time and Events Table for Protocol LPL112498

Procedure	Screening (up to 30 days prior to Day 1)	Study Day (each dosing session)																	
		Day -1	Day 1													Day 2		Day 3	Day 4
			Pre-dose	0 h	0.5 h	1 h	2 h	3 h	4 h	6 h	9 h	10 h	12 h	18 h	24 h	32 h	48 h	72 h	96 h
Admission to Unit		X																	
Informed Consent	X																		
Demographics	X																		
Full Physical Exam	X																		
Brief Physical Exam		X																	
Medical/medication/ drug/alcohol history	X																		
12-lead ECG	X																		
Vital signs	X	X	X														X		
Urine Drug/Alcohol	X	X																	
Serum β-hCG (women)	X	X																	
Hema/Chem/Urinalysis tests	X	X															X		
Meal		X	X							X		X			X	X			
Dosing				X															
Pharmacokinetic Sampling			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Pharmacodynamic Sampling			X																
Adverse Event Review[1]			X						X			X			X	X	X	X	X
Concomitant Medication Review		X	X														X	X	X
Discharge																	X		
Outpatient Visit	X																	X	X

1. AEs will NOT be noted until after the first dose of study drug

REPEAT DOSE PORTION OF STUDY

Day:	RD 1	RD 2	RD 3	RD 4	RD 5	RD 6	RD 7	RD 8	RD 9	RD10	RD11	RD12	RD13	RD14	RD15	RD16	RD17	RD18	RD19	RD20	RD21	RD22	RD23	RD24	RD25	RD26	RD27	RD28
Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient stay									X	X																	X	X
Outpatient visit	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Discharge											X																	
Vital signs														X														X
AE assessment	Ongoing																											
Con.Medication Review	Ongoing																											
Meal served	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sample										X[1]																X[2]	X[2]	X[1]
PD blood sample										X[1]																		X[1]

Continued

PK/PD SAMPLING AFTER LAST REPEAT DOSE:

Day:	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	Follow-up
Outpatient visit		X	X	X	X	X	X			X			X			X			X			X			X			X	X
PK blood sample[3]	X	X	X	X	X	X	X			X			X			X			X			X			X			X	
PD blood sample[3]	X	X	X	X	X	X	X			X			X			X			X			X			X			X	
Discharge	X																												
12-lead ECG																													X
Vital signs																													X
Serum β-hCG (women)																													X
Hema/Chem/Urinalysis tests																													X
AE assessment														X															X
Con.Medication Review														X															X

1. Samples will be obtained at 0, 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24 hours post dose
2. Day 26 and Day 27 of repeat dosing require trough PK samples
3. After LAST day of repeat dosing PK and PD samples will be obtained at 32, 48, 72, 96, 120, 144, 168, 240, 312, 384, 456, 528, 600 and 672 hours post-dose

Division: World Wide Development
Retention Category: GRS019
Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for LPL112498 A study to evaluate the pharmacokinetics of the enteric-coated micronized free base formulation of DARAPLADIB™ and its metabolites in healthy volunteers.

Compound Number: SB-480848

Effective Date: 14-NOV-2008

Description:

Identifier/Version Number: CH2008/00038/00

Subject: Infection, Quality of Life

Author's Name, Title and Functional Area:

[redacted] Statistician (Co-op), Discovery biometrics, MP
[redacted] Principal Statistician, Discovery Biometrics, MP
[redacted] (CSSO)
[redacted] (MDC)
[redacted] (CPMS)

Approved by: E-mail Approval obtained

[redacted]
Manager, Statistics and Programming
Discovery Biometrics, MP

Date: 14-Nov-2008

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CONFIDENTIAL CH2008/00038/00
LPL112498

ABBREVIATIONS

AE	Adverse Event
ADME	Absorption Distribution Metabolism Elimination
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
ß-hCG	Beta-Human Chorionic Gonadotropin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	Maximum observed concentration
CO2	Carbon dioxide
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case Report Form
CSSO	Clinical Science and Study Operations
CV	Coefficient of variance
DB	Discovery Biometrics
DMPK	Drug Metabolism and Pharmacokinetics
EC	Enteric coated
ECG	Electrocardiogram
4-FBCl	4-fluorobenzyl chloride
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
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)
IB	Investigator’s Brochure
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	intrauterine system
Kg	Kilogram
LDH	Lactate dehydrogenase
LDL	low density lipoprotein
Lp-PLA2	lipoprotein-associated phospholipase A2
Lyso-PC	lysophosphatidylcholine
MDC	Medicine Development Cente
Mg	Milligrams

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mL	Milliliters
MSDS	Material Safety Data Sheet
msec	Milliseconds
PAF	platelet-activating factor
PAF-AH	platelet-activating factor acetyl hydrolase
PD	Pharmacodynamic
PK	Pharmacokinetic
RCmax	Cmax accumulation ratio
Ro	Observed accumulation ratio
Rp	Predicted accumulation ratio
Rs	Steady-state accumulation ratio
RBC	Red blood cells
SAE	Serious adverse event(s)
SD	Standard deviation
SPM	Study Procedures Manual
T½	Half life
Tmax	Time of maximal plasma concentration
ULN	Upper limit of normal
WBC	White blood cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DARAPLADIB

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NONMEM
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1. INTRODUCTION

The purpose of this reporting and analysis plan is to describe the analyses to be included in the Clinical Pharmacology Study Report for Protocol LPL112498, [GlaxoSmithKline Document Number ZM2008/00108/00]. Further information can be found in the study protocols and associated amendments (if applicable).

The reporting and analysis plan (RAP) is based on standard operating procedure regarding the Development, Review and Approval of Reporting and Analysis Plans. In addition, the RAP was developed per the document standard for Reporting and Analysis Plans.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

Primary

1. To characterize the pharmacokinetics of single and repeat oral doses of DARAPLADIB™ and its metabolites (M10, M3 and M4) in healthy adult subjects
2. To monitor the safety and tolerability of single and repeat oral doses of DARAPLADIB in healthy adult subjects

Secondary

1. To evaluate the inhibition of plasma Lp-PLA2 activity after repeat dosing of 160 mg of enteric-coat free base (micronised) DARAPLADIB

2.2. Study Endpoint(s)

Primary

1. The primary PK endpoints will include AUC and Cmax of DARAPLADIB and its metabolites (M10, M3 and M4) following single and repeat oral doses. Metabolite to parent AUC and Cmax ratio for each metabolite will be calculated as data permit.
2. Clinical safety data (spontaneous AE reporting, vital signs, nursing/physician observation, and clinical laboratory tests) will be the primary safety endpoint.

Secondary

1. Secondary PK endpoints will include Tmax and T½ of DARAPLADIB and its metabolites (M10, M3 and M4) as data permit.
2. Plasma Lp-PLA2 activity, expressed in terms of percent inhibition relative to baseline, as data permit.

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2.3. Statistical Hypotheses

No formal hypotheses will be tested. An estimation approach will be taken and appropriate corresponding confidence intervals will be used to address the comparisons of interest.

2.4. Pharmacokinetic (PK) and PK/Pharmacodynamic (PD) hypotheses

For the planned pharmacokinetic analysis, the pharmacokinetic parameters of SB-480848 (parent), SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) on Day 10 and Day 28 (Period 2, repeat dose) will be compared to those on Day 1 (Period 1, single dose) separately. The comparisons of interest will be expressed as the accumulation ratios (Ro, Rp, Rs and Rcmax), as the data permit. For each metabolite, AUC and Cmax metabolite to parent ratio will be calculated on each day (Day 1 Period 1 and Days 10 and 28 Period 2).

For the planned pharmacodynamic analysis, plasma Lp-PLA2 activity and percent inhibition of plasma Lp-PLA2 activity relative to baseline will be calculated and summarized at each time point.

3. STUDY DESIGN

This will be single center, an open label study where each subject will participate in 2 study sessions, a Single Dose Session and a Repeat Dose Session. All subjects will receive 160 mg of EC micronized free-base DARAPLADIB as a single dose and as repeated daily doses for 28 days. There will be at least 4 days between dosing in the Single Dose Session and the first dose of the Repeat Dose Session due to the 96-hour PK sampling period following the single dose. PK samples will be collected over a 96-hour period after single dose in Session 1, and over a 24-hour period after Days 10 and 28 of repeat dosing, as well as over a 28-day duration following the last day of dosing of the repeat dose session. PD samples will be collected over a 24-hour period after Days 10 and 28 of repeat dosing, as well as over the 28-day duration following the last day of dosing of the repeat dose session.

Subjects will return approximately 28 days after the last dose of study medication for a follow-up visit. The total study duration for each subject including the screening, treatment and follow-up periods will be approximately 12 weeks.

All subjects will be assigned to receive 160 mg of EC micronized free-base DARAPLADIB as a single dose and as repeated daily doses for 28 days.

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Product Name:	DARAPLADIB
Dosage form:	Enteric coated, free base (micronized) tablet
Unit dose strength(s)/dosage level(s)	160 mg
Route/ Administration/ Duration	Route: oral Administered: daily Duration: Single dose, followed by 28 days of repeat dosing
Dosing instructions:	Take with food. Swallow whole, do not chew.
Manufacturer/ Source of procurement	GSK

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal interim statistical analysis is planned. After the last dose of DARAPLADIB and before database freeze, Clinical Pharmacology Modeling and Simulation will assess preliminary pharmacokinetic data based on nominal time.

4.2. Final Analysis

The final planned analyses will be performed after all subjects have completed the study and after database freeze. Please refer to Section 11 and Section 12 for all final planned analyses for this study.

5. SAMPLE SIZE CONSIDERATIONS

Sample size is based on feasibility. However, some justification is provided below.

Based on study SB480848/015, the maximum within subject standard deviation (SD) for metabolite to parent ratio is 3.1%. Assuming similar variability of metabolite to parent ratio in current study, the half width of 90% confidence interval (CI) of metabolite to parent ratio will be about 1.8%. Based on study LPL107988, the CVw% for SB-480848 Cmax is 26.0%, and the CVw% for AUC is 18.3%. Based on the CVs and 10 subjects, the half width of 90% CI for Rcmax will be within 22.4% of point estimate and for Ro, Rp and Rs will be within 15.1% of point estimate.

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6. ANALYSIS POPULATIONS

Safety: All subjects who receive at least one dose of DARAPLADIB will be included in the Safety Population.

Pharmacokinetic:, For PK concentration and each PK parameter endpoints, all evaluable pharmacokinetic data will be included in the corresponding formal statistical analysis.

Pharmacodynamic: All subjects with evaluable pharmacodynamic data will be included in the summary statistics.

7. TREATMENT COMPARISONS

7.1. Data Display Treatment and Other Sub-group Descriptors

For the planned pharmacokinetic analysis, the pharmacokinetic parameters of SB-480848 (parent), SB-553253 (M4), SB554008 (M10) and SB-823094 (M3) on Day 10 and Day 28 (Period 2) will be compared to those on Day 1 (Period 1) separately. The comparisons of interest will be expressed as the accumulation ratios (R_o, R_p, R_s and R_{cmax}), as the data permit, according to the equations below:

$$\text{Observed Accumulation Ratio } (R_o) = \frac{AUC_{(0-\tau)} \text{ of Day 10, Day 28}}{AUC_{(0-\tau)} \text{ of Day 1}}$$

$$\text{Predicted Accumulation Ratio } (R_p) = \frac{AUC_{(0-\infty)} \text{ of Day 1}}{AUC_{(0-\tau)} \text{ of Day 1}}$$

$$\text{Steady-State Accumulation Ratio } (R_s) = \frac{AUC_{(0-\tau)} \text{ of Day 10, Day 28}}{AUC_{(0-\infty)} \text{ of Day 1}}$$

$$\text{Cmax Accumulation Ratio } (R_{cmax}) = \frac{C_{max} \text{ of Day 10, Day 28}}{C_{max} \text{ of Day 1}}$$

For each metabolite, AUC and C_{max} metabolite to parent ratio will be calculated on each day (Day 1 Period 1 and Days 10 and 28 Period 2).

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1. Multicentre Studies

This is a single centre study.

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8.2. Data Management

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
PK Blood	SMS2000	SMS2000 system	To be completed by DMPK	DMPK, PK sample receipt recon by CPDS
PD Blood	Quest Diagnostics	SI SAS datasets	DBF, forecasted for 14Jan09	Quest provides data to GSK - CPDS delivers to DB
Safety Labs Urine & Blood	[redacted]	SI SAS datasets	DBF, forecasted for 14Jan09	[redacted] provides data to GSK - CPDS delivers to DB
CRF data	InForm	SI SAS datasets	DBF, forecasted for 14Jan09	CPDS

This is for study teams to determine upfront if there is a possibility of not meeting the completion of the CPSR within 6 months of LSLV (i.e. novel data that may not be available until several months after LSLV).

8.3. Other Strata and Covariates

There are no other strata planned.

8.4. Examination of Subgroups

There are no subgroup analyses planned.

8.5. Multiple Comparisons and Multiplicity

No multiplicity adjustment will be made.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

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

If a subject is withdrawn from the study and is on site, safety assessments (AEs, Clinical safety labs, 12-lead ECG, and vitals) should be preformed prior to discharge of the subject.

Unevaluable subjects may be replaced with another subject assigned the same treatment or sequence with respect to active doses with approval from GSK.

No imputation will be performed for missing values.

9.2. Derived and Transformed Data

All pharmacokinetic parameters except Tmax will be $\log_e$ transformed before formal statistical analysis.

For each metabolite [SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3)], AUC and Cmax metabolite to parent [SB-480848] ratio will be calculated on each day (Day 1 Period 1 and Days 10 and 28 Period 2).

Plasma Lp-PLA2 activity, will be summarized as percent inhibition of plasma Lp-PLA2

Activity from baseline using the following formula:

100 x [(Activity at baseline – Activity at time x) / Activity at baseline]

where Activity represents plasma Lp-PLA2 activity, and baseline is defined as predose at Day1 period 1

9.3. Baseline Definition

The following table indicates the baseline day to be used in the analysis:

Parameter	Baseline (Predose) Days Collected			Baseline (Predose) Day Used in Analysis
	Screening	Day -1	Day 1 predose	
Safety :				
Vital Signs	X	X	X	Day 1 predose
ECG	X			Screening
Lab	X	X		Day -1
PD				
PD			X	Day 1 predose

1. Use the mean of replicate assessments at any given time point as the value for that time point in all summaries, figures and statistical analyses.
2. Unscheduled measurements at baseline will be listed only and will not be considered in any calculation and derivation. If the baseline value defined above is missing, no imputation will be made.

9.4. Assessment Windows

Only scheduled visits will be listed and summarized. Any unscheduled visits will be listed but not summarized.

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9.5. Values of Clinical Concern

ECG, vitals and safety laboratory data will be flagged against normal ranges and ranges of potential clinical importance. Any values that fall outside the potential clinical importance ranges will be listed by regimen and time. Values of clinical importance will be reviewed by the investigators and the medical monitor. If any laboratory test results are outside of the reference range, they will be flagged in the listing. Standard values of potential clinical concern for healthy volunteers will be used.

10. STUDY POPULATION

10.1. Disposition of Subjects

Subjects who discontinue from study early, along with the date of withdrawal, will be listed according to current ISDL standards.

10.2. Protocol Deviations

Protocol deviations will be reported to GlaxoSmithKline and will be documented in the clinical study report. Any changes form the analyses described within this reporting and analysis plan will be stated in the final study report.

10.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed by individual and summarized according to current IDSL standards.

10.4. Treatment Compliance

Treatment compliance will be summarized and listed according to current IDSL standards.

11. SAFETY ANALYSES

No formal statistical analysis of safety data will be performed. Following the completion of the study, safety data will be presented in tabular format following GSK IDSL standard.

11.1. Extent of Exposure

Exposure to study drug will be summarised and listed according to Investigational Product Exposure Core IDSL guidelines.

The summary table will include the number of subjects exposed to the treatment, the total number of subjects exposed to DARAPLADIB and the duration of exposure. The data listing will include the start date and time of the investigational product, and the total dose received on each day.

11.2. Adverse Events

Adverse events will be presented according to Clinical Pharmacology IDSL guidelines.

Summaries of subjects with all adverse events, subjects with drug-related adverse events and subjects with serious adverse events will be produced. All summary tables will present the number and percentage of subjects with adverse events. The tables will be sorted by MedDRA System Organ Classes (SOCs), in descending order from the SOC with the highest total incidence (i.e., summed across all treatment groups) for any adverse event within the class, to the SOC with the lowest total incidence. Adverse events will be grouped by the Preferred Term (PT).

The association between the adverse event system organ class, preferred terms and the verbatim text will also be summarised.

A listing of the subjects reporting all adverse events and drug-related adverse events will be produced. The listing will include the number of events reported as well as the number of subjects reporting an event.

Listings of all adverse events, fatal serious adverse events, non-fatal serious adverse events, and drug-related adverse events will be produced.

11.3. Deaths and Serious Adverse Events

Any deaths and serious AEs will be summarized and listed as specified in Section 11.2.

11.4. Device Incidents and Near Incidents

Not applicable.

11.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Any adverse events leading to discontinuation of investigational product and/or withdrawal from the study will be summarized and listed as specified in Section 12.2.

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11.6. Pregnancies (as applicable)

A listing of subjects who become pregnant during the study will be provided.

11.7. Clinical Laboratory Evaluations

Laboratory data will be presented according to Clinical Pharmacology and Core IDSL guidelines. Urinalysis data will be presented according to Core IDSL guidelines. Clinical laboratory evaluations will be summarized and any values of potential clinical importance will be listed and summarized.

11.8. Other Safety Measures

Other safety measures will be listed and summarized. Listings and summaries of vital signs, ECG and vital signs and ECG changes from baseline will be produced. Vital sign and ECG data outside potential clinical importance range will be listed.

12. CLINICAL PHARMACOLOGY DATA ANALYSES

12.1. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department (CPMS), GlaxoSmithKline. Plasma concentration-time data of each analyte 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 following both single dose and repeat dose sessions, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC), and apparent terminal phase half-life (t1/2). AUC and Cmax following single and repeat doses may be used for assessment of metabolite to parent ratio. Trough concentration ($C\tau$) samples collected on the specified days will be used to assess attainment of steady state, as appropriate. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro), the predicted accumulation ratio (Rp), the steady-state accumulation ratio (Rs) and Cmax accumulation ratio (Rcmax) will be determined, as data permit.

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 Discovery Biometrics, GlaxoSmithKline.

$C\tau$ data will be presented graphically for visual assessment of steady state.

Descriptive statistics (n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum, CVb%) will be calculated for all metabolite to parent ratio by day.

Following loge-transformation, AUC and Cmax will be separately analyzed using a mixed effect model, fitting day as fixed effects and subject as a random effect. Point estimates and associated 90% confidence intervals for the comparison of interests will be constructed using the residual variance. The point estimates and associated 90% confidence intervals will then be exponentially back-transformed to provide point estimates and 90% confidence intervals for the ratios (e.g., Ro, Rs and Rcmax). Similar analysis will be done with day 1 AUC (0 - ∞) and AUC (0 - τ) data fitting PK parameter as fixed effect and subject as random effect to provide point estimate and 90% confidence intervals for the ratio of Rp.

The within-subject coefficients of variation (CVw) for AUC and Cmax will be calculated based on the loge –normal distribution.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of 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. Alternative analyses of the data will be performed if any of the model assumptions appear to be violated.

Descriptive statistics (n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum, CVb%) will be calculated for all pharmacokinetic endpoints by day.

In addition, for AUC (0-t), AUC (0 - ∞), AUC (0 - τ), Cmax, T½,and Cτ, geometric means and their 95% confidence intervals will be calculated.

12.2. Pharmacodynamic Analyses

Pharmacodynamic analyses will be the responsibility of Discovery Biometrics, GlaxoSmithKline.

Time course data for both plasma activity and percent inhibition of plasma activity from baseline will be descriptively and graphically summarized.

12.3. Pharmacokinetic/Pharmacodynamic Analyses

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

PK data will be analyzed with the use of the nonlinear mixed effects modeling program (NONMEM). During each step in the model building process, improvements to the model will be assessed by evaluation of the agreement between the observed and predicted plasma concentrations, reductions in the range of weighted residuals, uniformity of the distribution of the weighted residuals versus the predicted concentrations about the line of identity, and increases in the precision of the parameter estimates, as well as reduction of the terms for interindividual variability and random residual variability. Assessment of the log likelihood ratio test will also be conducted as a means of assessing improvement in the model.

Merged PK/PD analysis dataset will be provided by Discovery Biometrics.

13. REFERENCES

GlaxoSmithKline Document Number ZM2008/00108/00: A Study to Evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of DARAPLADIB and its Metabolites in Healthy Volunteers. Effective Date: 26-Aug-2008

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14. ATTACHMENTS

14.1. Table of Contents for Data Display Specifications

For PK Report:

1. Randomization Schedule of Intent and Actual Dosing (Not shown).
2. In-text table of Main Results for comparisons of interest.
3. Summary of Results of Statistical Analyses for Derived Pharmacokinetic comparisons.
4. Appendix of Statistical analysis details (not shown).
5. Data Listing and Summary Statistics of PK Parameters.
6. Data Listing and Summary Statistics of PK Concentration-Time Data
7. Mean and Median Plasma SB-480848 $C\tau$ Plot
8. Mock up of PK/PD dataset format for PK/PD modelling

For PD Report:

1. Summary Statistics for Plasma Lp-PLA2 Enzyme Activity and % Inhibition of Plasma Lp-PLA2 Parameters.
2. Listing of Plasma Lp-PLA2 Enzyme Activity and % Inhibition of Plasma Lp-PLA2 Enzyme Activity.
3. Mean (±SE) Plot for Lp-PLA2 Enzyme Activity and % Inhibition of Plasma Lp-PLA2 Enzyme Activity.

14.2. Standard Safety and Study Populations Displays

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Data Group	Report Section	Output order	HARP Display (Parallel Group)	Title	T/L/F
DM	A. Study Pop	9.2	DM1	Summary of Demographic Characteristics	Table
DM	A. Study Pop	9.5	DM6	Summary of Race and Racial Combination Details	Table
ES	A. Study Pop	9.4	ES4	Summary of Withdrawal Due to Adverse Events	Table
ES	A. Study Pop	9.1	ES1	Summary of Subject Disposition	Table
EX	B. Safety	10.1	EX1	Summary of Exposure to Study Drug	Table
AE	B. Safety	10.2	AE1	Summary of All Adverse Events	Table
AE	B. Safety	10.3	AE1	Summary of All Drug Related Adverse Events	Table
LB	B. Safety	10.4	LB1 (Core standard)	Summary of Chemistry/Haematology Data	Table
LB	B. Safety	10.6	UR1 (Core standard)	Summary of Urinalysis Data	Table
LB	D. ICH Specified Appendix	10.7	LB5 (Core standard) / LB2 (CP standard)	Listing of All Clinical Chemistry/Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	Table
EG	B. Safety	10.8	EG1	Summary of ECG Findings	Table
EG	B. Safety	10.9	EG1	Summary of ECG Values	Table
EG	D. ICH Specified Appendix	10.10	EG3	Listing of ECG Data for Subjects with Abnormalities of potential clinical importance	Table
EG	D. ICH Specified Appendix	10.11	EG3	Listing of ECG Values of Potential Clinical Importance	Table
VS	B. Safety	10.12	VS1	Summary of Vital Signs	Table
VS	B. Safety	10.13	VS1	Summary of Change from Baseline for Vital Signs	Table
VS	B. Safety	10.14	VS4	Listing of Vital Signs Data for Subjects with Abnormalities of potential clinical importance	Table
PK	C. Other Figures/Tables	11.1	PKHARP	Figure: Individual plots of Concentration vs Time	Figure
PK	C. Other Figures/Tables	11.2	PKHARP	Figure: Mean Concentration vs Time	Figure
PK	C. Other Figures/Tables	11.3	PKHARP	Figure: Median Concentration vs Time	Figure
PK	C. Other Figures/Tables	11.1	PKHARP	Table: PK Concentration-Time Summary	Table

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Data Group	Report Section	Output order	HARP Display (Parallel Group)	Title	T/L/F
DM	D. ICH Specified Appendix	9.1	DM9	Listing of Race	Listing
EX	D. ICH Specified Appendix	10.1	EX3	Listing of Exposure Data	Listing
ES	D. ICH Specified Appendix	9.2	ES2	Listing of Reasons for Withdrawal	Listing
IE	D. ICH Specified Appendix	9.3	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	Listing
DM	D. ICH Specified Appendix	9.4	DM2	Listing of Demographic Characteristics	Listing
CM	D. ICH Specified Appendix	9.5	CM5?	Listing of Concomitant Medications by Generic Terms	Listing
AE	D. ICH Specified Appendix	10.2	AE7	Listing of Subject Numbers for Individual Adverse Events	Listing
AE	D. ICH Specified Appendix	10.3	AE8	Listing of All Adverse Events	Listing
LB	D. ICH Specified Appendix	10.13	UR2a (Core standard)	Listing of Urinalysis Data	Listing
EG	D. ICH Specified Appendix	10.8	EG5	Listing of Abnormal ECG Findings only	Table
PK	E. Other Data Listings	11.1	PKHARP	Listing: PK Concentration-Time	Listing

Key:

ICH Required Table/Listing
Optional Table/listing

14.3. Data Display Specifications

Data Displays will be available upon request.

Synopsis

Identifier: ZM2009/00013/00 **Study Number:** LPL112498

Title: A Study to evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of Darapladib and its Metabolites in Healthy Volunteers

Investigator(s):

The study investigator was [redacted] MD

Study center(s):

The study was conducted at one center in the United States (US):

[redacted]

Publication(s):

There are no publications as of the date of this report.

Study period:

Initiation Date: 12 SEP 2008

Completion Date: 02 DEC 2008

Phase of development: I

Objectives:

Primary:

Characterize the pharmacokinetics of single and repeat oral doses of darapladib and its metabolites (M10, M3 and M4) in healthy adult subjects

Monitor the safety and tolerability of single and repeat oral doses of darapladib in healthy adult subjects

Secondary:

Evaluate the inhibition of plasma Lp-PLA_2 activity after repeat dosing of 160 mg of enteric-coat free base (micronised) darapladib

Methodology:

Data from a previous human ADME study (Study 015) showed that the principal radioactive component in all plasma samples following single and repeat oral administration was unchanged SB-480848 (darapladib). Five and eight metabolites were identified in plasma following single and repeat oral administration, respectively. Three noteworthy metabolites were observed in plasma, the result of hydroxylation of the cyclo penta pyrimidinone moiety (M3, SB-823094), N-deethylation (M4, SB-553253) and the formation of a uracil derivative following loss of the fluorobenzylthiol group (M10, SB-554008). M4, which is pharmacologically active, has been quantified in all preclinical toxicity studies, as well as in all clinical studies.

Darapladib is known to undergo acid hydrolysis, with the major acid degradant being M10. The clinical formulation of darapladib is enteric coated to minimize acid hydrolysis in the stomach. Formation of M10 following administration of the enteric coated formulation with food was likely to be substantially less than that observed in the human ADME study considering the radiolabelled [^{14}C]SB-480848 was formulated as a solution and administered with food in the human ADME study.

This study was designed to further assess the pharmacokinetics of darapladib and its metabolites (M10, M3 and M4) using the enteric coated formulation of darapladib and a newly developed sensitive LC/MS assay to quantify M10 and M3 following single and 28 days of repeat dosing of darapladib.

Number of subjects:

Twenty subjects were enrolled and 17 subjects completed the study, as planned. Refer to the table below for additional details of subject disposition.

Subject Disposition and Demographics:

Number of Subjects	LPL112498
Number of subjects planned, N:	10
Number of subjects entered, N:	20
Number of subjects included in All subjects (safety) population, n (%):	20
Number of subjects included in PK population, n (%):	20 (100%)
Number of subjects completed as planned, n (%):	17 (85%)
Number of subjects withdrawn (any reason), n (%):	3 (15%)
Number of subjects withdrawn for SAE, n (%):	0 (0%)
Number of subjects withdrawn for AE, n (%):	0 (0%)
Reasons for subject withdrawal, n (%)	
Withdrew consent	3 (15%)
Demographics	LPL112498
Age in Years, Mean (SD)	31.7 (11.4)
Sex, n (%)	
Female:	6 (30%)
Male:	14 (70%)
BMI (kg/m^2), Mean (SD)	25.6 (3.1)
Height (cm), Mean (SD)	174.1 (8.3)
Weight (kg), Mean (SD)	78.3 (15.1)
Ethnicity, n (%)	
Hispanic or Latino:	2 (10%)
Not Hispanic or Latino:	18 (90%)
Race, n (%)	
African American/African Heritage	3 (15%)
American Indian or Alaskan Native	1 (5%)
Asian – South East Asian Heritage	1 (5%)
White – White/Caucasian/European Heritage	14 (70%)
Mixed Race	1 (5%)

Diagnosis and main criteria for inclusion:

Healthy adult males and females aged 18 to 65, inclusive, and weighing ≥ 50 kg at screening with a body mass index within the range 19 – 30 kg/m^2 were eligible for this study.

Treatment administration:

All subjects were assigned to receive 160 mg of enteric coated micronized free-base darapladib as a single dose and as repeated daily doses for 28 days. All study medication was administered with food and tablets were swallowed whole. Darapladib 160 mg (batch number 081164493) was supplied by GlaxoSmithKline as enteric-coated, micronised free base, white round tablets.

Criteria for evaluation:

The primary safety endpoints were clinical safety data from spontaneous adverse event (AE) reporting, 12-lead electrocardiogram (ECG) recording, vital sign measurement, nursing/physician observation and clinical laboratory examination. The primary pharmacokinetic endpoints of interest were AUC and Cmax of darapladib and its metabolites (M10, M3 and M4) following single and repeat oral doses. Metabolite to parent AUC and Cmax ratio for each metabolite was calculated as data permitted.

The secondary PK endpoints of interest included tmax and half-life ($t_{½}$) of darapladib and its metabolites (M10, M3 and M4) as data permitted. An additional secondary endpoint was plasma Lp-PLA_2 activity, expressed in terms of percent inhibition relative to baseline, as data permitted.

Statistical and pharmacokinetic/pharmacodynamic analyses methods:

All safety, PK and PD data were listed and descriptively summarized as appropriate.

No formal inferential analysis of the safety data was performed. Safety endpoints, including clinical laboratory test results, AEs, 12-lead ECG parameters, and vital sign measurements were tabulated and listed by treatment.

The pharmacokinetics of darapladib, M3, M4 and M10 were assessed by determining AUC, Cmax, tmax, t1/2, and $C\tau$ following single and multiple dosing, as the data permitted. PK analyses of darapladib, M3, M4 and M10 plasma concentration-time data were conducted using noncompartmental methods.

Following $\log_e$-transformation, AUC and Cmax of darapladib and its metabolites M3, M4 and M10 were separately analyzed using a mixed effects model, fitting day as a fixed effect and subject as a random effect. Point estimates and associated 90% confidence intervals for the comparison of interests were constructed using the residual variance. The point estimates and associated 90% confidence intervals were then exponentially back-transformed to provide point estimates and 90% confidence intervals for the observed accumulation ratio (Ro), steady-state accumulation ratio (Rs), and maximum plasma concentration accumulation ratio (Rcmax). Similar analysis was done with day 1 AUC ($0 - \infty$) and AUC ($0 - \tau$) data fitting PK parameter as fixed effect and subject as random effect to provide point estimate and 90% confidence intervals for the predicted accumulation ratio (Rp). The within-subject coefficients of variation (CVw) for AUC and Cmax were calculated based on the $\log_e$ –normal distribution.

The observed accumulation ratio (Ro), the predicted accumulation ratio (Rp), the steady-state accumulation ratio (Rs) and Cmax accumulation ratio (Rcmax) were determined to estimate the extent of accumulation after repeat dosing.

The metabolite to parent ratios for both AUC and Cmax were summarized.

The relationship between darapladib plasma concentration and plasma Lp-PLA_2 activity data was explored graphically. Time course data for both plasma activity and percent inhibition of plasma activity from baseline was descriptively and graphically summarized.

Based on graphical assessment and historical data, a direct effect inhibitory Emax model was used to describe the pharmacokinetic/pharmacodynamic (PK/PD) relationship. The PK/PD model was parameterized for baseline plasma Lp-PLA_2 activity (Eo) and the plasma concentration of darapladib causing 50% inhibition of Lp-PLA_2 activity (IC_{50}). Sigmoid Emax model with the addition of Hill coefficient (γ) was also investigated. The PK/PD data were analyzed using Nonlinear Mixed Effect Modeling as implemented in the computer program NONMEM (Version V, level 1.0). The First- Order Conditional Estimation with interaction (FOCE-I) method was employed in the model development process.

The following criteria were used to compare and select different candidate models:

- A significant reduction in the objective function value (≥ 6.64, $\chi^2 < 0.01$) for FOCE-I based on the likelihood ratio test
- Increase in the precision of the estimated PK/PD parameters
- Decrease in the interindividual and/or residual errors
- Improvement in the fits of the diagnostic scatter plots (e.g., more random distribution in the weighted residual plots vs. predicted concentration and time plots; random distribution of the observed versus predicted concentrations values across the identity line)
- Model performance parameters (i.e., convergence of the minimization, termination of the covariance step without warning messages, and correlation between model parameters < 0.95)

There were no changes to the planned analyses.

Summary:

Safety:

There were no deaths, serious AEs (SAEs), or withdrawals due to AEs during the study. No clinically significant changes in laboratory, vital sign, or 12-lead ECG parameters were reported for any treatment regimen.

The most common AEs (occurring in greater than 2 subjects in a treatment group) are presented in the table below.

Preferred Term	Single Dose 160 mg darapladib N=20	Repeat Dose 160 mg darapladib N=20
	n (%)	n (%)
Subjects with Any AE	5 (25)	12 (60)
Subjects with AE related to investigational product	5 (25)	7 (35)
Most Common AEs (greater than 2 subjects in any treatment group):	Single Dose 160 mg darapladib N=20	Repeat Dose 160 mg darapladib N=20
	n (%)	n (%)
Diarrhoea	2 (10)	4 (20)
Headache	2 (10)	4 (20)
Fatigue	2 (10)	2 (10)
Abdominal Pain	0 (0)	2 (10)
Urine odour abnormal	2 (10)	0 (0)

Pharmacokinetics:

PK parameters for darapladib and its metabolites are summarized below.

Pharmacokinetic Parameters Following Single Oral Dose of 160 mg Enteric Coated Tablets of Micronized Free-base darapladib (SB-480848) in Healthy Volunteers

	AUC(0-t)		Cmax		Tmax
n = 20	ng•hr/mL	% Parent	ng/mL	% Parent	hr
SB-480848	456.1 (48.9%)	--	18.6 (65.3%)	--	9.0 (4.0 – 24.0)
SB-553253 (M4)	14.6[1] (82.7%)	3.2%[1] (1.2 – 5.4%)	1.6 (109.7%)	9.0% (3.3–15.2%)	7.5 (6.0 – 24.0)
SB-823094 (M3)	16.2[1] (83.7%)	3.6%[1] (1.2 – 7.6%)	2.0 (107.5%)	11.3% (4.5–17.8%)	9.0 (6.0 – 24.0)
SB-554008 (M10)	Not quantifiable				

AUC(0-t) and Cmax values are presented as geometric mean (CV%); Tmax presented as median (range); % Parent as mean (range);
1. n = 18

Pharmacokinetic Parameters Following 10-day Repeat Oral Doses of 160 mg Enteric Coated Tablets of Micronized Free-base darapladib (SB-480848) in Healthy Volunteers

	AUC(0-τ)		Cmax		Tmax
n = 19	ng•hr/mL	% Parent	ng/mL	% Parent	hr
SB-480848	362.2 (33.7%)	--	25.1 (38.9%)	--	9.0 (0.0 – 23.9)
SB-553253 (M4)	17.0 (51.0%)	4.9% (2.6 – 6.7%)	2.0 (69.0%)	8.8% (3.6–16.7%)	9.0 (4.1 – 23.9)
SB-823094 (M3)	20.2 (53.9%)	5.8% (3.1 – 9.1%)	2.7 (61.2%)	11.1% (6.5–19.6%)	9.0 (0.0 – 23.9)
SB-554008 (M10)	5.3 (41.4%)	1.5% (0.8 – 2.7%)	0.3 (41.0%)	1.1% (0.7 – 1.6%)	9.0 (0.0 – 23.9)

AUC(0-τ) and Cmax values are presented as geometric mean (CV%); Tmax presented as median (range); % Parent as mean (range)

Pharmacokinetic Parameters Following 28-day Repeat Oral Doses of 160 mg Enteric Coated Tablets of Micronized Free-base darapladib (SB-480848) in Healthy Volunteers

	AUC(0-τ)		Cmax		Tmax	t1/2
n = 19	ng•hr/mL	% Parent	ng/mL	% Parent	hr	hr
SB-480848	315.1 (40.5%)	--	17.5 (49.8%)	--	6.0 (0.5–12.0)	126.3 (29.7%)
SB-553253 (M4)	14.7 (59.2%)	4.8% (2.9-8.7%)	1.2 (99.3%)	7.5% (3.1-20.8%)	6.0 (0.0–12.0)	285.2[1] (25.2%)
SB-823094 (M3)	15.1 (73.5%)	5.1% (3.1-10.7%)	1.4 (105.6%)	8.7% (3.7-22.3%)	6.0 (0.0-9.0)	96.4[2] (27.9%)
SB-554008 (M10)	7.7 (34.8%)	2.5% (1.7-4.0%)	0.4 (36.2%)	2.2% (1.4-3.8%)	9.0 (0.0-12.2)	148.2[2] (36.6%)

AUC(0-τ) and Cmax values are presented as geometric mean (CV%); Tmax presented as median (range); % Parent as mean (range);

1. n = 15;
2. n = 16

Assessment of Accumulation for darapladib (SB-480848), SB-553253 (M4), and SB-823094 (M3) Plasma PK Parameters

Analyte	Parameter	Comparison	Ratio[1]	90% Confidence Interval	%CVw
SB-480848	Rcmax	Day 10 : Day 1	1.35	(1.08, 1.67)	41.76
		Day 28 : Day 1	0.94	(0.76, 1.17)	
	Ro	Day 10 : Day 1	2.39	(1.76, 3.25)	61.09
		Day 28 : Day 1	2.08	(1.53, 2.82)	
	Rp	Day 1 AUC(0-∞) : Day 1 AUC(0-τ)	3.70	(2.89, 4.72)	47.11
	Rs	Day 10 : Day 1	0.64	(0.55, 0.76)	30.40
		Day 28 : Day 1	0.56	(0.48, 0.66)	
SB-553253 (M4)	Rcmax	Day 10 : Day 1	1.29	(0.92, 1.80)	68.19
		Day 28 : Day 1	0.76	(0.54, 1.06)	
	Ro	Day 10 : Day 1	1.46	(1.17, 1.82)	36.22
		Day 28 : Day 1	1.27	(1.02, 1.58)	
SB-823094 (M3)	Rcmax	Day 10 : Day 1	1.35	(0.95, 1.91)	71.71
		Day 28 : Day 1	0.70	(0.49, 0.99)	
	Ro	Day 10 : Day 1	1.35	(1.03, 1.77)	46.85
		Day 28 : Day 1	1.01	(0.77, 1.33)	

1. Ratio: Adjusted geometric mean ratio

Conclusions:

The following can be concluded from this study:

- There were no deaths, SAEs or withdrawals due to AEs, and no clinically significant changes in laboratory, vital sign, or 12-lead ECG parameters in any subjects during the study.

- After single oral dose of enteric-coated darapladib at a dose level of 160 mg, darapladib was rapidly converted to M4 and M3. The mean metabolite to parent ratios for AUC(0-t) and Cmax were 3.2% and 9.0% for M4 and 3.6% and 11.3% for M3, respectively. No M10 was detected in any plasma sample following single oral dose of darapladib.

- After steady-state dosing of enteric-coated darapladib at a dose level of 160 mg for 28 days, M4, M3 and M10 were circulating in the plasma at low concentrations. The mean metabolite to parent ratios for AUC(0-τ) and Cmax were 4.8% and 7.5% for M4, 5.1% and 8.7% for M3, 2.5% and 2.2% for M10, respectively.

- Mean half-lives of darapladib, M4, M3 and M10 were 126, 285, 96 and 148 hour, respectively. Although the half-life of darapladib following 28-day sampling was longer than noted in previous studies, exposure following 28-day dosing is not higher than that following 10-day dosing and therefore, the longer half-life does not contribute significantly to the accumulation of darapladib beyond 10-day dosing.

- Modest accumulation was observed for darapladib in plasma following repeat daily dosing as shown by the observed accumulation ratios for AUC(0- τ) on Day 10 and Day 28 of 2.39 and 2.08, respectively. Consistent with historical data, darapladib appears to exhibit time-dependent pharmacokinetics as the observed accumulation was considerably less than that predicted from single dose pharmacokinetic data (3.70)

- Similar to the parent compound, M4 exhibited modest accumulation following repeat daily dosing of SB-480848. The accumulation of M3 was minimal. It was not possible to quantitate the accumulation of M10 as this metabolite was not present following single dose of darapladib.

- Inhibition of Lp-PLA_2 activity, measured by colorimetric assay method (CAM), (approximately 75%) was observed following repeat oral administration of darapladib. Levels of Lp-PLA_2 activity returned to baseline approximately 28 days after last dose.

- The PK/PD relationship between darapladib and plasma Lp-PLA_2 activity was described by a sigmoid inhibitory Emax model.

Date of Report:

June 2009

Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Pharmacology Protocol

Title:	A Study to Evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of Darapladib and its Metabolites in Healthy Volunteers.

Compound Number: SB-480848

Effective Date: 26-AUG-2008

Description: Darapladib (SB-480848) is a novel, selective and orally active inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) in development for the treatment of atherosclerosis.

This will be an open label study where each subject will participate in 2 study sessions, a Single Dose Session and a Repeat Dose Session. All subjects will receive 160 mg of EC micronized free-base darapladib as a single dose and as repeated daily doses for 28 days.

The purpose of this study is to characterize the pharmacokinetics of single and repeat oral doses of darapladib and its metabolites (M10, M3 and M4) in healthy adult subjects.

Subject: Healthy volunteer, SB-480848 metabolite characterization

Author(s): [redacted] (CSSO); [redacted] (MDC); [redacted] (DB); [redacted] (CPMS)

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SPONSOR SIGNATORY:

[redacted]
SVP, Drug Discovery

26 Aug 2008
Date

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Regulatory Agency Identifying Number(s): 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.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption Distribution Metabolism Elimination
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
β-hCG	Beta-Human Chorionic Gonadotropin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	Maximum observed concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case Report Form
CSSO	Clinical Science and Study Operations
CV	Coefficient of variance
DB	Discovery Biometrics
DMPK	Drug Metabolism and Pharmacokinetics
EC	Enteric coated
ECG	Electrocardiogram
4-FBCl	4-fluorobenzyl chloride
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
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)
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	intrauterine system
Kg	Kilogram
LDH	Lactate dehydrogenase
LDL	low density lipoprotein
Lp-PLA_2	lipoprotein-associated phospholipase A_2
Lyso-PC	lysophosphatidylcholine
MDC	Medicine Development Center
Mg	Milligrams
mL	Milliliters

MSDS	Material Safety Data Sheet
msec	Milliseconds
PAF	platelet-activating factor
PAF-AH	platelet-activating factor acetyl hydrolase
PD	Pharmacodynamic
PK	Pharmacokinetic
R_{Cmax}	Cmax accumulation ratio
R_o	Observed accumulation ratio
R_p	Predicted accumulation ratio
R_s	Steady-state accumulation ratio
RBC	Red blood cells
SAE	Serious adverse event(s)
SD	Standard deviation
SPM	Study Procedures Manual
T½	Half life
Tmax	Time of maximal plasma concentration
ULN	Upper limit of normal
WBC	White blood cells

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1. INTRODUCTION

1.1. Background

Darapladib (SB-480848) has potential for the treatment of atherosclerosis. The compound was selected on the basis of its potency and efficacy, both *in vitro* and *in vivo*, as an inhibitor of Lp-PLA_2 in animal models [GlaxoSmithKline Document Number RM2003/00513/01].

The sub-endothelial oxidation of low density lipoprotein (LDL) is a key process in atherosclerotic lesion development [Ross, 1999]. One of the earliest events in LDL oxidation is the hydrolysis of oxidatively modified phosphatidylcholine, generating lysophosphatidylcholine (lyso-PC) and oxidized fatty acids. This hydrolysis is mediated by lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an enzyme that is associated predominantly with LDL in human plasma [Tew, 1996]. Lp-PLA_2 is often referred to in the literature as platelet-activating factor acetyl hydrolase (PAF-AH), since it was first characterized as a plasma enzyme activity that hydrolysed exogenously added PAF. A significant body of evidence has accumulated in favor of both by-products, especially lyso-PC, being proinflammatory and proatherogenic mediators [Macphee, 1999]. Consistent with this notion are recent observations that plasma levels of Lp-PLA_2 represent an independent predictor of coronary heart disease [Packard, 2000; Garza, 2007].

Darapladib may prevent the accumulation of lyso-PC and other pro-inflammatory lipid by-products generated during the oxidation of LDL. Lyso-PC has several pro-atherogenic activities ascribed to it, including monocyte chemotaxis and induction of endothelial dysfunction, both of which facilitate monocyte-derived macrophage accumulation within the artery wall. Subsequently, an inhibitor of Lp-PLA_2 such as darapladib is predicted to inhibit intimal macrophage accumulation and cell death, therefore retard development of high risk atherosclerotic lesions [GlaxoSmithKline Document Number RM2003/00513/01].

Clinical experience with darapladib to date

To date, 23 Phase I studies have been completed, with 606 healthy volunteers and 34 asthmatic subjects exposed to at least 1 dose of darapladib. In four completed Phase II studies, 1051 patients have received darapladib for periods of up to 12 months, and 371 patients have received darapladib enteric coated tablets 160 mg once daily for 12 weeks or longer. [GlaxoSmithKline Document Number RM2003/00513/01]

Darapladib has been generally safe and well tolerated over the doses administered in the completed clinical pharmacology studies. The most frequently reported AEs in the completed clinical pharmacology studies included headache, abnormal urine (abnormal odor), diarrhoea and abdominal pain. There have been no SAEs or deaths considered related to study drug by the investigators. There have been no clinically significant treatment-related changes in laboratory values, vital signs (heart rate, systolic and diastolic blood pressure) or 12-lead ECG findings in healthy volunteer studies completed to date [GlaxoSmithKline Document Number RM2003/00513/01].

1.2. Rationale

1.2.1. Study Rationale

Data from the human ADME study (Study 015) showed that the principal radioactive component in all plasma samples following single and repeat oral administration was unchanged darapladib, SB-480848. Five and eight metabolites were identified in plasma following single and repeat oral administration, respectively. Three noteworthy metabolites were observed in plasma, the result of hydroxylation of the cyclo penta pyrimidinone moiety (M3, SB-823094), N-deethylation (M4, SB-553253) and the formation of a uracil derivative following loss of the fluorobenzylthiol group (M10, SB-554008). M4, which is pharmacologically active, has been quantified in all preclinical toxicity studies, as well as in all clinical studies. Safety coverage for this metabolite has been demonstrated. M10 and M3 were present in the circulation at very low levels (M10 at 6.4±4.3% and 9.0±2.5% and M3 at 5.9±3.2% and 7.5±3.1% of parent compound after single and repeat oral dosing respectively). M10 is human specific, while M3 is found in the dog, but not in the rat. The remaining metabolites included M9 (N-desethyl uracil), M14 (desfluorobenzylthiol), M22 (mono-oxygenated metabolite), and co-eluting M11 and M8 (unassigned), each accounting for 1% or less of the plasma radioactivity.

Darapladib is known to undergo acid hydrolysis, with the major acid degradant being M10. The clinical formulation of darapladib is enteric coated to minimize acid hydrolysis in the stomach. Formation of M10 following administration of the enteric coated formulation with food is likely to be substantially less than that observed in the human ADME study considering the radiolabelled [^{14}C]SB-480848 was formulated as a solution and administered with food in the human ADME study.

This study is thus designed to further assess the pharmacokinetics of darapladib and its metabolites (M10, M3 and M4) using the enteric coated formulation of darapladib and a newly developed sensitive LC/MS assay to quantify M10 and M3 following single and 28 days of repeat dosing of darapladib.

Additionally, in the Phase IIB dose ranging study (LPL104884), measurable concentrations of darapladib were observed in plasma samples taken at the follow-up visit (approximately 14-day post-last-dose) in >50% of patients. These data are not supported by the half-life estimates (approximately 25-45 hours) obtained from Phase I studies all of which had sampling durations of up to 96 hours post-dose. Extending the sampling duration to 28-day post-repeat-dose in this study will allow definitive estimation of the half-life of darapladib and its metabolites that are being quantified.

Plasma Lp-PLA$_2$ activity will also be analyzed to assess the time course of enzyme activity following repeat dosing and during the off-drug period.

1.2.2. Dose Rationale

The dose of the enteric-coated free base (micronised) darapladib tablet in this study is 160 mg. This was the dose studied in the recently completed IBIS II study and was the highest dose studied in the Phase IIB dose ranging study of darapladib. This dose and

formulation are also being progressed into Phase III. [GlaxoSmithKline Document Number RM2003/00513/01]

1.3. Summary of Risk Management

1.3.1. 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 RM2003/00513/01]. 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 breakfast 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 Investigator's Brochure [GlaxoSmithKline Document Number RM2003/00513/01].

1.3.2. Allergic Reaction

All of the side effects of darapladib may not be known. A recent study suggested that PAF (platelet activating factor) is positively correlated and PAF-AH (platelet activating factor acetylhydrolase) inversely correlated with anaphylaxis severity in patients with acute allergic reactions [Vadas, 2008]. A separate retrospective analysis in the same study 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. Therefore, subjects with a history of anaphylaxis, anaphylactoid reactions or severe allergic responses are excluded.

2. OBJECTIVE(S)

2.1. Primary

1. To characterize the pharmacokinetics of single and repeat oral doses of darapladib and its metabolites (M10, M3 and M4) in healthy adult subjects
2. To monitor the safety and tolerability of single and repeat oral doses of darapladib in healthy adult subjects

2.2. Secondary

1. To evaluate the inhibition of plasma Lp-PLA_2 activity after repeat dosing of 160 mg of enteric-coat free base (micronised) darapladib

3. ENDPOINT(S)

3.1. Primary

1. The primary PK endpoints will include AUC and Cmax of darapladib and its metabolites (M10, M3 and M4) following single and repeat oral doses. Metabolite to parent AUC and Cmax ratio for each metabolite will be calculated as data permit.
2. Clinical safety data (spontaneous AE reporting, vital signs, nursing/physician observation, and clinical laboratory tests) will be the primary safety endpoint.

3.2. Secondary

1. Secondary PK endpoints will include Tmax and T½ of darapladib and its metabolites (M10, M3 and M4) as data permit.
2. Plasma Lp-PLA_2 activity, expressed in terms of percent inhibition relative to baseline, as data permit.

4. INVESTIGATIONAL PLAN

4.1. Discussion of Design

This will be an open label study where each subject will participate in 2 study sessions, a Single Dose Session and a Repeat Dose Session. All subjects will receive 160 mg of EC micronized free-base darapladib as a single dose and as repeated daily doses for 28 days. There will be at least 4 days between dosing in the Single Dose Session and the first dose of the Repeat Dose Session due to the 96-hour PK sampling period following the single dose. PK samples will be collected over a 96-hour period after single dose in Session 1, and over a 24-hour period after Days 10 and 28 of repeat dosing, as well as over a 28-day duration following the last day of dosing of the repeat dose session. PD samples will be collected over a 24-hour period after Days 10 and 28 of repeat dosing, as well as over the 28-day duration following the last day of dosing of the repeat dose session.

Subjects will return approximately 28 days after the last dose of study medication for a follow-up visit. The total study duration for each subject including the screening, treatment and follow-up periods will be approximately 12 weeks.

4.2. Treatment Assignment

All subjects will be assigned to receive 160 mg of EC micronized free-base darapladib as a single dose and as repeated daily doses for 28 days.

4.3. Investigational Product Dosage/Administration

Product name:	darapladib
Dosage form:	Enteric coated , free base (micronized) tablet
Unit dose strength(s)/Dosage level(s):	160 mg
Route/ Administration/ Duration:	Route: oral Administered: daily Duration: Single dose, followed by 28 days of repeat dosing
Dosing instructions:	Take with food. Swallow whole, do not chew.
Manufacturer/ source of procurement:	GSK

4.3.1. Dose Adjustment/Stopping Safety Criteria

4.3.1.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of investigational product and the follow-up period. Although routine safety assessments in this study will only be done at the screening and follow-up visits (see Section 4.4), the criteria below is being included in the case of any unscheduled assessments. Investigational product will be stopped if either of the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (> 35% direct)
- ALT ≥ 3xULN

Refer to Section 13, Liver Chemistry Testing Procedures, for details of the required assessments if a subject meets either of the above criteria (the required assessments differ for each of the criteria).

4.3.1.2. QTc Withdrawal Criteria

The only planned ECG measures in this study are at the screening visit and follow-up visits (see Section 4.4). However in the case of an unscheduled ECG, a subject that meets the criteria below will be withdrawn from the study.

- QTcB or QTcF > 500 msec (machine or manual overread)
- If subject has bundle branch block then criteria is QTcB or QTcF > 530 msec

These criteria are based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

4.4. Time and Events Table

Procedure	Screening (up to 30 days prior to Day 1)	Study Day (each dosing session)																		
		Day -1	Day 1														Day 2		Day 3	Day 4
			Pre-dose	0 h	0.5 h	1 h	2 h	3 h	4 h	6 h	9 h	10 h	12 h	18 h	24 h		32 h	48 h	72 h	96 h
Admission to Unit		X																		
Informed Consent	X																			
Demographics	X																			
Full Physical Exam	X																			
Brief Physical Exam		X																		
Medical/medication/ drug/alcohol history	X																			
12-lead ECG	X																			
Vital signs	X	X	X															X		
Urine Drug/Alcohol	X	X																		
Serum β-hCG (women)	X	X																		
Hema/Chem/Urinalysis tests	X	X																X		
Meal		X	X							X		X			X		X			
Dosing				X																
Pharmacokinetic Sampling			X		X	X	X	X	X	X	X		X	X	X		X	X	X	X
Pharmacodynamic Sampling			X																	
Adverse Event Review[1]			X						X			X			X		X	X	X	X
Concomitant Medication Review		X	X															X	X	X
Discharge																		X		
Outpatient Visit	X																		X	X

1. AEs will NOT be noted until after the first dose of study drug

REPEAT DOSE PORTION OF STUDY

Day:	RD 1	RD 2	RD 3	RD 4	RD 5	RD 6	RD 7	RD 8	RD 9	RD10	RD11	RD12	RD13	RD14	RD15	RD16	RD17	RD18	RD19	RD20	RD21	RD22	RD23	RD24	RD25	RD26	RD27	RD28
Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient stay									X	X																	X	X
Outpatient visit	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Discharge											X																	
Vital signs														X														X
AE assessment	Ongoing																											
Con.Medication Review	Ongoing																											
Meal served	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sample										X[1]																X[2]	X[2]	X[1]
PD blood sample										X[1]																		X[1]

PK/PD SAMPLING AFTER LAST REPEAT DOSE:

Day:	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	Follow-up
Outpatient visit		X	X	X	X	X	X			X			X			X			X			X			X			X	X
PK blood sample[3]	X	X	X	X	X	X	X			X			X			X			X			X			X			X	
PD blood sample[3]	X	X	X	X	X	X	X			X			X			X			X			X			X			X	
Discharge	X																												
12-lead ECG																													X
Vital signs																													X
Serum β-hCG (women)																													X
Hema/Chem/Urinalysis tests																													X
AE assessment														X															X
Con.Medication Review														X															X

1. Samples will be obtained at 0, 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24 hours post dose
2. Day 26 and Day 27 of repeat dosing require trough PK samples
3. After LAST day of repeat dosing PK and PD samples will be obtained at 32, 48, 72, 96, 120, 144, 168, 240, 312, 384, 456, 528, 600 and 672 hours post-dose

5. STUDY POPULATION

5.1. Number of Subjects

A sufficient number of subjects will be enrolled so that at least 10 subjects complete the study. Only subjects who the primary or sub-investigators believe will be able to comply with the requirements of the protocol should be included in the study.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

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

1. Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and ECG. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the Investigator and the GSK Medical Monitor agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
2. Male or female between 18 and 65 years of age inclusive, at the time of signing the informed consent.
3. 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; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MlU/ml and estradiol < 40 pg/ml (<140 pmol/L) is confirmatory].
    - Child-bearing potential and agrees to use one of the contraception methods listed in Section 8.1 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 follow-up visit.
4. Body weight ≥ 50 kg and BMI within the range 19 – 30 kg/m^2 (inclusive).
5. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
6. QTcB or QTcF < 450 msec; or QTc < 480 msec in subjects with Bundle Branch Block.

5.2.2. Exclusion Criteria

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

1. A positive pre-study drug/alcohol screen.
2. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening
3. A positive test for HIV antibody.
4. 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.
5. 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).
6. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
7. 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.
8. Consumption of grapefruit or grapefruit juice within 7 days prior to first dose of study medication.
9. History of drug abuse.
10. History of sensitivity to any of the study medications, 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.
11. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions (refer to Appendix 2: Clinical criteria for diagnosing anaphylaxis [Sampson, 2006]), or severe allergic responses.
12. History of cholecystectomy or biliary tract disease, or a history of liver disease with elevated liver function tests of known or unknown etiology.
13. History of sensitivity to heparin or heparin-induced thrombocytopenia (if heparin is to be used for flushing a cannula).
14. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.
15. Use of oral, injected and implanted hormonal methods of contraception for female subjects.

16. Pregnant females as determined by positive serum hCG test at screening or prior to dosing.
17. Lactating females.
18. Unwillingness or inability to follow the procedures outlined in the protocol.
19. Subject is mentally or legally incapacitated.

5.2.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study:

- Investigator Brochure, Version 04 [GlaxoSmithKline Document Number RM2003/00513/01]

6. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

6.1. Hypotheses and Treatment Comparisons

No formal hypotheses will be tested.

For the planned pharmacokinetic analysis, the pharmacokinetic parameters of SB-480848 (parent), SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) on Day 10 and Day 28 (Period 2) will be compared to those on Day 1 (Period 1) separately. The comparisons of interest will be expressed as the accumulation ratios (Ro, Rp, Rs and Rcmax), as the data permit. For each metabolite, AUC and Cmax metabolite to parent ratio will be calculated on each day (Day 1 Period 1 and Days 10 and 28 Period 2).

For the planned pharmacodynamic analysis, percent inhibition of plasma Lp-PLA_2 activity will be calculated and summarized at each time point.

6.2. Sample Size Considerations

6.2.1. Sample Size Assumptions

Sample size is based on feasibility. Based on study SB480848/015, the maximum within subject standard deviation (SD) for metabolite to parent ratio is 3.1%. Assuming similar variability of metabolite to parent ratio in current study, the half width of 90% confidence interval (CI) of metabolite to parent ratio will be about 1.8%. Based on study LPL107988, the CVw% for SB-480848 Cmax is 26.0%, and the CVw% for AUC is 18.3%. Based on the CVs and 10 subjects, the half width of 90% CI for Rcmax will be within 22.4% of point estimate and for Ro, Rp and Rs will be within 15.1% of point estimate.

6.2.2. Sample Size Sensitivity

6.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

6.3. Data Analysis Considerations

6.3.1. Analysis Populations

Safety: All subjects who receive at least one dose of darapladib will be included in the Safety Population.

Pharmacokinetic: All subjects who receive at least one dose of darapladib and provide evaluable pharmacokinetic data will be included in the formal statistical analysis of the pharmacokinetic data. The impact of subjects with incomplete data will be evaluated, as appropriate.

Pharmacodynamic: Subjects will be included in the summary statistics if they provide sufficient data to calculate percent inhibition of plasma Lp-PLA_2 activity, i.e. provide data from baseline and at least one post-dose sample.

6.3.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GlaxoSmithKline. Plasma concentration-time data of each analyte 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 following both single dose and repeat dose sessions, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC), and apparent terminal phase half-life (t1/2). AUC and Cmax following single and repeat doses may be used for assessment of metabolite to parent ratio. Trough concentration (C24) samples collected on the specified days will be used to assess attainment of steady state, as appropriate. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro), the predicted accumulation ratio (Rp), the steady-state accumulation ratio (Rs) and Cmax accumulation ratio (Rcmax) will be determined, as data permit.

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 Discovery Biometrics, GlaxoSmithKline. Details of the planned statistical analyses will be provided in the Reporting and Analysis Plan.

6.3.3. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic analysis is the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GlaxoSmithKline. Details of the planned pharmacokinetic/pharmacodynamic analysis will be provided in the Reporting and Analysis Plan.

6.3.4. Pharmacodynamic/Biomarker Analyses

Statistical analyses of the pharmacodynamic data (plasma Lp-PLA_2 activity) will be the responsibility of Discovery Biometrics, GlaxoSmithKline.

Percent inhibition of plasma Lp-PLA_2 activity will be derived and then summarized at each time point. Lp-PLA2 activity and percent inhibition profile will be graphically presented.

Details of the planned statistical analyses will be provided in the Reporting and Analysis Plan.

7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 4.4). Detailed procedures for obtaining each assessment are provided in the Study Procedures Manual (SPM). Whenever vitals 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.

7.1. Demographic/Medical History Assessments

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

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 5.2.

7.2. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 4.4). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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).

Vital Signs

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

Electrocardiogram (ECG)

- 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 QTc intervals. Refer to Section 4.3.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

Clinical Laboratory Assessments

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Other tests

HIV
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result)
FSH and estradiol (as appropriate)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

7.3. Pregnancy

7.3.1. Time period for collecting pregnancy information

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

7.3.2. 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 (see AE/SAE section of the protocol and the SPM for definitions and a description of follow-up).

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 investigational product by the investigator, will be reported to GSK as described in Section 12. 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.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic analysis of darapladib, SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) will be collected at the time points indicated in Section 4.4, Time and Events Table. 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.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM).

7.4.2. Sample Analysis

Plasma sample analysis will be performed under the management of Worldwide Bioanalysis, DMPK, GlaxoSmithKline. Concentrations of darapladib, SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline. Once the plasma has been analyzed for darapladib, SB-553253 (M4), SB-554008 (M10) and SB-823094 (M3) any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol.

7.5. Biomarker(s)/Pharmacodynamic Markers

7.5.1. Blood Sample Collection

Blood samples for pharmacodynamic analysis of Lp-PLA_2 activity will be collected at the time points indicated in Section 4.4, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PD samples may be altered and/or PD samples may be obtained at additional time points to ensure thorough PD monitoring.

Details of PD blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM).

7.5.2. Assay Methodology

Plasma samples will be assayed for Lp-PLA_2 activity using an approved method under the management of GlaxoSmithKline Pharmaceuticals.

8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

8.1. Contraception Requirements

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%.

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%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% effectiveness criteria as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

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.

8.2. 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 must abstain from ingestion of alcohol and caffeine- or xanthine-containing products 24 hours prior to first dose until collection of the final blood sample in the study
- Subjects will not be allowed to drink grapefruit juice or eat grapefruit within 7 days prior to first dose until collection of the final blood sample in the study
- Water may be consumed ad libitum beginning 2 hour 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 at approximately 6 and 10 hours after dosing respectively. An evening snack will be permitted up to 2200 hours.
- A standard breakfast will be provided and given approximately 1 hour before dosing at each of the outpatient visits

8.3. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Permitted Medications

Occasional use of paracetamol or acetaminophen at doses of ≤ 2 grams/day may be acceptable, at the discretion of the Principal Investigator or his/her designee. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

9.2. Prohibited Medications

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. The investigator must be informed as soon as possible about any medication taken from the time of screening until completion of follow-up procedures.

Use of oral, injected and implanted hormonal methods of contraception for female subjects is prohibited.

10. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

10.1. Subject Completion

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

10.2. Subject Withdrawal Criteria

A subject may withdraw from investigational product 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.

10.3. Subject Withdrawal Procedures

10.3.1. Subject Withdrawal from Study/Investigational Product

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

10.4. Treatment After the End of the Study

Subjects will not receive any additional treatment after completion of the study because only healthy volunteers are eligible for study participation.

10.5. Screen and Baseline Failures

Data for screen and baseline failures will not be collected.

11. INVESTIGATIONAL PRODUCT(S)

Investigational product dosage and administration details are listed in Section 4.3.

11.1. Blinding

This will be an open-label study.

11.2. Packaging and Labeling

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

11.3. Preparation/Handling/Storage/Accountability

No special preparation of investigational product is required.

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff. Investigational product is to be stored up to 30°C (86°F) and protected from light and moisture.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. The investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of investigational product received from and returned to GSK and the amount supplied to and returned by subjects. The required accountability unit for this study will be tablet. Discrepancies are to be reconciled or resolved.

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.

11.4. Assessment of Compliance

When subjects are dosed at the study site, they will receive investigational products 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 investigational product(s) 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 investigational product. Study site personnel will examine each subject's mouth to ensure that the investigational product was ingested.

11.5. Treatment of Investigational Product Overdose

For this study, any dose of SB-480848 > 160 mg within a 24 hour time period [± 1 hour] will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

12. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

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

AEs will be collected from the start of Investigational Product and until the follow-up contact. Medical occurrences that begin prior to the start of investigational product 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. investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.7.

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 investigational product or study participation, the investigator would promptly notify GSK.

12.1. 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 investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

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.

12.2. Definition of Serious Adverse Events

If an event is not an AE per Section 12.1, then it can not 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.

12.3. 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?"

12.4. 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 of 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.

12.5. Evaluating AEs and SAEs

12.5.1. 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 pre-defined outcomes as described in the definition of an SAE.

12.5.2. Assessment of Causality

The investigator is obligated to assess the relationship between investigational product 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 investigational product 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.

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.

12.6. 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.

12.7. 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 Section 12.5.2, Assessment of Causality.

The primary mechanism for reporting SAEs to GSK will be the electronic data collection tool (e.g., InForm system). 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 both the GSK Medical Monitor and protocol contact. 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.

12.8. 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.

13. LIVER CHEMISTRY TESTING PROCEDURES

Refer to the diagram in Appendix 1 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 4.3.1.1:

- Immediately and permanently withdraw the subject from investigational product
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject's investigational product 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 12.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with investigational product.

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 bilirubin ≥1.5xULN:

- 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.

In addition, for all subjects with ALT ≥3xULN, 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 (if subject resides outside the USA or Canada, or has traveled outside USA or Canada in past 3 months).

- Blood sample for pharmacokinetic (PK) analysis. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose can not be approximated OR a PK sample can not be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 1.5xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant 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 ≥3xULN **and** bilirubin ≥1.5xULN but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

14. STUDY CONDUCT CONSIDERATIONS

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

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

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

The study will also be conducted in accordance with "good clinical practice" (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2004 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)

14.2. 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

14.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

14.4. 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. 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.

14.5. 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.

14.6. Provision of Study Results and Information to Investigators

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, GSK will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the subjects, as appropriate. In addition, the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at a GSK site or other mutually agreeable location.

14.7. Data Management

GSK Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets which support the protocol objectives. Subject data will be entered into GSK defined CRFs and combined with data provided from other sources (e.g. diary data, laboratory data) in a validated data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events and concomitant medications terms will be coded using validated dictionaries. Original CRFs will be retained by GSK, while the investigator will retain a copy. In all cases, subject initials will not be collected nor transmitted to GSK.

15. REFERENCES

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GlaxoSmithKline Document Number RM2003/00513/01. SB-480848 Darapladib Investigator's Brochure Version 04. Effective date: 25-Apr-2008

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Packard CJ, O'Reilly DJ, Caslake MJ et al. Lipoprotein associated phospholipase A_2 as an independent predictor of coronary heart disease. *New Eng J Med.*, 2000; 343:1148-1155.

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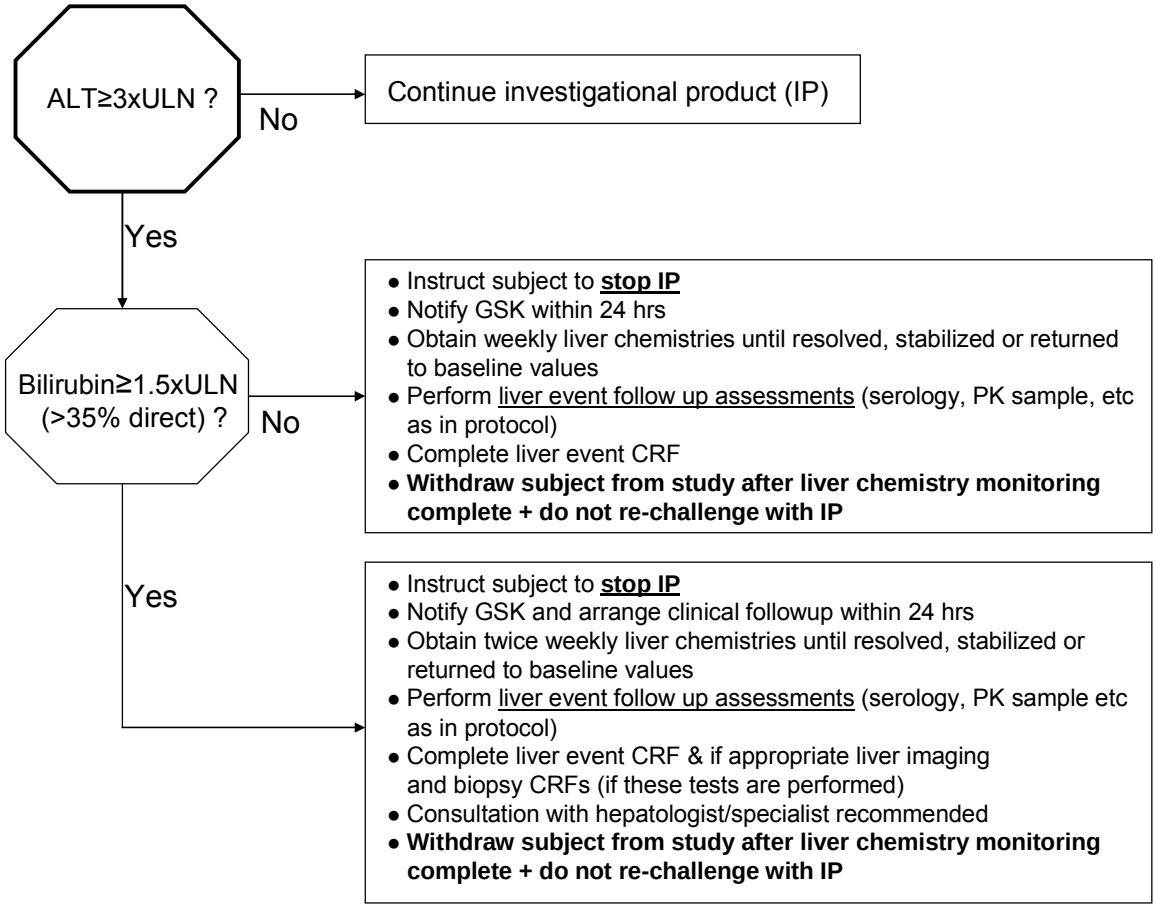
APPENDICES

APPENDIX 1: LIVER SAFETY ALGORITHMS



APPENDIX 2: CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS [SAMPSON, 2006]

Anaphylaxis is likely when any <u>one</u> of the following 3 criteria is fulfilled.

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (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 <u>likely</u> 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[1]

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

1. 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.

Annotated Design For Trial: lpl112498_128

Protocol: LPL112498

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September 16, 2008 8:10PM

lpl112498_128 : INFORM SCREENING (SCREEN)		
INFORM SCREENING		
1.*	Subject initials [*hidden*]	A3 (MAPPINGS1:t_SCREEN.txtScrSINIT)
2.	Date of birth	Req / Req / Req (1900-2009) (MAPPINGS1:t_SCREEN.BIRTHDT)
* Item is not required		

Form Design Note:
Trial designers must use this form as specified here. Allowed changes are mentioned in the particular item level notes.

Item Design Notes:	
Item No.	**Design Note**
1.	This item is hidden to all users and will be autopopulated by the system as "---"
2.	Will be automatically mapped to demography form from screening form

CDD: MAPPINGS1 Table: t_SCREEN Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
txtScrSINIT	STRING(3) - A3	
BIRTHDT	DATE - DDMONYYYY	

lpl112498_128 : INFORM ENROLMENT (ENROL)			
SUBJECT NUMBER			
1.	Subject number	A6	(MAPPINGS1:t_ENROL.mtxtSubjectNumber)

CDD: MAPPINGS1 Table: t_ENROL Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
mtxtSubjectNumber	STRING(6) - A6	

lpl112498_128 : DATE OF VISIT (DoV)

Adverse Events/Concomitant Medications
» Record details of any new serious adverse event or any changes to ongoing serious adverse events in the SAE form in the Logs/Rpts visit.
» From visit S1D1 onwards, record details of any new non-serious adverse event or any changes to ongoing non-serious adverse events in the appropriate AE form in the Logs/Rpts visit
» Record any changes to the subject's concomitant medication or any new medication taken since the last visit in the Con Meds form in the Logs/Rpts visit.

DATE OF VISIT/ASSESSMENT

1.	Date of visit/assessment	Req / Req / Req (2008- 2009) (MAPPINGS1:t_VISIT.DOV)

CDD: MAPPINGS1 Table: t_VISIT Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
DOV	DATE - DDMONYYYY	

lpl112498_128 : DEMOGRAPHY (Demog)		
DEMOGRAPHY		
1.	Date of birth	Req / Req / Req (1900- 2009) (MAPPINGS1:t_DEMO.BIRTHDT)
2.	Sex	(MAPPINGS1:t_DEMO.SEX) *[M]* Male **[F]** (MAPPINGS1:t_DEMO.CHDPOTCD) Female : Record child-bearing potential *[1]* Pre-menarcheal *[2]* Post-menopausal *[3]* Sterile (of child-bearing age) *[4]* Potentially able to bear children
3.	Ethnicity	(MAPPINGS1:t_DEMO.ETHNICCD) *[1]* Hispanic or Latino *[2]* Not Hispanic or Latino
4.	Geographic ancestry	Check all that apply (MAPPINGS1:t_DEMO.RACECCD11) *[11]* African American/African Heritage (MAPPINGS1:t_DEMO.RACECCD12) *[12]* American Indian or Alaskan Native (MAPPINGS1:t_DEMO.RACECCD13) *[13]* Asian - Central/South Asian Heritage (MAPPINGS1:t_DEMO.RACECCD14) *[14]* Asian - East Asian Heritage (MAPPINGS1:t_DEMO.RACECCD15) *[15]* Asian - Japanese Heritage (MAPPINGS1:t_DEMO.RACECCD16) *[16]* Asian - South East Asian Heritage (MAPPINGS1:t_DEMO.RACECCD17) *[17]* Native Hawaiian or Other Pacific Islander (MAPPINGS1:t_DEMO.RACECCD18) *[18]* White - Arabic/North African Heritage (MAPPINGS1:t_DEMO.RACECCD19) *[19]* White - White/Caucasian/European Heritage

Item Design Notes:	
Item No.	**Design Note**
1.	Will be automatically mapped to demography form from screening form

CDD: MAPPINGS1 Table: t_DEMO Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
BIRTHDT	DATE - DDMONYYYY	
SEX	STRING(1)	
CHDPOTCD	STRING(1)	
ETHNICCD	STRING(1)	
RACECCD11	STRING(255)	
RACECCD12	STRING(255)	
RACECCD13	STRING(255)	
RACECCD14	STRING(255)	
RACECCD15	STRING(255)	
RACECCD16	STRING(255)	
RACECCD17	STRING(255)	

RACECCD18	STRING(255)	
RACECCD19	STRING(255)	

lpl112498_128 : VITAL SIGNS (VS)

Screening (seated)

1.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_A_SCR.VSACTDTTM) Req : Req *24-hour clock*
2.	Height	xxx (n >= 0) cm (MAPPINGS1:t_VITALS_A_SCR.HEIGHT)
3.	Weight	xxx.x (n >= 0.0) kg (MAPPINGS1:t_VITALS_A_SCR.WEIGHT)
	Body mass index	(MAPPINGS1:t_VITALS_A_SCR.VSBMI)
4.	Blood pressure	xxx (n >= 0) / (MAPPINGS1:t_VITALS_A_SCR.SYSBP) xxx (n >= 0) mmHg (MAPPINGS1:t_VITALS_A (systolic/diastolic)
5.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_A_SCR.HEART)

Form Design Note:
Screening vital signs

Item Design Notes:

Item No.	Design Note
itmVSBMI	Item to be calculated as: Weight in kilograms divided by the square of height in meters

CDD: MAPPINGS1 Table: t_VITALS_A_SCR Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
VSACTDTTM	DATE - DDMONYYYY HHMM	
HEIGHT	NUMERIC - N3	
WEIGHT	FLOAT - F5.1	
VSBMI	STRING(255)	
SYSBP	NUMERIC - N3	
DIABP	NUMERIC - N3	
HEART	NUMERIC - N3	

lpl112498_128 : 12-LEAD ECG (ECG)		
Screening		
1.	Date and Time of ECG Hr:Min (00:00-23:59)	Req / Req / Req (2008- 2009) (MAPPINGS1:t_ECG_A_SCR.EGDTTM) Req : Req *24-hour clock*
2.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_ECG_A_SCR.EGHR)
3.	PR Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_A_SCR.PR__)
4.	QRS Duration	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_A_SCR.QRS__)
5.	Uncorrected QT Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_A_SCR.QT__)
6.	QTc Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_A_SCR.QTC__)
7.	Method of QTc Calculation	(MAPPINGS1:t_ECG_A_SCR.EGMTCLCD) *[1]* ◯ Machine *[2]* ◯ Manual
8.	Result of the ECG	(MAPPINGS1:t_ECG_A_SCR.EGINTPCD) *[1]* ◯ Normal *[2]* ◯ Abnormal - Not clinically significant *[3]* ◯ Abnormal - Clinically significant *(complete the ECG abnormality form for all clinically significant abnormalities, and additionally complete the AE form if the abnormality meets the protocol definition for an AE)* *[4]* ◯ No result (not available)

Form Design Note:
Screening ECG

CDD: MAPPINGS1	Table: t_ECG_A_SCR	Key Type: PATIENTVISIT
Column Name	**Column Data Type**	**Design Note**
EGDTTM	DATE - DDMONYYYY HHMM	
EGHR	NUMERIC - N3	
PR__	FLOAT - F6.0	
QRS__	FLOAT - F6.0	
QT__	FLOAT - F6.0	
QTC__	FLOAT - F6.0	
EGMTCLCD	STRING(1)	
EGINTPCD	STRING(1)	

lpl112498_128 : ELECTRONICALLY TRANSFERRED LAB DATA (Lab)		
Screening		
1.	Haematology Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_A.rdcLABDTTM) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_A.LBDTTM1) Req : Req *24-hour clock* *[ND]* ◯ Not Done
2.	Clinical Chemistry Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_A.rdcLABDTTM1) *[-98]* ◯ Same as the Haematology sample **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_A.LBDTTM2) Req : Req *24-hour clock* *[ND]* ◯ Not Done
3.	Urinalysis Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_A.rdcLABDTT1) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_A.LBDTTM3) Req : Req *24-hour clock* *[ND]* ◯ Not Done

Form Design Note:
Screening

Section Design Notes:	
Title	**Design Note**
Screening	If only one sample date and time is needed for all lab tests performed remove the last two items and modify the text of the first item

Item Design Notes:	
Item No.	**Design Note**
1.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.
2.	Time is optional. Use this item for all other samples on the form
3.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.

CDD: MAPPINGS1 Table: t_LABLINK_X1_A Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
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rdcLABDTTM1	STRING(3)	
LBDTTM2	DATE - DDMONYYYY HHMM	
rdcLABDTT1	STRING(3)	
LBDTTM3	DATE - DDMONYYYY HHMM	

lpl112498_128 : ELIGIBILITY QUESTION (ELIG)

ELIGIBILITY QUESTION

1.	Did the subject meet all the entry criteria?	(MAPPINGS1:t_ELIG.IEELIG) *[Y]* ○ Yes **[N]** ○ No, please select all boxes corresponding to violations of any inclusion/exclusion criteria **Inclusion Criteria** (MAPPINGS1:t_ELIG.IECRTNUMI01) *[I01]* ☐ Inclusion Criteria 1 (MAPPINGS1:t_ELIG.IECRTNUMI02) *[I02]* ☐ Inclusion Criteria 2 (MAPPINGS1:t_ELIG.IECRTNUMI03) *[I03]* ☐ Inclusion Criteria 3 (MAPPINGS1:t_ELIG.IECRTNUMI04) *[I04]* ☐ Inclusion Criteria 4 (MAPPINGS1:t_ELIG.IECRTNUMI05) *[I05]* ☐ Inclusion Criteria 5 (MAPPINGS1:t_ELIG.IECRTNUMI06) *[I06]* ☐ Inclusion Criteria 6 **Exclusion Criteria** (MAPPINGS1:t_ELIG.IECRTNUME01) *[E01]* ☐ Exclusion Criteria 1 (MAPPINGS1:t_ELIG.IECRTNUME02) *[E02]* ☐ Exclusion Criteria 2 (MAPPINGS1:t_ELIG.IECRTNUME03) *[E03]* ☐ Exclusion Criteria 3 (MAPPINGS1:t_ELIG.IECRTNUME04) *[E04]* ☐ Exclusion Criteria 4 (MAPPINGS1:t_ELIG.IECRTNUME05) *[E05]* ☐ Exclusion Criteria 5 (MAPPINGS1:t_ELIG.IECRTNUME06) *[E06]* ☐ Exclusion Criteria 6 (MAPPINGS1:t_ELIG.IECRTNUME07) *[E07]* ☐ Exclusion Criteria 7 (MAPPINGS1:t_ELIG.IECRTNUME08) *[E08]* ☐ Exclusion Criteria 8 (MAPPINGS1:t_ELIG.IECRTNUME09) *[E09]* ☐ Exclusion Criteria 9 (MAPPINGS1:t_ELIG.IECRTNUME10) *[E10]* ☐ Exclusion Criteria 10 (MAPPINGS1:t_ELIG.IECRTNUME11) *[E11]* ☐ Exclusion Criteria 11 (MAPPINGS1:t_ELIG.IECRTNUME12) *[E12]* ☐ Exclusion Criteria 12 (MAPPINGS1:t_ELIG.IECRTNUME13) *[E13]* ☐ Exclusion Criteria 13 (MAPPINGS1:t_ELIG.IECRTNUME14) *[E14]* ☐ Exclusion Criteria 14 (MAPPINGS1:t_ELIG.IECRTNUME15) *[E15]* ☐ Exclusion Criteria 15 (MAPPINGS1:t_ELIG.IECRTNUME16) *[E16]* ☐ Exclusion Criteria 16 (MAPPINGS1:t_ELIG.IECRTNUME17) *[E17]* ☐ Exclusion Criteria 17 (MAPPINGS1:t_ELIG.IECRTNUME18) *[E18]* ☐ Exclusion Criteria 18 (MAPPINGS1:t_ELIG.IECRTNUME19) *[E19]* ☐ Exclusion Criteria 19

Form Design Note:
IDSL Version 02.00A - 22 NOV 06

CDD: MAPPINGS1 Table: t_ELIG Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
IEELIG	STRING(1)	
IECRTNUMI01	STRING(255)	
IECRTNUMI02	STRING(255)	
IECRTNUMI03	STRING(255)	
IECRTNUMI04	STRING(255)	
IECRTNUMI05	STRING(255)	
IECRTNUMI06	STRING(255)	
IECRTNUME01	STRING(255)	
IECRTNUME02	STRING(255)	
IECRTNUME03	STRING(255)	
IECRTNUME04	STRING(255)	
IECRTNUME05	STRING(255)	
IECRTNUME06	STRING(255)	
IECRTNUME07	STRING(255)	
IECRTNUME08	STRING(255)	
IECRTNUME09	STRING(255)	
IECRTNUME10	STRING(255)	
IECRTNUME11	STRING(255)	
IECRTNUME12	STRING(255)	
IECRTNUME13	STRING(255)	
IECRTNUME14	STRING(255)	
IECRTNUME15	STRING(255)	
IECRTNUME16	STRING(255)	
IECRTNUME17	STRING(255)	
IECRTNUME18	STRING(255)	
IECRTNUME19	STRING(255)	

lpl112498_128 : SUBJECT IDENTIFICATION (Subj ID)			
SUBJECT NUMBER			
1.	Subject number	A6	(MAPPINGS1:t_SUBID.mtxtSubjectNumber)

CDD: MAPPINGS1 Table: t_SUBID Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
mtxtSubjectNumber	STRING(6) - A6	

lpl112498_128 : VITAL SIGNS (VS)		
Day -1 (seated)		
1.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_X1_A.VSACTDTTM) Req : Req *24-hour clock*
2.	Blood pressure	xxx (n >= 0) / (MAPPINGS1:t_VITALS_X1_A.SYSBP) xxx (n >= 0) mmHg (MAPPINGS1:t_VITALS_X1 (systolic/diastolic)
3.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_X1_A.HEART)

Form Design Note:
S1D-1

CDD: MAPPINGS1 Table: t_VITALS_X1_A Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
VSACTDTTM	DATE - DDMONYYYY HHMM	
SYSBP	NUMERIC - N3	
DIABP	NUMERIC - N3	
HEART	NUMERIC - N3	

lpl112498_128 : ELECTRONICALLY TRANSFERRED LAB DATA (Lab)		
Day -1		
1.	Haematology Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_B.rdcLABDTTM) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_B.LBDTTM1) Req : Req *24-hour clock* *[ND]* ◯ Not Done
2.	Clinical Chemistry Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_B.rdcLABDTTM1) *[-98]* ◯ Same as the Haematology sample **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_B.LBDTTM2) Req : Req *24-hour clock* *[ND]* ◯ Not Done
3.	Urinalysis Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_B.rdcLABDTT1) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_B.LBDTTM3) Req : Req *24-hour clock* *[ND]* ◯ Not Done

Form Design Note:
S1D-1

Section Design Notes:	
Title	**Design Note**
Day -1	If only one sample date and time is needed for all lab tests performed remove the last two items and modify the text of the first item

Item Design Notes:	
Item No.	**Design Note**
1.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.
2.	Time is optional. Use this item for all other samples on the form
3.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.

CDD: MAPPINGS1 Table: t_LABLINK_X1_B Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
rdcLABDTTM	STRING(3)	
LBDTTM1	DATE - DDMONYYYY HHMM	
rdcLABDTTM1	STRING(3)	
LBDTTM2	DATE - DDMONYYYY HHMM	
rdcLABDTT1	STRING(3)	
LBDTTM3	DATE - DDMONYYYY HHMM	

lpl112498_128 : VITAL SIGNS (seated) (VS)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_X3_A.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_X3_A.VSACTDTTM) Req : Req *24-hour clock*
3.	Blood pressure	xxx (n >= 0) / (MAPPINGS1:t_VITALS_X3_A.SYSBP) xxx (n >= 0) mmHg (MAPPINGS1:t_VITALS_X (systolic/diastolic)
4.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_X3_A.HEART)
48 hours post dose		
5.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_X3_A.VSACTDTT1) Req : Req *24-hour clock*
6.	Blood pressure	xxx (n >= 0) / (MAPPINGS1:t_VITALS_X3_A.SYSB1) xxx (n >= 0) mmHg (MAPPINGS1:t_VITALS_X (systolic/diastolic)
7.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_X3_A.HEAR1)

* Item is not required

Form Design Note:
S1D1

CDD: MAPPINGS1 Table: t_VITALS_X3_A Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
VSACTDTTM	DATE - DDMONYYYY HHMM	
SYSBP	NUMERIC - N3	
DIABP	NUMERIC - N3	
HEART	NUMERIC - N3	
VSACTDTT1	DATE - DDMONYYYY HHMM	
SYSB1	NUMERIC - N3	
DIAB1	NUMERIC - N3	
HEAR1	NUMERIC - N3	

lpl112498_128 : PHARMACOKINETICS BLOOD - SB-480848, M4, M10, M3 (PK)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTTM)
0.5 hours post dose		
3.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT1)
1 hour post dose		
4.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT2)
2 hours post dose		
5.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT3)
3 hours post dose		
6.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT4)
4 hours post dose		
7.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT5)
6 hours post dose		
8.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT6)
9 hours post dose		
9.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_A.CDDPKSTT7)
12 hours post dose		
10.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTTM) Req : Req *24-hour clock*
18 hours post dose		
11.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTT1) Req : Req *24-hour clock*
24 hours post dose		
12.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTT2) Req : Req *24-hour clock*
32 hours post dose		
13.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTT3) Req : Req *24-hour clock*
48 hours post dose		
14.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTT4) Req : Req *24-hour clock*
72 hours post dose		
15.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTT5) Req : Req *24-hour clock*
96 hours post dose		
16.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_A.PKSTDTT6)

		Req : Req	*24-hour clock*

* Item is not required

Form Design Note:
S1D1

CDD: MAPPINGS1	**Table: t_PK_X20_A**	**Key Type: PATIENTVISIT**
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
CDDPKSTTM	DATE - HHMM	
CDDPKSTT1	DATE - HHMM	
CDDPKSTT2	DATE - HHMM	
CDDPKSTT3	DATE - HHMM	
CDDPKSTT4	DATE - HHMM	
CDDPKSTT5	DATE - HHMM	
CDDPKSTT6	DATE - HHMM	
CDDPKSTT7	DATE - HHMM	
PKSTDTTM	DATE - DDMONYYYY HHMM	
PKSTDTT1	DATE - DDMONYYYY HHMM	
PKSTDTT2	DATE - DDMONYYYY HHMM	
PKSTDTT3	DATE - DDMONYYYY HHMM	
PKSTDTT4	DATE - DDMONYYYY HHMM	
PKSTDTT5	DATE - DDMONYYYY HHMM	
PKSTDTT6	DATE - DDMONYYYY HHMM	

lpl112498_128 : PHARMACODYNAMICS - Lp-PLA2 (BLOOD) (PD)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X1_A.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X1_A.PDACTDTTM) Req : Req *24-hour clock*
* Item is not required		

Form Design Note:
S1D1

CDD: MAPPINGS1 Table: t_PD_X1_A Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
PDACTDTTM	DATE - DDMONYYYY HHMM	

lpl112498_128 : ELECTRONICALLY TRANSFERRED LAB DATA (Lab)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_D.CDDDOSEDTTM) Req : Req *24-hour clock*
48 hours post dose		
2.	Haematology Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_D.rdcLABDTTM) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_D.LBDTTM1) Req : Req *24-hour clock* *[ND]* ◯ Not Done
3.	Clinical Chemistry Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_D.rdcLABDTTM1) *[-98]* ◯ Same as the Haematology sample **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_D.LBDTTM2) Req : Req *24-hour clock* *[ND]* ◯ Not Done
4.	Urinalysis Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_D.rdcLABDTT1) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_D.LBDTTM3) Req : Req *24-hour clock* *[ND]* ◯ Not Done
* Item is not required		

Form Design Note:
S1D1

Section Design Notes:	
Title	**Design Note**
48 hours post dose	If only one sample date and time is needed for all lab tests performed remove the last two items and modify the text of the first item

Item Design Notes:	
Item No.	**Design Note**
2.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.
3.	Time is optional. Use this item for all other samples on the form
4.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.

CDD: MAPPINGS1 Table: t_LABLINK_X1_D Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
rdcLABDTTM	STRING(3)	
LBDTTM1	DATE - DDMONYYYY HHMM	
rdcLABDTTM1	STRING(3)	
LBDTTM2	DATE - DDMONYYYY HHMM	

rdcLABDTT1	STRING(3)	
LBDTTM3	DATE - DDMONYYYY HHMM	

lpl112498_128 : RANDOMISATION NUMBER (Rand)		
RANDOMISATION		
1.	Was the subject able to be randomised?	(MAPPINGS1:t_RAND.rdcRandYN) **[Y]** ○ Yes, provide: Randomisation number (MAPPINGS1:t_RAND.RANDNUM) xxxxxx Date of randomisation Req / Req / Req (2008-2009) (MAPPINGS1:t_RAND.RANDDT) *[N]* ○ No

CDD: MAPPINGS1 Table: t_RAND Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
rdcRandYN	STRING(1)	
RANDNUM	NUMERIC - N6	
RANDDT	DATE - DDMONYYYY	

lpl112498_128 : INVESTIGATIONAL PRODUCT (Dose)		
INVESTIGATIONAL PRODUCT		
1.	Date/time of dose	Req / Req / Req (2008-2009) (MAPPINGS1:t_EXPOSURE_SINGLE_A.EXSTDTTM) Req : Req *24-hour clock*
TREATMENT CONFIRMATION		
2.	Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?	(MAPPINGS1:t_EXPOSURE_SINGLE_A.EXTRTCFM) *[Y]* ○ Yes **[N]** ○ No, record reason(s) (MAPPINGS1:t_EXPOSURE_SINGLE_A.EXTRTRS) A200

Form Design Note:
used on all dosing days

CDD: MAPPINGS1 Table: t_EXPOSURE_SINGLE_A Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
EXSTDTTM	DATE - DDMONYYYY HHMM	
EXTRTCFM	STRING(1)	
EXTRTRS	STRING(200) - A200	

lpl112498_128 : Session 2 Day 10 PHARMACOKINETICS BLOOD - SB-480848, M4, M10, M3 (PK)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_B.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTTM)
0.5 hours post dose		
3.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT1)
1 hour post dose		
4.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT2)
2 hours post dose		
5.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT3)
3 hours post dose		
6.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT4)
4 hours post dose		
7.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT5)
6 hours post dose		
8.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT6)
9 hours post dose		
9.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_B.CDDPKSTT7)
12 hours post dose		
10.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_B.PKSTDTTM) Req : Req *24-hour clock*
18 hours post dose		
11.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_B.PKSTDTT1) Req : Req *24-hour clock*
24 hours post dose		
12.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_B.PKSTDTT2) Req : Req *24-hour clock*
* Item is not required		

Form Design Note:
S2D10

CDD: MAPPINGS1 Table: t_PK_X20_B Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
CDDPKSTTM	DATE - HHMM	
CDDPKSTT1	DATE - HHMM	

CDDPKSTT2	DATE - HHMM	
CDDPKSTT3	DATE - HHMM	
CDDPKSTT4	DATE - HHMM	
CDDPKSTT5	DATE - HHMM	
CDDPKSTT6	DATE - HHMM	
CDDPKSTT7	DATE - HHMM	
PKSTDTTM	DATE - DDMONYYYY HHMM	
PKSTDTT1	DATE - DDMONYYYY HHMM	
PKSTDTT2	DATE - DDMONYYYY HHMM	

lpl112498_128 : Session 2 Day 10 PHARMACODYNAMICS - Lp-PLA2 (BLOOD) (PD)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_A.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTTM)
0.5 hours post dose		
3.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT1)
1 hour post dose		
4.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT2)
2 hours post dose		
5.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT3)
3 hours post dose		
6.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT4)
4 hours post dose		
7.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT5)
6 hours post dose		
8.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT6)
9 hours post dose		
9.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_A.CDDPDACTT7)
12 hours post dose		
10.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_A.PDACTDTTM) Req : Req *24-hour clock*
18 hours post dose		
11.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_A.PDACTDTT1) Req : Req *24-hour clock*
24 hours post dose		
12.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_A.PDACTDTT2) Req : Req *24-hour clock*

* Item is not required

Form Design Note:
S2D10

CDD: MAPPINGS1	**Table: t_PD_X20_A**	**Key Type: PATIENTVISIT**
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
CDDPDACTTM	DATE - HHMM	
CDDPDACTT1	DATE - HHMM	
CDDPDACTT2	DATE - HHMM	

CDDPDACTT3	DATE - HHMM	
CDDPDACTT4	DATE - HHMM	
CDDPDACTT5	DATE - HHMM	
CDDPDACTT6	DATE - HHMM	
CDDPDACTT7	DATE - HHMM	
PDACTDTTM	DATE - DDMONYYYY HHMM	
PDACTDTT1	DATE - DDMONYYYY HHMM	
PDACTDTT2	DATE - DDMONYYYY HHMM	

lpl112498_128 : VITAL SIGNS (VS)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_X1_B.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose (seated)		
2.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_X1_B.VSACTDTTM) Req : Req *24-hour clock*
3.	Blood pressure	xxx (n >= 0) / (MAPPINGS1:t_VITALS_X1_B.SYSBP) xxx (n >= 0) mmHg (MAPPINGS1:t_VITALS_X (systolic/diastolic)
4.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_X1_B.HEART)

* Item is not required

Form Design Note:
S2D14,S2D28

CDD: MAPPINGS1 Table: t_VITALS_X1_B Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
VSACTDTTM	DATE - DDMONYYYY HHMM	
SYSBP	NUMERIC - N3	
DIABP	NUMERIC - N3	
HEART	NUMERIC - N3	

lpl112498_128 : PHARMACOKINETICS BLOOD - SB-480848, M4, M10, M3 (PK)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X1_A.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X1_A.PKSTDTTM) Req : Req *24-hour clock*
* Item is not required		

Form Design Note:
S2D26, S2D27

CDD: MAPPINGS1 Table: t_PK_X1_A Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
PKSTDTTM	DATE - DDMONYYYY HHMM	

lpl112498_128 : Session 2 Day 28 PHARMACOKINETICS BLOOD - SB-480848, M4, M10, M3 (PK)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTTM)
0.5 hours post dose		
3.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT1)
1 hour post dose		
4.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT2)
2 hours post dose		
5.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT3)
3 hours post dose		
6.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT4)
4 hours post dose		
7.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT5)
6 hours post dose		
8.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT6)
9 hours post dose		
9.	Actual time	Req : Req *24-hour clock* (MAPPINGS1:t_PK_X20_C.CDDPKSTT7)
12 hours post dose		
10.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTTM) Req : Req *24-hour clock*
18 hours post dose		
11.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT1) Req : Req *24-hour clock*
24 hours post dose		
12.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT2) Req : Req *24-hour clock*
32 hours post dose		
13.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT3) Req : Req *24-hour clock*
48 hours (2 days) post dose		
14.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT4) Req : Req *24-hour clock*
72 hours (3 days) post dose		
15.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT5) Req : Req *24-hour clock*
96 hours (4 days) post dose		
16.	Actual date/time	

		Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT6) Req : Req *24-hour clock*
120 hours (5 days) post dose		
17.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT7) Req : Req *24-hour clock*
144 hours (6 days) post dose		
18.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT8) Req : Req *24-hour clock*
168 hours (7 days) post dose		
19.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDTT9) Req : Req *24-hour clock*
240 hours (10 days) post dose		
20.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT10) Req : Req *24-hour clock*
312 hours (13 days) post dose		
21.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT11) Req : Req *24-hour clock*
384 hours (16 days) post dose		
22.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT12) Req : Req *24-hour clock*
456 hours (19 days) post dose		
23.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT13) Req : Req *24-hour clock*
528 hours (22 days) post dose		
24.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT14) Req : Req *24-hour clock*
600 hours (25 days) post dose		
25.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT15) Req : Req *24-hour clock*
672 hours (28 days) post dose		
26.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_X20_C.PKSTDT16) Req : Req *24-hour clock*

* Item is not required

Form Design Note:
S2D28

CDD: MAPPINGS1 Table: t_PK_X20_C Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
CDDPKSTTM	DATE - HHMM	

CDDPKSTT1	DATE - HHMM	
CDDPKSTT2	DATE - HHMM	
CDDPKSTT3	DATE - HHMM	
CDDPKSTT4	DATE - HHMM	
CDDPKSTT5	DATE - HHMM	
CDDPKSTT6	DATE - HHMM	
CDDPKSTT7	DATE - HHMM	
PKSTDTTM	DATE - DDMONYYYY HHMM	
PKSTDTT1	DATE - DDMONYYYY HHMM	
PKSTDTT2	DATE - DDMONYYYY HHMM	
PKSTDTT3	DATE - DDMONYYYY HHMM	
PKSTDTT4	DATE - DDMONYYYY HHMM	
PKSTDTT5	DATE - DDMONYYYY HHMM	
PKSTDTT6	DATE - DDMONYYYY HHMM	
PKSTDTT7	DATE - DDMONYYYY HHMM	
PKSTDTT8	DATE - DDMONYYYY HHMM	
PKSTDTT9	DATE - DDMONYYYY HHMM	
PKSTDT10	DATE - DDMONYYYY HHMM	
PKSTDT11	DATE - DDMONYYYY HHMM	
PKSTDT12	DATE - DDMONYYYY HHMM	
PKSTDT13	DATE - DDMONYYYY HHMM	
PKSTDT14	DATE - DDMONYYYY HHMM	
PKSTDT15	DATE - DDMONYYYY HHMM	
PKSTDT16	DATE - DDMONYYYY HHMM	

lpl112498_128 : Session 2 Day 28 PHARMACODYNAMICS - Lp-PLA2 (BLOOD) (PD)		
DOSING DATE AND TIME		
1.*	Dosing date/time [*read-only*]	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.CDDDOSEDTTM) Req : Req *24-hour clock*
Predose		
2.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTTM)
0.5 hours post dose		
3.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT1)
1 hour post dose		
4.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT2)
2 hours post dose		
5.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT3)
3 hours post dose		
6.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT4)
4 hours post dose		
7.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT5)
6 hours post dose		
8.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT6)
9 hours post dose		
9.	Time of sample	Req : Req *24-hour clock* (MAPPINGS1:t_PD_X20_B.CDDPDACTT7)
12 hours post dose		
10.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTTM) Req : Req *24-hour clock*
18 hours post dose		
11.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT1) Req : Req *24-hour clock*
24 hours post dose		
12.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT2) Req : Req *24-hour clock*
32 hours post dose		
13.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT3) Req : Req *24-hour clock*
48 hours (2 days) post dose		
14.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT4) Req : Req *24-hour clock*
72 hours (3 days) post dose		
15.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT5) Req : Req *24-hour clock*
96 hours (4 days) post dose		
16.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT6)

		Req : Req *24-hour clock*
120 hours (5 days) post dose		
17.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT7) Req : Req *24-hour clock*
144 hours (6 days) post dose		
18.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT8) Req : Req *24-hour clock*
168 hours (7 days) post dose		
19.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDTT9) Req : Req *24-hour clock*
240 hours (10 days) post dose		
20.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT10) Req : Req *24-hour clock*
312 hours (13 days) post dose		
21.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT11) Req : Req *24-hour clock*
384 hours (16 days) post dose		
22.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT12) Req : Req *24-hour clock*
456 hours (19 days) post dose		
23.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT13) Req : Req *24-hour clock*
528 hours (22 days) post dose		
24.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT14) Req : Req *24-hour clock*
600 hours (25 days) post dose		
25.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT15) Req : Req *24-hour clock*
672 (28 days) hours post dose		
26.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_X20_B.PDACTDT16) Req : Req *24-hour clock*

* Item is not required

Form Design Note:
S2D28

CDD: MAPPINGS1	**Table: t_PD_X20_B**	**Key Type: PATIENTVISIT**
Column Name	**Column Data Type**	**Design Note**
CDDDOSEDTTM	DATE - DDMONYYYY HHMM	
CDDPDACTTM	DATE - HHMM	
CDDPDACTT1	DATE - HHMM	

CDDPDACTT2	DATE - HHMM	
CDDPDACTT3	DATE - HHMM	
CDDPDACTT4	DATE - HHMM	
CDDPDACTT5	DATE - HHMM	
CDDPDACTT6	DATE - HHMM	
CDDPDACTT7	DATE - HHMM	
PDACTDTTM	DATE - DDMONYYYY HHMM	
PDACTDTT1	DATE - DDMONYYYY HHMM	
PDACTDTT2	DATE - DDMONYYYY HHMM	
PDACTDTT3	DATE - DDMONYYYY HHMM	
PDACTDTT4	DATE - DDMONYYYY HHMM	
PDACTDTT5	DATE - DDMONYYYY HHMM	
PDACTDTT6	DATE - DDMONYYYY HHMM	
PDACTDTT7	DATE - DDMONYYYY HHMM	
PDACTDTT8	DATE - DDMONYYYY HHMM	
PDACTDTT9	DATE - DDMONYYYY HHMM	
PDACTDT10	DATE - DDMONYYYY HHMM	
PDACTDT11	DATE - DDMONYYYY HHMM	
PDACTDT12	DATE - DDMONYYYY HHMM	
PDACTDT13	DATE - DDMONYYYY HHMM	
PDACTDT14	DATE - DDMONYYYY HHMM	
PDACTDT15	DATE - DDMONYYYY HHMM	
PDACTDT16	DATE - DDMONYYYY HHMM	

lpl112498_128 : VITAL SIGNS (VS)

VITAL SIGNS (seated)

1.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_Z_FU.VSACTDTTM) Req : Req *24-hour clock*
2.	Blood pressure	xxx (n >= 0) / (MAPPINGS1:t_VITALS_Z_FU.SYSBP) xxx (n >= 0) mmHg (MAPPINGS1:t_VITALS_Z_ (systolic/diastolic)
3.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_Z_FU.HEART)

Form Design Note:
Follow-up vital signs

CDD: MAPPINGS1 Table: t_VITALS_Z_FU Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
VSACTDTTM	DATE - DDMONYYYY HHMM	
SYSBP	NUMERIC - N3	
DIABP	NUMERIC - N3	
HEART	NUMERIC - N3	

lpl112498_128 : 12-LEAD ECG (ECG)		
12-LEAD ECG		
1.	Date and Time of ECG Hr:Min (00:00-23:59)	Req / Req / Req (2008- 2009) (MAPPINGS1:t_ECG_Z_FU.EGDTTM) Req : Req *24-hour clock*
2.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_ECG_Z_FU.EGHR)
3.	PR Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_Z_FU.PR__)
4.	QRS Duration	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_Z_FU.QRS__)
5.	Uncorrected QT Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_Z_FU.QT__)
6.	QTc Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_Z_FU.QTC__)
7.	Method of QTc Calculation	(MAPPINGS1:t_ECG_Z_FU.EGMTCLCD) *[1]* Machine *[2]* Manual
8.	Result of the ECG	(MAPPINGS1:t_ECG_Z_FU.EGINTPCD) *[1]* Normal *[2]* Abnormal - Not clinically significant *[3]* Abnormal - Clinically significant *(complete the ECG abnormality form for all clinically significant abnormalities, and additionally complete the AE form if the abnormality meets the protocol definition for an AE)* *[4]* No result (not available)

Form Design Note:
Follow-up ECG

CDD: MAPPINGS1	**Table: t_ECG_Z_FU**	**Key Type: PATIENTVISIT**
Column Name	**Column Data Type**	**Design Note**
EGDTTM	DATE - DDMONYYYY HHMM	
EGHR	NUMERIC - N3	
PR__	FLOAT - F6.0	
QRS__	FLOAT - F6.0	
QT__	FLOAT - F6.0	
QTC__	FLOAT - F6.0	
EGMTCLCD	STRING(1)	
EGINTPCD	STRING(1)	

lpl112498_128 : ELECTRONICALLY TRANSFERRED LAB DATA (Lab)		
Follow-up		
1.	Haematology Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_C.rdcLABDTTM) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_C.LBDTTM1) Req : Req *24-hour clock* *[ND]* ◯ Not Done
2.	Clinical Chemistry Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_C.rdcLABDTTM1) *[-98]* ◯ Same as the Haematology sample **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_C.LBDTTM2) Req : Req *24-hour clock* *[ND]* ◯ Not Done
3.	Urinalysis Date and time sample taken Hr:Min (00:00-23:59)	(MAPPINGS1:t_LABLINK_X1_C.rdcLABDTT1) **[-99]** ◯ Date Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_X1_C.LBDTTM3) Req : Req *24-hour clock* *[ND]* ◯ Not Done

Form Design Note:
Follow-up

Section Design Notes:	
Title	**Design Note**
Follow-up	If only one sample date and time is needed for all lab tests performed remove the last two items and modify the text of the first item

Item Design Notes:	
Item No.	**Design Note**
1.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.
2.	Time is optional. Use this item for all other samples on the form
3.	Time is optional. Use this item as the first item on this form. For additional tests, use the second item.

CDD: MAPPINGS1 Table: t_LABLINK_X1_C Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
rdcLABDTTM	STRING(3)	
LBDTTM1	DATE - DDMONYYYY HHMM	
rdcLABDTTM1	STRING(3)	
LBDTTM2	DATE - DDMONYYYY HHMM	
rdcLABDTT1	STRING(3)	
LBDTTM3	DATE - DDMONYYYY HHMM	

lpl112498_128 : STUDY CONCLUSION (Conclusion)

If the subject completed the study
»Date of last contact must match the last scheduled study visit date.
If the subject withdrew
»Date of decision to withdraw must match the date of decision to withdraw the subject from the study before normal completion.
»Date of last contact must match the last actual contact with the subject whether or not the contact was a clinic visit. Do not record dates of unsuccessful attempts to contact the subject.
Note: *An 'actual contact' is defined as an interaction between the subject and the investigator or investigator's designee, where the investigator/designee has the opportunity to query the subject about the subject's status. This would include clinic visits and telephone contacts, but normally would not include mail correspondence or third party reports.*

STUDY CONCLUSION

1.	Date of last contact	Req / Req / Req (2008-2009) (MAPPINGS1:t_DS_CONCLUSION.DSSTDT)
2.	Was the subject withdrawn from the study?	(MAPPINGS1:t_DS_CONCLUSION.DSFAIL1) *[N]* ○ No **[Y]** ○ Yes; complete details : Date of decision to withdraw Req / Req / Req (2008-2009) (MAPPINGS1:t_DS_CONCLUSION.DSSTD1) (MAPPINGS1:t_DS_CONCLUSION.DSRSCD) Primary reason for withdrawal *[1]* ○ Adverse Event *Record details on the Non-Serious Adverse Events or Serious Adverse Events forms as appropriate.* *[2]* ○ Lack of efficacy *[3]* ○ Protocol deviation *[4]* ○ Subject reached protocol defined stopping criteria *[5]* ○ Study closed/terminated *[6]* ○ Lost to Follow-up **[7]** ○ Investigator discretion, specify (MAPPINGS1:t_DS_CONCLUSION.DSRSSP) *Select this reason if none of the other primary reasons are appropriate.* A200 *[8]* ○ Withdrew consent
3.*	Case book ready for signature [*hidden*]	(MAPPINGS1:t_DS_CONCLUSION.chkReadyForSig) *[Y]* ☐ Yes *Data owner should check the box when data cleaning is complete*
	Office Use 1 [*hidden*]	(MAPPINGS1:t_DS_CONCLUSION.COMPLETERADIO) *[N]* ○ No *[Y]* ○ Yes
	Office Use 2 [*hidden*]	(MAPPINGS1:t_DS_CONCLUSION.REASONRADIO) **[?]** ○ 1 **[?]** ○ 2 **[?]** ○ 3 **[?]** ○ 4 **[?]** ○ 5 **[?]** ○ 6 **[?]** ○ 7 **[?]** ○ 8 **[?]** ○ 9

* Item is not required

Form Design Note:
IDSL version 01.01A - 15 MAY 07 (modified for Phase 1 template)

Section Design Notes:	
Title	**Design Note**
STUDY CONCLUSION	Alignment of predefined sub-reasons will be rectified once eCRF Designer has replaced [?] by valid codes.

Item Design Notes:	
Item No.	**Design Note**
2.	Pre-defined sub-reasons are optional. The following primary reasons are optional : Lack of efficacy, Subject reached protocol-defined stopping criteria, Investigator discretion.

CDD: MAPPINGS1 Table: t_DS_CONCLUSION Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
DSSTDT	DATE - DDMONYYYY	
DSFAIL1	STRING(1)	
DSSTD1	DATE - DDMONYYYY	
DSRSCD	STRING(1)	
DSRSSP	STRING(200) - A200	
chkReadyForSig	STRING(255)	
COMPLETERADIO	STRING(1)	
REASONRADIO	STRING(42)	

lpl112498_128 : PREGNANCY INFORMATION (Preg F)		
PREGNANCY INFORMATION		
1.	Did the subject become pregnant during the study? *If Yes, complete the **paper** Pregnancy Notification form*	(MAPPINGS1:t_STATUS_PREG_F.PGYN) *[N]* ◯ No *[Y]* ◯ Yes

Form Design Note:
This is an optional form but is conditional upon females in the trial; This form will be dynamically generated to appear at the End visit if Female is selected on the Demographics form

CDD: MAPPINGS1 Table: t_STATUS_PREG_F Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
PGYN	STRING(1)	

lpl112498_128 : LOGS AND REPEATS (Logs/Rpts)

Date below is the start of the study for this subject

DATE OF VISIT/ASSESSMENT		
1.	Date of visit/assessment	Req / Req / Req (2008- 2009) (MAPPINGS1:t_STATUS_LOGS.DOV)
ADVERSE EVENT/CONCOMITANT MEDICATION/REPEAT ASSESSMENT CHECK QUESTIONS		
2.	Were any concomitant medications taken by the subject during the study?	(MAPPINGS1:t_STATUS_LOGS.CMANY) *[Y]* Yes *[N]* No
3.	Did the subject experience any non-serious adverse events during the study?	(MAPPINGS1:t_STATUS_LOGS.AEANY) *[Y]* Yes *[N]* No
4.	Did the subject experience any serious adverse events during the study?	(MAPPINGS1:t_STATUS_LOGS.SAEANY) *[Y]* Yes *[N]* No
5.	Were any abnormal, clinically significant ECG measurements recorded for this subject during the study?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigger) *[Y]* Yes *[N]* No
6.	Were any repeat haematology or clinical chemistry samples taken?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigge1) *[Y]* Yes *[N]* No
7.	Were any repeat urinalysis samples taken?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigge2) *[Y]* Yes *[N]* No
8.	Were any repeat ECGs performed?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigge3) *[Y]* Yes *[N]* No
9.	Were any repeat vital signs recorded?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigge4) *[Y]* Yes *[N]* No
10.	Were any repeat PK blood samples taken?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigge5) *[Y]* Yes *[N]* No
11.	Were any repeat PD samples taken?	(MAPPINGS1:t_STATUS_LOGS.rdcRptTrigge6) *[Y]* Yes *[N]* No
LIVER EVENT		
If liver event occurred, stop investigational product, complete date stopped on Investigational Product form and contact GSK within 24 hours of occurrence of liver event by phone or fax. If the liver event meets the definition of an SAE, the SAE form must be completed and faxed to GSK. * Obtain tests as per protocol * Obtain blood samples for Pharmacokinetics (PK) analysis within 24 hours or 3 half-lives *{insert value of whichever is longer}* of last dose * Complete Liver Event Forms *(completed Liver Event Forms do not need to be supplied to GSK within 24 hours)*		
12.	Have liver chemistry results reached or exceeded protocol-defined investigational product stopping criteria?	(MAPPINGS1:t_STATUS_LOGS.LVEVTANY) *[Y]* Yes *[N]* No If Yes to Liver Events, go to the LE DETAILS visit and complete the Liver Event forms

Item Design Notes:

Item No.	Design Note
12.	If response is Yes to Liver Events, go to the LE DETAILS tab and complete the liver events forms.

CDD: MAPPINGS1 Table: t_STATUS_LOGS Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
DOV	DATE - DDMONYYYY	
CMANY	STRING(1)	
AEANY	STRING(1)	
SAEANY	STRING(1)	

rdcRptTrigger	STRING(1)	
rdcRptTrigge1	STRING(1)	
rdcRptTrigge2	STRING(1)	
rdcRptTrigge3	STRING(1)	
rdcRptTrigge4	STRING(1)	
rdcRptTrigge5	STRING(1)	
rdcRptTrigge6	STRING(1)	
LVEVTANY	STRING(1)	

lpl112498_128 : NON-SERIOUS ADVERSE EVENT (AE) - Repeating Form

#		Event	Start Date and Time	Outcome	Frequency	Maximum Intensity	Action Taken	Subject Withdrawn?	Relatio
1									

NON-SERIOUS ADVERSE EVENT

1.*	Sequence Number [*hidden*]	A5 (MAPPINGS1:t_AE.AESEQ)
2.	Event Diagnosis Only *(if known)* Otherwise Sign/Symptom	A100 (MAPPINGS1:t_AE.AETERM)
3.*	Modified term [*hidden*]	A100 (MAPPINGS1:t_AE.AEMODIFY)
	MedDRA synonym [*hidden*]	(MAPPINGS1:t_AE.AEMEDSYN)
	MedDRA lower level term code [*hidden*]	(MAPPINGS1:t_AE.AELLTCD)
	Failed coding [*hidden*]	(MAPPINGS1:t_AE.calAE_FAILED)
4.	Start Date and Time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_AE.AESTDTTM) NReq : NReq *24-hour clock*
5.	Outcome / End Date and Time Hr:Min (00:00-23:59)	(MAPPINGS1:t_AE.AEOUTCD) **[1]** Recovered/Resolved, provide End Date and Time Req / Req / Req (2008-2009) (MAPPINGS1:t_AE.AEENDTTM1) NReq : NReq *24-hour clock* *[2]* Recovering/Resolving *[3]* Not recovered/Not resolved **[4]** Recovered/Resolved with sequelae, provide End Date and Time Req / Req / Req (2008-2009) (MAPPINGS1:t_AE.AEENDTTM2) NReq : NReq *24-hour clock*
6.	Frequency	(MAPPINGS1:t_AE.AEFREQCD) *[1]* Single Episode *[2]* Intermittent
7.*	Maximum Intensity	(MAPPINGS1:t_AE.AESEVCD) *[1]* Mild *[2]* Moderate *[3]* Severe *[X]* Not applicable
8.*	Maximum Grade [*hidden*]	(MAPPINGS1:t_AE.AETOXCD) *[1]* Grade 1 *[2]* Grade 2 *[3]* Grade 3 *[4]* Grade 4 *[5]* Grade 5 *[X]* Not applicable
9.*	Maximum Grade or Intensity [*hidden*]	(MAPPINGS1:t_AE.AETXHVCD) *[1]* Mild or Grade 1 *[2]* Moderate or Grade 2

		[3] Severe or Grade 3 *[4]* Grade 4 *[5]* Grade 5 *[X]* Not applicable
10.	Action Taken with Investigational Product(s) as a Result of the AE	(MAPPINGS1:t_AE.AEACTRCD) *[1]* Investigational product(s) withdrawn *[2]* Dose reduced *[3]* Dose increased *[4]* Dose not changed *[5]* Dose interrupted *[X]* Not applicable
11.	Did the subject withdraw from study as a result of this AE?	(MAPPINGS1:t_AE.AEWD) *[Y]* Yes *[N]* No
12.	Is there a reasonable possibility that the AE may have been caused by the investigational product?	(MAPPINGS1:t_AE.AEREL) *[Y]* Yes *[N]* No
13.*	Duration of AE if < 24 hours [*hidden*]	xx (0 =< n <= 23) (MAPPINGS1:t_AE.AEDURHR) Hr(s) xx (0 =< n <= 59) (MAPPINGS1:t_AE.AE Min(s)
14.*	Time to Onset Since Last Dose [*hidden*]	xx (MAPPINGS1:t_AE.AEONLDSH) Hr(s) xx (0 =< n <= 59) (MAPPINGS1:t_AE.AEONLDSM) Min(s)

* Item is not required

Form Design Note:
IDSL Version 03.01A - 16 NOV 2005

Item Design Notes:	
Item No.	**Design Note**
4.	Start Time is optional
5.	End Time is optional
6.	This item is optional
7.	**Optional item:** This item may be hidden if either the "Maximum Grade" or "Maximum Grade or Intensity" item has been used. Grade 5 is optional.
8.	**Optional item:** This item may be hidden if either the "Maximum Intensity" or "Maximum Grade or Intensity" item has been used Grade 5 is optional.
9.	**Optional item:** This item may be hidden if either the "Maximum Intensity" or "Maximum Grade" item has been used Grade 5 is optional.
13.	If AE start and end time are used this item must be hidden.
14.	This item is optional

CDD: MAPPINGS1 Table: t_AE Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
AESEQ	STRING(5) - A5	
AETERM	STRING(100) - A100	
AEMODIFY	STRING(100) - A100	
AEMEDSYN	STRING(255)	
AELLTCD	STRING(255)	
calAE_FAILED	STRING(255)	
AESTDTTM	DATE - DDMONYYYY HHMM	
AEOUTCD	STRING(1)	
AEENDTTM1	DATE - DDMONYYYY HHMM	
AEENDTTM2	DATE - DDMONYYYY HHMM	
AEFREQCD	STRING(1)	
AESEVCD	STRING(1)	
AETOXCD	STRING(1)	
AETXHVCD	STRING(1)	
AEACTRCD	STRING(1)	
AEWD	STRING(1)	
AEREL	STRING(1)	
AEDURHR	NUMERIC - N2	
AEDURMIN	NUMERIC - N2	
AEONLDSH	NUMERIC - N2	
AEONLDSM	NUMERIC - N2	

lpl112498_128 : SERIOUS ADVERSE EVENTS (SAE) - Repeating Form

#		Initial Report	Follow-Up Report	Did SAE occur after initiation of study medication?	SERIOUS ADVERSE EVENT	Serious?	RELEVANT CONCOMITANT/TREATMENT MEDICATIONS	
1								

**If you wish to record a new SAE please determine if the new SAE is clinically or temporally
Entry' button in this form. If not clinically or temporally related, create a new SAE form fo
randomization events on the same form.**

TYPE OF REPORT		
1.*	Initial Report [*read-only*]	(MAPPINGS1:t_AE_SER.chkSAE) *[1]* ☐ Initial
2.*	Follow-Up Report [*read-only*]	(MAPPINGS1:t_AE_SER.chkFU) *[2]* ☐ Follow-Up
RANDOMISATION		
3.	Did SAE occur after initiation of study medication?	(MAPPINGS1:t_AE_SER.rdcSAERAND) *[N]* ◯ No *[Y]* ◯ Yes

	SAE Sequence Number	Event	Modified term	MedDRA synonym	MedDR lower level te code
4.	[*hidden*]		[*hidden*]	[*hidden*]	[*hidde*

SERIOUS ADVERSE EVENT Entry	
4.a*	SAE Sequence Number [*hidden*]
4.b	Serious Adverse Event Diagnosis Only *(if known)* Otherwise Sign/Symptom
4.c*	Modified term [*hidden*]
	MedDRA synonym [*hidden*]
	MedDRA lower level term code [*hidden*]
	Failed coding [*hidden*]
4.d	Start Date and Time Hr:Min (00:00-23:59)
4.e	Outcome / End Date and Time Hr:Min (00:00-23:59)
4.f*	Maximum Intensity

4.g*	Maximum Grade [*hidden*]
4.h*	Maximum Grade or Intensity [*hidden*]
4.i	Action Taken with Investigational Product(s) as a Result of the AE
4.j	Did the subject withdraw from study as a result of this AE?
4.k	Is there a reasonable possibility that the AE may have been caused by the investigational product?
4.l*	Duration of AE if < 24 hours [*hidden*]
4.m*	Time to Onset Since Last Dose [*hidden*]
4.n	Was SAE caused by activities related to study participation (e.g. procedures)?
4.o*	Was the event serious? [*hidden*]

SERIOUSNESS		
Specify the reason for considering this an SAE. Check all that apply.		
5.	Seriousness?	(MAPPINGS1:t_AE_SER.AESERDTH) *[A]* ☐ Results in death (MAPPINGS1:t_AE_SER.AESERLIF) *[B]* ☐ Is life-threatening (MAPPINGS1:t_AE_SER.AESERHOS) *[C]* ☐ Requires hospitalisation or prolongation of existing hospitalisation (MAPPINGS1:t_AE_SER.AESERDIS) *[D]* ☐ Results in disability/incapacity (MAPPINGS1:t_AE_SER.AESERCON) *[E]* ☐ Congenital anomaly/birth defect (MAPPINGS1:t_AE_SER.AESEROTH) *[F]* ☐ Other, specify within general narrative comment

		(MAPPINGS1:t_AE_SER.AESERPROTSP) *[G]* ☐ [Enter protocol specific definition here]			
	CM Sequence Number	**Drug Name** **(Trade Name preferred)**	**Dose**	**Unit**	**Freque**
6.	[*hidden*]				

RELEVANT CONCOMITANT/TREATMENT MEDICATIONS Entry

Include details of any medication that may have contributed to the SAE or was used to treat the SAE.

6.a*	CM Sequence Number [*hidden*]	A4 (MAPPINGS1:t_
6.b	Drug Name (Trade Name preferred)	A100
6.c*	Dose	xxxxxxxxx. (MAPPIN
6.d*	Unit	Pulldown List 1 (MA
6.e*	Frequency	Pulldown List 2 (MA
6.f*	Route	Pulldown List 3 (MA
6.g*	Start Date	Req/Unk / Req/U
6.h*	Ongoing?	(MAPPINGS1:t_AE_SE *[Y]* Yes **[N]** No, specify En Req/Unk /
6.i*	Primary Indication	A50
6.j	Drug Type	Pulldown List 4 (MA

	MHx Sequence Number	**Specific Condition Name**	**Date of onset**	**Continuing?**
7.	[*hidden*]			

RELEVANT MEDICAL CONDITIONS/RISK FACTORS Entry

Specify past or current medical disorders, allergies, surgeries, family or social history that may help explain the SAE

7.a*	MHx Sequence Number [*hidden*]	A4 (MAPPINGS1:t_AE_SER.txtMHXSEQ)
7.b	Specific Condition Name	A100 (MAPPINGS1:t_AE_SER.txtSA
7.c*	Date of onset	Req/Unk / Req/Unk / Req (1970-2010) (MAPPINGS1:t_AE_SER.dtm
7.d*	Continuing?	(MAPPINGS1:t_AE_SER.rdcMHCONT) *[Y]* Yes **[N]** No, specify date of last occurrence Req/Unk / Req/Unk / Req (1970-2010) (MAPPINGS1:t_AE_SER.d *[U]* Unknown

8.*	Relevant Medical History / Risk Factors not noted above	A1000			
	Lab Sequence Number	**Test Name**	**Test Date**	**Test Result**	**Test U**
9.	[*hidden*]				

RELEVANT DIAGNOSTIC RESULTS Entry

Provide details of any tests or procedures carried out to diagnose the SAE.

9.a*	Lab Sequence Number [*hidden*]	A4 (MAPPINGS1:t_AE_SER.txtSAELI
9.b	Test Name	Pulldown List 5 (MAPPINGS1:t_AE_
9.c	Test Date	Req/Unk / Req/Unk / Req
9.d	Test Result	A50
9.e*	Test Units	A35 (M
9.f*	Normal Low Range	xxxxxxx. (MAPPINGS1:t_AE_SER.txt
9.g*	Normal High Range	xxxxxxx. (MAPPINGS1:t_AE_SER.txt

10.*	Relevant diagnostic results not noted above	A1000 A1000

INVESTIGATIONAL PRODUCTS

11.*	If Investigational product(s) stopped, did the reported event(s) recur after further investigational product(s) were administered?	(MAPPINGS1:t_AE_SER.rdcSAEIP) *[N]* ○ No *[Y]* ○ Yes *[U]* ○ Unknown at this time *[X]* ○ Not applicable

GENERAL NARRATIVE COMMENTS

Provide a brief narrative description of SAE, possible other causes of the event (e.g. lack of efficacy, withdrawal of investigational product, the disease under study or other medical conditions) and details of the treatment.

12.	General narrative comments	A1000 A1000

NON CLINICAL

13.*	Send incomplete SAE data to GSK Safety [*hidden*]	(MAPPINGS1:t_AE_SER.chkSAESENDI) *[3]* ☐ Incomplete SAE
14.*	Receipt by GSK date [*hidden*]	Req / Req / Req (2004-2010) (MAPPINGS1:t_AE_SER.dtmSAEDTM) Req : Req *24-hour clock*
15.*	Was the event serious? [*hidden*]	(MAPPINGS1:t_AE_SER.AESE1) *[Y]* ○ Yes *[N]* ○ No
16.*	SAE Sequence Number [*hidden*]	A5 (MAPPINGS1:t_AE_SER.AESE2)

17.*	Version Number [*hidden*]	A4	(MAPPINGS1:t_AE_SER.txtSAEVERSION)
18.*	Case ID [*hidden*]	A20	(MAPPINGS1:t_AE_SER.txtSAEID)
19.*	Randomisation Number [*hidden*]	A255	(MAPPINGS1:t_AE_SER.txtSAERNDNO)
20.*	OCEANS Code [*hidden*]	A13	(MAPPINGS1:t_AE_SER.txtOCEANSCD)
	Email Flag [*hidden*]	(MAPPINGS1:t_AE_SER.calSAEEmailFlag)	

* Item is not required

Form Design Note:
Version 05.04A - 18 OCT 2006

Item Design Notes:	
Item No.	**Design Note**
4.d	Start Time is optional
4.e	End Time is optional
4.f	**Optional item:** This item may be hidden if either the "Maximum Grade" or "Maximum Grade or Intensity" item has been used. Grade 5 is optional.
4.g	**Optional item:** This item may be hidden if either the "Maximum Intensity" or "Maximum Grade or Intensity" item has been used Grade 5 is optional.
4.h	**Optional item:** This item may be hidden if either the "Maximum Intensity" or "Maximum Grade" item has been used Grade 5 is optional.
4.l	If AE start and end time are used this item must be hidden.
4.m	This item is optional
5.	**Optional Criterion** G is an optional criterion and may be removed
13.	**This item is optional**

Pulldown List 1:			
RefName	**Display Text**	**Value**	**Design Note**
estrSaeUnitACTU	Actuation	ACTU	
estrSaeUnitAMP	Ampoule	AMP	
estrSaeUnitAPP	Application	AP	
estrSaeUnitBOT	Bottle	BT	
estrSaeUnitCAP	Capsule	CAP	
estrSaeUnitCC	Cubic centimeter	CC	
estrSaeUnitGTT	Drops	031	
estrSaeUnitGM	Gram	002	
estrSaeUnitIU	International units	025	

estrSaeUnitIUKG	International units per kilogram	028	
estrSaeUnitIUML	International units per millilitre	IUML	
estrSaeUnitL	Litre	011	
estrSaeUnitLPM	Litre per minute	LM	
estrSaeUnitLOZ	Lozenge	LOZ	
estrSaeUnitMU	Megaunits (million units)	MEGU	
estrSaeUnitMCG	Microgram (MCG)	004	
estrSaeUnitUG	Microgram (UG)	004	
estrSaeUnitMCGKG	Microgram/kilogram	008	
estrSaeUnitMCGKGMIN	Microgram/kilogram per minute	MCG/KG/MIN	
estrSaeUnitMCGMIN	Micrograms per minute	MCG/MIN	
estrSaeUnitMCL	Microlitre	013	
estrSaeUnitMEQ	Milliequivalent	029	
estrSaeUnitMEQ24HR	Milliequivalent per 24 hours	MEQ24	
estrSaeUnitMG	Milligram	003	
estrSaeUnitMGPER	Milligrams percent	MGPER	
estrSaeUnitMGHR	Milligram per hour	MGH	
estrSaeUnitMGKG	Milligram/kilogram	007	
estrSaeUnitMGKGHR	Milligram/kilogram per hour	MGKH	
estrSaeUnitMGKGMIN	Milligram/kilogram per minute	MGKM	
estrSaeUnitMGM2	Milligram/metre squared	009	
estrSaeUnitMGML	Milligram/millilitre	MGML	
estrSaeUnitML	Millilitre	012	
estrSaeUnitMLHR	Millilitre per hour	MLH	
estrSaeUnitMLMIN	Millilitre per minute	MLM	
estrSaeUnitMMOL	Millimole	023	
estrSaeUnitMIU	Million international units	027	
estrSaeUnitMAC	Minimum alveolar concentration	MAC	
estrSaeUnitNEB	Nebule	NEB	
estrSaeUnitPATCH	Patch	PAT	
estrSaeUnitPer	Percent	030	
estrSaeUnitPUFF	Puff	PUFF	
estrSaeUnitSACH	Sachet	SAC	
estrSaeUnitSP	Spray	SPR	
estrSaeUnitSUPP	Suppository	SUP	
estrSaeUnitTBSP	Tablespoon	TBS	
estrSaeUnitTAB	Tablet	TAB	
estrSaeUnitTSP	Teaspoon	TSP	
estrSaeUnitUNIT	Units	UNT	
estrSaeUnitUNK	Unknown	U	
estrSaeUnitVIAL	Vial	VIA	

Pulldown List 2:

RefName	Display Text	Value	Design Note
estrSaeFreq2XWK	2 times per week	2W	
estrSaeFreq3XWK	3 times per week	3W	

estrSaeFreq4XWK	4 times per week	4W	
estrSaeFreq5XD	5 times per day	5D	
estrSaeFreq5XWK	5 times per week	5W	
estrSaeFreqAC	AC	AC	
estrSaeFreqBID	BID	2D	
estrSaeFreqCINF	Continuous infusion	CO	
estrSaeFreqQ2WK	Every 2 weeks	FO	
estrSaeFreqQ3WK	Every 3 weeks	Q3WK	
estrSaeFreqQ3M	Every 3 months	Q3M	
estrSaeFreqQOD	Every other day	AD	
estrSaeFreqHS	At Bedtime	1N	
estrSaeFreqQM	Once a month	MO	
estrSaeFreqQWK	Once a week	WE	
estrSaeFreqQD	Once daily	1D	
estrSaeFreqONE	Once only	1S	
estrSaeFreqPC	PC	PC	
estrSaeFreqPRN	PRN	PRN	
estrSaeFreqQ2H	Q2H	12D	
estrSaeFreqQ3D	Q3D	Q3D	
estrSaeFreqQ4D	Q4D	Q4D	
estrSaeFreqQ4H	Q4H	6D	
estrSaeFreqQ6H	Q6H	4D	
estrSaeFreqQ8H	Q8H	3D	
estrSaeFreqQ12H	Q12H	2D	
estrSaeFreqQAM	QAM	1M	
estrSaeFreqQH	QH	24D	
estrSaeFreqQID	QID	4D	
estrSaeFreqQPM	QPM	1N	
estrSaeFreqTID	TID	3D	
estrSaeFreqUNK	Unknown	U	

Pulldown List 3:			
RefName	**Display Text**	**Value**	**Design Note**
estrSaeRouteOU	Both eyes	047	
estrSaeRouteEP	Epidural	008	
estrSaeRouteGTT	Gastrostomy tube	GT	
estrSaeRouteIH	Inhalation	055	
estrSaeRouteINJ	Injection	INJ	
estrSaeRouteIA	Intra-arterial	013	
estrSaeRouteIB	Intra-bursa	IBU	
estrSaeRouteIL	Intralesional	026	
estrSaeRouteIM	Intramuscular	030	
estrSaeRouteIN	Intranasal	045	
estrSaeRouteIO	Intraocular	031	
estrSaeRouteIOS	Intraosteal	IOS	
estrSaeRouteIP	Intraperitoneal	033	

estrSaeRouteIT	Intrathecal	037	
estrSaeRouteIU	Intrauterine	015	
estrSaeRouteIV	Intravenous	042	
estrSaeRouteNS	Nasal	045	
estrSaeRoutePO	Oral	048	
estrSaeRoutePR	Rectal	054	
estrSaeRouteSC	Subcutaneous	058	
estrSaeRouteSL	Sublingual	060	
estrSaeRouteTP	Topical	061	
estrSaeRouteTD	Transdermal	062	
estrSaeRouteUNK	Unknown	065	
estrSaeRouteVG	Vaginal	067	

Pulldown List 4:

RefName	Display Text	Value	Design Note
estrDRUGTYPE01	Concomitant	2	
estrDRUGTYPE02	Treatment	T	
estrDRUGTYPE03	Cause of SAE	1	

Pulldown List 5:

RefName	Display Text	Value	Design Note
estrSAELBTST01	Activated partial thromboplastin time	Activated partial thromboplastin time	
estrSAELBTST02	Albumin	Albumin	
estrSAELBTST03	Alkaline phosphatase	Alkaline phosphatase	
estrSAELBTST04	Amylase	Amylase	
estrSAELBTST05	Basophils	Basophils	
estrSAELBTST06	Bicarbonate	Bicarbonate	
estrSAELBTST07	Bilirubin	Bilirubin	
estrSAELBTST08	Bilirubin direct	Bilirubin direct	
estrSAELBTST09	Bilirubin total	Bilirubin total	
estrSAELBTST10	Blood myoglobin	Blood myoglobin	
estrSAELBTST11	Blood pH	Blood pH	
estrSAELBTST12	Blood pressure	Blood pressure	
estrSAELBTST13	Blood urea nitrogen	Blood urea nitrogen	
estrSAELBTST14	Body temperature	Body temperature	
estrSAELBTST15	Calcium	Calcium	
estrSAELBTST16	CD4 lymphocytes	CD4 lymphocytes	
estrSAELBTST17	CD8 lymphocytes	CD8 lymphocytes	
estrSAELBTST18	Chloride	Chloride	
estrSAELBTST19	Cholesterol total	Cholesterol total	
estrSAELBTST20	C-reactive protein	C-reactive protein	
estrSAELBTST21	Creatine	Creatine	
estrSAELBTST22	Creatine phosphokinase	Creatine phosphokinase	
estrSAELBTST23	Creatine phosphokinase MB	Creatine phosphokinase MB	
estrSAELBTST24	Creatinine	Creatinine	
estrSAELBTST25	Creatinine clearance	Creatinine clearance	

estrSAELBTST26	Diastolic blood pressure	Diastolic blood pressure	
estrSAELBTST27	Eosinophils	Eosinophils	
estrSAELBTST28	Erythrocyte sedimentation rate	Erythrocyte sedimentation rate	
estrSAELBTST29	Fasting blood glucose	Fasting blood glucose	
estrSAELBTST30	FEV 1	FEV 1	
estrSAELBTST31	Gamma-glutamyltransferase	Gamma-glutamyltransferase	
estrSAELBTST32	Glutamic-oxaloacetic transferase	Glutamic-oxaloacetic transferase	
estrSAELBTST33	Glutamic-pyruvate transaminase	Glutamic-pyruvate transaminase	
estrSAELBTST34	HbA1c	HbA1c	
estrSAELBTST35	HBV-DNA decreased	HBV-DNA decreased	
estrSAELBTST36	HBV-DNA increased	HBV-DNA increased	
estrSAELBTST37	Heart rate	Heart rate	
estrSAELBTST38	Hematocrit	Hematocrit	
estrSAELBTST39	Hemoglobin	Hemoglobin	
estrSAELBTST40	High density lipoprotein	High density lipoprotein	
estrSAELBTST41	HIV viral load	HIV viral load	
estrSAELBTST42	INR	INR	
estrSAELBTST43	Lactic dehydrogenase	Lactic dehydrogenase	
estrSAELBTST44	Lipase	Lipase	
estrSAELBTST45	Low density lipoprotein	Low density lipoprotein	
estrSAELBTST46	Lymphocytes	Lymphocytes	
estrSAELBTST47	Magnesium	Magnesium	
estrSAELBTST48	Mean cell hemoglobin concentration	Mean cell hemoglobin concentration	
estrSAELBTST49	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin	
estrSAELBTST50	Mean corpuscular volume	Mean corpuscular volume	
estrSAELBTST51	Monocytes	Monocytes	
estrSAELBTST52	Neutrophils	Neutrophils	
estrSAELBTST53	Oxygen saturation	Oxygen saturation	
estrSAELBTST54	pCO2	pCO2	
estrSAELBTST55	pH	pH	
estrSAELBTST56	Phosphate	Phosphate	
estrSAELBTST57	Platelet count	Platelet count	
estrSAELBTST58	pO2	pO2	
estrSAELBTST59	Potassium	Potassium	
estrSAELBTST60	Protein total	Protein total	
estrSAELBTST61	Prothrombin time	Prothrombin time	
estrSAELBTST62	Red blood cell count	Red blood cell count	
estrSAELBTST63	Respiratory rate	Respiratory rate	
estrSAELBTST64	Reticulocyte count	Reticulocyte count	
estrSAELBTST65	Serum glucose	Serum glucose	
estrSAELBTST66	Serum uric acid	Serum uric acid	
estrSAELBTST67	Sodium	Sodium	
estrSAELBTST68	Systolic blood pressure	Systolic blood pressure	
estrSAELBTST69	Thrombin time	Thrombin time	
estrSAELBTST70	Total lung capacity	Total lung capacity	
estrSAELBTST71	Triglycerides	Triglycerides	

estrSAELBTST72	Troponin	Troponin	
estrSAELBTST73	Troponin I	Troponin I	
estrSAELBTST74	Troponin T	Troponin T	
estrSAELBTST75	Urine myoglobin	Urine myoglobin	
estrSAELBTST76	Urine pH	Urine pH	
estrSAELBTST77	Vital capacity	Vital capacity	
estrSAELBTST78	White blood cell count	White blood cell count	

CDD: MAPPINGS1 Table: t_AE_SER Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
chkSAE	STRING(255)	
chkFU	STRING(255)	
rdcSAERAND	STRING(1)	
AESEQ	STRING(5) - A5	
AETERM	STRING(100) - A100	
AEMODIFY	STRING(100) - A100	
AEMEDSYN	STRING(255)	
AELLTCD	STRING(255)	
calAE_FAILED	STRING(255)	
AESTDTTM	DATE - DDMONYYYY HHMM	
AEOUTCD1	STRING(1)	
AEENDTTM1	DATE - DDMONYYYY HHMM	
AEENDTTM2	DATE - DDMONYYYY HHMM	
AEENDTTM3	DATE - DDMONYYYY HHMM	
AESEVCD	STRING(1)	
AETOXCD	STRING(1)	
AETXHVCD	STRING(1)	
AEACTRCD	STRING(1)	
AEWD	STRING(1)	
AEREL	STRING(1)	
AEDURHR	NUMERIC - N2	
AEDURMIN	NUMERIC - N2	
AEONLDSH	NUMERIC - N2	
AEONLDSM	NUMERIC - N2	
rdcAESREL	STRING(1)	
AESER	STRING(1)	
AESERDTH	STRING(255)	
AESERLIF	STRING(255)	
AESERHOS	STRING(255)	
AESERDIS	STRING(255)	
AESERCON	STRING(255)	
AESEROTH	STRING(255)	
AESERPROTSP	STRING(255)	
txtSAECMSEQ	STRING(4) - A4	
txtCMTERM	STRING(100) - A100	
txtSAECMDOS	FLOAT - F10.0	

pdcCMUNIT	STRING(255) - ACTU, AMP, AP, BT, CAP, CC, 031, 002, 025, 028, IUML, 011, LM, LOZ, MEGU, 004, 004, 008, MCG/KG/MIN , MCG/MIN , 013, 029, MEQ24, 003, MGPER, MGH, 007, MGKH, MGKM, 009, MGML, 012, MLH, MLM, 023, 027, MAC, NEB, PAT, 030, PUFF, SAC, SPR, SUP, TBS, TAB, TSP, UNT, U, VIA	
pdcSAECMFRQ	STRING(255) - 2W, 3W, 4W, 5D, 5W, AC, 2D, CO, FO, Q3WK, Q3M, AD, 1N, MO, WE, 1D, 1S, PC, PRN, 12D, Q3D , Q4D, 6D, 4D, 3D, 2D, 1M, 24D, 4D, 1N, 3D, U	
pdcCMROUTCD	STRING(255) - 047, 008, GT, 055, INJ, 013, IBU, 026, 030, 045, 031, IOS, 033, 037, 015, 042, 045, 048, 054, 058, 060, 061, 062, 065, 067	
dtmSAECMSTD	DATE - DDMONYYYY	
rdcSAECMONG	STRING(1)	
dtmSAECMEND	DATE - DDMONYYYY	
txtCMIND	STRING(50) - A50	
pdcCMDRGTYP	STRING(255) - 2, T, 1	
txtMHXSEQ	STRING(4) - A4	
txtSAEMHTRM	STRING(100) - A100	
dtmMHSTDTM	DATE - DDMONYYYY	
rdcMHCONT	STRING(1)	
dtmMHLSTOC	DATE - DDMONYYYY	
txtSAELBSEQ	STRING(4) - A4	
pdcLBTST	STRING(255) - Activated partial thromboplastin time, Albumin, Alkaline phosphatase, Amylase, Basophils, Bicarbonate, Bilirubin, Bilirubin direct, Bilirubin total, Blood myoglobin, Blood pH, Blood pressure, Blood urea nitrogen, Body temperature, Calcium, CD4 lymphocytes, CD8 lymphocytes, Chloride, Cholesterol total, C-reactive protein, Creatine, Creatine phosphokinase, Creatine phosphokinase MB, Creatinine, Creatinine clearance, Diastolic blood pressure, Eosinophils, Erythrocyte sedimentation rate, Fasting blood glucose, FEV 1, Gamma-glutamyltransferase, Glutamic-oxaloacetic transferase, Glutamic-pyruvate transaminase, HbA1c, HBV-DNA decreased, HBV-DNA increased, Heart rate, Hematocrit, Hemoglobin, High density lipoprotein, HIV viral load, INR, Lactic dehydrogenase, Lipase, Low density lipoprotein, Lymphocytes, Magnesium, Mean cell hemoglobin concentration, Mean corpuscular hemoglobin, Mean corpuscular volume, Monocytes, Neutrophils, Oxygen saturation, pCO2, pH, Phosphate, Platelet count, pO2, Potassium, Protein total, Prothrombin time, Red blood cell count, Respiratory rate, Reticulocyte count, Serum glucose, Serum uric acid, Sodium, Systolic blood pressure, Thrombin time, Total lung capacity, Triglycerides, Troponin, Troponin I, Troponin T, Urine myoglobin, Urine pH, Vital capacity, White blood cell count	
dtmLABDTM	DATE - DDMONYYYY	
txtLABRES	STRING(50) - A50	
txtLABUNIT	STRING(35) - A35	
txtLABNLR	FLOAT - F8.0	
txtLABNHR	FLOAT - F8.0	
rdcSAEIP	STRING(1)	
chkSAESENDI	STRING(255)	
dtmSAEDTM	DATE - DDMONYYYY HHMM	
AESE1	STRING(1)	
AESE2	STRING(5) - A5	
txtSAEVERSION	STRING(4) - A4	
txtSAEID	STRING(20) - A20	
txtSAERNDNO	STRING(255) - A255	
txtOCEANSCD	STRING(13) - A13	
calSAEEmailFlag	STRING(255)	

lpl112498_128 : CONCOMITANT MEDICATIONS (Con Meds) - Repeating Form

#		Sequence Number	Drug Name (Trade Name preferred)	Unit Dose	Units	Frequency	Route	Reason for Medication	Start Date and Time	Taken Prior to Study?	Ongoing?	
1												

CONCOMITANT MEDICATIONS

	Sequence Number	(MAPPINGS1:t_CONMEDS.CMSEQ)
1.	Drug Name (Trade Name preferred)	A100 (MAPPINGS1:t_CONMEDS.CMTERM)
2.*	Modified reported term [*hidden*]	A100 (MAPPINGS1:t_CONMEDS.CMMODIFY)
	GSK Drug synonym [*hidden*]	(MAPPINGS1:t_CONMEDS.CMDRGSYN)
	GSK Drug Collection code [*hidden*]	(MAPPINGS1:t_CONMEDS.CMDRGCOL)
	Failed coding [*hidden*]	(MAPPINGS1:t_CONMEDS.calCM_FAILED)
3.	Unit Dose	A10 (MAPPINGS1:t_CONMEDS.CMUDOS)
4.	Units	Pulldown List 1 (MAPPINGS1:t_CONMEDS.CMUNIT)
5.	Frequency	Pulldown List 2 (MAPPINGS1:t_CONMEDS.CMFREQ)
6.	Route	Pulldown List 3 (MAPPINGS1:t_CONMEDS.CMROUTCD)
7.	Reason for Medication	A70 (MAPPINGS1:t_CONMEDS.CMREAS)
8.	Start Date and Time Hr:Min (00:00-23:59)	Req/Unk / Req/Unk / Req/Unk (1900-2009) (MAPPINGS1:t_CONMEDS.CMSTDTTM) NReq : NReq *24-hour clock*
9.	Taken Prior to Study?	(MAPPINGS1:t_CONMEDS.CMPRIOR) *[Y]* ◯ Yes *[N]* ◯ No
10.	Ongoing? Hr:Min (00:00-23:59)	(MAPPINGS1:t_CONMEDS.CMONGO) *[Y]* ◯ Yes **[N]** ◯ No, specify End Date and Time Req/Unk / Req/Unk / Req/Unk (2008-2009) (MAPPINGS1:t_CONMEDS.CMENDTTM) NReq : NReq *24-hour clock*

* Item is not required

Item Design Notes:

Item No.	Design Note
3.	This item is conditional

Pulldown List 1:

RefName	Display Text	Value	Design Note
mestrUnitACTU	Actuation	ACTU	
mestrUnitAMP	Ampoule	AMP	
mestrUnitAPP	Application	APP	

mestrUnitAUC	Area under curve	AUC	
mestrUnitBOT	Bottle	BOT	
mestrUnitCAP	Capsule	CAP	
mestrUnitCC	Cubic centimeter	CC	
mestrUnitCUP	Cup	CUP	
mestrUnitGAKGM	Gamma per kilogram per minute	GA/KG/MIN	
mestrUnitGM	Gram	G	
mestrUnitGTT	Drops	GTT	
mestrUnitHIUML	100 International units/ml	100IU/ML	
mestrUnitINH	Inhalation	INH	
mestrUnitIU	International units	IU	
mestrUnitIUKG	International units per kilogram	IU/KG	
mestrUnitIUKGH	International units per kilogram per hour	IU/KG/HR	
mestrUnitIUML	International units per millilitre	IU/ML	
mestrUnitL	Litre	L	
mestrUnitLOZ	Lozenge	LOZ	
mestrUnitLPM	Litre per minute	L/MIN	
mestrUnitMAC	Minimum alveolar concentration	MAC	
mestrUnitMBQ	Mega becquerels (MBq)	MBQ	
mestrUnitMCG	Microgram (MCG)	MCG	
mestrUnitMCGH	Micrograms per hour	MCG/HR	
mestrUnitMCGKG	Microgram/kilogram	MCG/KG	
mestrUnitMCGKGMIN	Microgram/kilogram per minute	MCG/KG/MIN	
mestrUnitMCGMIN	Micrograms per minute	MCG/MIN	
mestrUnitMCGML	Micrograms per millitre	MCG/ML	
mestrUnitMCL	Microlitre	MCL	
mestrUnitMEQ	Milliequivalent	MEQ	
mestrUnitMEQ24HR	Milliequivalent per 24 hours	MEQ/24HR	
mestrUnitMG	Milligram	MG	
mestrUnitMGD	Milligram per day	MG/DAY	
mestrUnitMGHR	Milligram per hour	MG/HR	
mestrUnitMGKG	Milligram/kilogram	MG/KG	
mestrUnitMGKGHR	Milligram/kilogram per hour	MG/KG/HR	
mestrUnitMGKGMIN	Milligram/kilogram per minute	MG/KG/MIN	
mestrUnitMGM2	Milligram/metre squared	MG/M2	
mestrUnitMGML	Milligram/millilitre	MG/ML	
mestrUnitMGPER	Milligrams percent	MG%	
mestrUnitMIU	Million international units	MIU	
mestrUnitML	Millilitre	ML	
mestrUnitMLHR	Millilitre per hour	ML/HR	
mestrUnitMLMIN	Millilitre per minute	ML/MIN	
mestrUnitMMOL	Millimole	MMOL	
mestrUnitMU	Megaunits (million units)	MU	
mestrUnitNEB	Nebule	NEB	
mestrUnitOZ	Ounce	OZ	
mestrUnitPATCH	Patch	PATCH	

mestrUnitPer	Percent	%	
mestrUnitPUFF	Puff	PUFF	
mestrUnitSACH	Sachet	SACH	
mestrUnitSP	Spray	SPR	
mestrUnitSUPP	Suppository	SUPP	
mestrUnitTAB	Tablet	TAB	
mestrUnitTBSP	Tablespoon	TBLSP	
mestrUnitTSP	Teaspoon	TSP	
mestrUnitUG	Microgram (UG)	UG	
mestrUnitUHR	Units per hour	U/HR	
mestrUnitUKGM	Units per kilogram per minute	U/KG/MIN	
mestrUnitUMN	Units per minute	U/MIN	
mestrUnitUNIT	Units	U	
mestrUnitUNK	Unknown	UNK	
mestrUnitVIAL	Vial	VIAL	

Pulldown List 2:			
RefName	**Display Text**	**Value**	**Design Note**
mestrFreq2XWK	2 times per week	2XWK	
mestrFreq3XWK	3 times per week	3XWK	
mestrFreq4XWK	4 times per week	4XWK	
mestrFreq5XD	5 times per day	5XD	
mestrFreq5XWK	5 times per week	5XWK	
mestrFreqAC	AC	AC	
mestrFreqBID	BID	BID	
mestrFreqCINF	Continuous infusion	CINF	
mestrFreqHS	HS	HS	
mestrFreqOD	Once daily	OD	
mestrFreqONE	Once only	ONE	
mestrFreqPC	PC	PC	
mestrFreqPRN	PRN	PRN	
mestrFreqQ12H	Q12H	Q12H	
mestrFreqQ2H	Q2H	Q2H	
mestrFreqQ2WK	Every 2 weeks	Q2WK	
mestrFreqQ3D	Q3D	Q3D	
mestrFreqQ3M	Every 3 months	Q3M	
mestrFreqQ3WK	Every 3 weeks	Q3WK	
mestrFreqQ4D	Q4D	Q4D	
mestrFreqQ4H	Q4H	Q4H	
mestrFreqQ6H	Q6H	Q6H	
mestrFreqQ8H	Q8H	Q8H	
mestrFreqQAM	QAM	QAM	
mestrFreqQH	QH	QH	
mestrFreqQID	QID	QID	
mestrFreqQM	Once a month	QM	
mestrFreqQOD	Every other day	QOD	

mestrFreqQPM	QPM	QPM	
mestrFreqQWK	Once a week	QWK	
mestrFreqTID	TID	TID	
mestrFreqUNK	Unknown	UNK	

Pulldown List 3:			
RefName	**Display Text**	**Value**	**Design Note**
mestrRouteEP	Epidural	EP	
mestrRouteGTT	Gastrostomy tube	GTT	
mestrRouteIA	Intra-arterial	IA	
mestrRouteIART	Intra-articular	IART	
mestrRouteIB	Intra-bursa	IB	
mestrRouteID	Intradermal	ID	
mestrRouteIH	Inhalation	IH	
mestrRouteIL	Intralesional	ILES	
mestrRouteIM	Intramuscular	IM	
mestrRouteIN	Intranasal	IN	
mestrRouteINJ	Injection	INJ	
mestrRouteIO	Intraocular	IO	
mestrRouteIOS	Intraosteal	IOS	
mestrRouteIP	Intraperitoneal	IP	
mestrRouteIT	Intrathecal	IT	
mestrRouteIU	Intrauterine	IU	
mestrRouteIV	Intravenous	IV	
mestrRouteNG	Nasogastric	NG	
mestrRouteNS	Nasal	NS	
mestrRouteOD	Right eye	OD	
mestrRouteOP	Ophthalmic	OP	
mestrRouteOS	Left eye	OS	
mestrRouteOT	Otic	OT	
mestrRouteOTH	Other	OTH	
mestrRouteOU	Both eyes	OU	
mestrRoutePO	Oral	PO	
mestrRoutePR	Rectal	PR	
mestrRouteSC	Subcutaneous	SC	
mestrRouteSL	Sublingual	SL	
mestrRouteTD	Transdermal	TD	
mestrRouteTP	Topical	TP	
mestrRouteUNK	Unknown	UNK	
mestrRouteVG	Vaginal	VG	

CDD: MAPPINGS1 Table: t_CONMEDS Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
CMSEQ	STRING(255)	
CMTERM	STRING(100) - A100	
CMMODIFY	STRING(100) - A100	

CMDRGSYN	STRING(255)	
CMDRGCOL	STRING(255)	
calCM_FAILED	STRING(255)	
CMUDOS	STRING(10) - A10	
CMUNIT	STRING(255) - ACTU, AMP, APP, AUC, BOT, CAP, CC, CUP, GA/KG/MIN, G, GTT, 100IU/ML, INH, IU, IU/KG, IU/KG/HR, IU/ML, L, LOZ, L/MIN, MAC, MBQ, MCG, MCG/HR, MCG/KG, MCG/KG/MIN, MCG/MIN, MCG/ML, MCL, MEQ, MEQ/24HR, MG, MG/DAY, MG/HR, MG/KG, MG/KG/HR, MG/KG/MIN, MG/M2, MG/ML, MG%, MIU, ML, ML/HR, ML/MIN, MMOL, MU, NEB, OZ, PATCH, %, PUFF, SACH, SPR, SUPP, TAB, TBLSP, TSP, UG, U/HR, U/KG/MIN, U/MIN, U, UNK, VIAL	
CMFREQ	STRING(255) - 2XWK, 3XWK, 4XWK, 5XD, 5XWK, AC, BID, CINF, HS, OD, ONE, PC, PRN, Q12H, Q2H, Q2WK, Q3D, Q3M, Q3WK, Q4D, Q4H, Q6H, Q8H, QAM, QH, QID, QM, QOD, QPM, QWK, TID, UNK	
CMROUTCD	STRING(255) - EP, GTT, IA, IART, IB, ID, IH, ILES, IM, IN, INJ, IO, IOS, IP, IT, IU, IV, NG, NS, OD, OP, OS, OT, OTH, OU, PO, PR, SC, SL, TD, TP, UNK, VG	
CMREAS	STRING(70) - A70	
CMSTDTTM	DATE - DDMONYYYY HHMM	
CMPRIOR	STRING(1)	
CMONGO	STRING(1)	
CMENDTTM	DATE - DDMONYYYY HHMM	

lpl112498_128 : ELECTRONICALLY TRANSFERRED LAB DATA (Lab Rpt) - Repeating Form				
#		Laboratory Test Type	Date	
1				

ELECTRONICALLY TRANSFERRED LAB DATA		
Record each repeat lab in a separate record		
1.	Laboratory Test Type	(MAPPINGS1:t_LABLINK_RPT.rdcLBType) *[H]* ◯ Haematology *[C]* ◯ Clinical Chemistry *[U]* ◯ Urinalysis
2.	Date and time sample taken Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_LABLINK_RPT.LBDTTM) Req : Req *24-hour clock*

Form Design Note:
Repeat Lablink

Item Design Notes:	
Item No.	**Design Note**
1.	Study team can add additional test types if needed for their protocol

CDD: MAPPINGS1 Table: t_LABLINK_RPT Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
rdcLBType	STRING(1)	
LBDTTM	DATE - DDMONYYYY HHMM	

lpl112498_128 : VITAL SIGNS (VS Rpt) - Repeating Form				
#		Actual	BP	HR
1				

VITAL SIGNS (seated)

1.	Actual date/time Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_VITALS_RPT.VSACTDTTM) Req : Req *24-hour clock*
2.	Blood pressure	(MAPPINGS1:t_VITALS_RPT.rdcBPRpt) *[ND]* Not Done **[Y]** xxx (n >= 0) / (MAPPINGS1:t_VITALS_RPT.SYSBP) xxx (n >= 0) mmHg (MAPPINGS1:t_VIT (systolic/diastolic)
3.	Heart rate	(MAPPINGS1:t_VITALS_RPT.rdcHEART) *[ND]* Not Done **[Y]** xxx (n >= 0) beats/min (MAPPINGS1:t_VITALS_RPT.HEART)

Form Design Note:
Repeat vital signs

CDD: MAPPINGS1 Table: t_VITALS_RPT Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
VSACTDTTM	DATE - DDMONYYYY HHMM	
rdcBPRpt	STRING(2)	
SYSBP	NUMERIC - N3	
DIABP	NUMERIC - N3	
rdcHEART	STRING(2)	
HEART	NUMERIC - N3	

lpl112498_128 : 12-LEAD ECG (ECG Rpt) - Repeating Form

#		Date	HR	PR	QRS	QT	QTC	Method QTc Calc	Result	
1										

12-LEAD ECG

1.	Date and Time of ECG Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_ECG_RPT.EGDTTM) Req : Req *24-hour clock*
2.	Heart rate	xxx (n >= 0) beats/min (MAPPINGS1:t_ECG_RPT.EGHR)
3.	PR Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_RPT.PR__)
4.	QRS Duration	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_RPT.QRS__)
5.	Uncorrected QT Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_RPT.QT__)
6.	QTc Interval	xxxxx. (n >= 0.0) msec (MAPPINGS1:t_ECG_RPT.QTC__)
7.	Method of QTc Calculation	(MAPPINGS1:t_ECG_RPT.EGMTCLCD) *[1]* ◯ Machine *[2]* ◯ Manual
8.	Result of the ECG	(MAPPINGS1:t_ECG_RPT.EGINTPCD) *[1]* ◯ Normal *[2]* ◯ Abnormal - Not clinically significant *[3]* ◯ Abnormal - Clinically significant *(complete the ECG abnormality form for all clinically significant abnormalities, and additionally complete the AE form if the abnormality meets the protocol definition for an AE)* *[4]* ◯ No result (not available)

Form Design Note:
Repeat ECG

CDD: MAPPINGS1 Table: t_ECG_RPT Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
EGDTTM	DATE - DDMONYYYY HHMM	
EGHR	NUMERIC - N3	
PR__	FLOAT - F6.0	
QRS__	FLOAT - F6.0	
QT__	FLOAT - F6.0	
QTC__	FLOAT - F6.0	
EGMTCLCD	STRING(1)	
EGINTPCD	STRING(1)	

lpl112498_128 : ECG ABNORMALITIES (ECG Abn) - Repeating Form

#		Date	Result	
1				

12-LEAD ECG ABNORMALITIES

1.	Date and Time of ECG Hr:Min (00:00-23:59)	Req / Req / Req (2008-2009) (MAPPINGS1:t_ECG_ABNORM.EGDTTM) Req : Req *24-hour clock*
2.	Record clinically significant abnormalities *(check all that apply)*	A. Rhythm (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_AAA) *[A1]* ☐ Sinus bradycardia (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_BBB) *[A21]* ☐ Sinus bradycardia (heart rate 40-50 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_CCC) *[A22]* ☐ Sinus bradycardia (heart rate 30-39 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_DDD) *[A23]* ☐ Sinus bradycardia (heart rate <30 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_EEE) *[A3]* ☐ Sinus pause (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_FFF) *[A2]* ☐ Sinus tachycardia (heart rate > 100 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_GGG) *[A4]* ☐ Ectopic supraventricular beats (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_HHH) *[A20]* ☐ Ectopic supraventricular rhythm (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_III) *[A17]* ☐ Wandering atrial pacemaker (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_JJJ) *[A26]* ☐ Multifocal atrial tachycardia (wandering atrial pacemaker w/rate >100 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_KKK) *[A6]* ☐ Supraventricular tachycardia (heart rate>100 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_LLL) *[A7]* ☐ Atrial flutter (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_MMM) *[A8]* ☐ Atrial fibrillation (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_NNN) *[A5]* ☐ Junctional rhythm (heart rate<=100 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_OOO) *[A25]* ☐ Junctional rhythm (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_PPP) *[A24]* ☐ Junctional tachycardia (heart rate>100 beats/min) (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_QQQ) *[A9]* ☐ Ectopic ventricular beats (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_RRR) *[A12]* ☐ Ventricular couplets (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_SSS) *[A13]* ☐ Bigeminy (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_TTT) *[A28]* ☐ Trigeminy (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_UUU) *[A14]* ☐ Electrical alternans (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_VVV) *[A29]* ☐ R on T phenomenon (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_WWW) *[A18]* ☐ Ventricular fibrillation (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_XXX) *[A19]* ☐ Idioventricular rhythm (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_YYY) *[A10]* ☐ Sustained ventricular tachycardia (MAPPINGS1:t_ECG_ABNORM.RHYTHM1_ZZZ)

[A11] ☐ Non-sustained ventricular tachycardia
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_GGG)
[A32] ☐ Wide QRS tachycardia (diagnosis unknown)
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_AAA)
[A27] ☐ Ventricular tachycardia
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_BBB)
[A30] ☐ Monomorphic ventricular tachycardia
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_CCC)
[A15] ☐ Torsades de Pointes (Polymorphic ventricular tachycardia with prolonged QT)
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_DDD)
[A31] ☐ Polymorphic (sustained and non-sustained) ventricular tachycardia
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_EEE)
[A16] ☐ Artificial Pacemaker
(MAPPINGS1:t_ECG_ABNORM.RHYTHM2_FFF)
[A99] ☐ Other abnormal rhythm, enter comment (MAPPINGS1:t_ECG_ABNORM.EGFOTHA)

A200

B. P-Wave Morphology
(MAPPINGS1:t_ECG_ABNORM.MORPHOLOGY_AAA)
[B1] ☐ Left atrial abnormality (P mitrale)
(MAPPINGS1:t_ECG_ABNORM.MORPHOLOGY_BBB)
[B2] ☐ Right atrial abnormality (P pulmonale)
(MAPPINGS1:t_ECG_ABNORM.MORPHOLOGY_CCC)
[B3] ☐ Right ventricular hypertrophy
(MAPPINGS1:t_ECG_ABNORM.MORPHOLOGY_DDD)
[B5] ☐ Intraatrial conduction delay
(MAPPINGS1:t_ECG_ABNORM.MORPHOLOGY_EEE)
[D14] ☐ Increased voltage consistent with left ventricular hypertrophy
(MAPPINGS1:t_ECG_ABNORM.MORPHOLOGY_FFF)
[B99] ☐ Other morphology, enter comment (MAPPINGS1:t_ECG_ABNORM.EGFOTHB)

A200

C. Conduction
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_AAA)
[C1] ☐ First degree AV block (PR interval > 200msec)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_TTT)
[C20] ☐ Short PR interval
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_BBB)
[C2] ☐ Second degree AV block (Mobitz type 1)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_CCC)
[C3] ☐ Second degree AV block (Mobitz type 2)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_DDD)
[C16] ☐ 2:1 AV block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_EEE)
[C4] ☐ Third degree AV block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_FFF)
[C5] ☐ Left axis deviation (QRS axis more negative than -30 degrees)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_GGG)
[C6] ☐ Right axis deviation (QRS axis more positive than +110 degrees)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_HHH)
[C7] ☐ Incomplete right bundle branch block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_III)
[C13] ☐ Incomplete left bundle branch block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_JJJ)
[C8] ☐ Right bundle branch block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_KKK)
[C14] ☐ Left anterior hemiblock (synonymous to left anterior fascicular block)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_LLL)
[C15] ☐ Left posterior hemiblock (synonymous to left posterior fascicular block)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_MMM)

[C9] ☐ Left bundle branch block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_NNN)
[C17] ☐ Bifascicular block
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_OOO)
[C10] ☐ Non-specific intraventricular conduction delay (QRS ≥ 120 msec)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_PPP)
[C11] ☐ Accessory pathway (Wolff-Parkinson White, Lown-Ganong-Levine)
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_UUU)
[C19] ☐ Prolonged QT interval
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_QQQ)
[C12] ☐ QT/QTc prolongation ≥ 500 msec
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_RRR)
[C18] ☐ AV dissociation
(MAPPINGS1:t_ECG_ABNORM.CONDUCTION_SSS)
[C99] ☐ Other conduction, enter comment (MAPPINGS1:t_ECG_ABNORM.EGFOTHC)

A200

D. Myocardial Infarction
(MAPPINGS1:t_ECG_ABNORM.MI_AAA)
[D1] ☐ Myocardial infarction, old
(MAPPINGS1:t_ECG_ABNORM.MI_BBB)
[D2] ☐ Myocardial infarction, anterior
(MAPPINGS1:t_ECG_ABNORM.MI_CCC)
[D3] ☐ Myocardial infarction, lateral
(MAPPINGS1:t_ECG_ABNORM.MI_DDD)
[D4] ☐ Myocardial infarction, posterior
(MAPPINGS1:t_ECG_ABNORM.MI_EEE)
[D5] ☐ Myocardial infarction, inferior
(MAPPINGS1:t_ECG_ABNORM.MI_FFF)
[D6] ☐ Myocardial infarction, septal
(MAPPINGS1:t_ECG_ABNORM.MI_GGG)
[D20] ☐ Myocardial infarction, Non Q-wave
(MAPPINGS1:t_ECG_ABNORM.MI_HHH)
[D98] ☐ Other myocardial infarction, enter comment (MAPPINGS1:t_ECG_ABNORM.EGFOTHD)

A200

E. Depolarisation/Repolarisation (QRS-T)
(MAPPINGS1:t_ECG_ABNORM.DEPO_AAA)
[D7] ☐ Non-specific ST-T changes
(MAPPINGS1:t_ECG_ABNORM.DEPO_BBB)
[D19] ☐ J point elevation
(MAPPINGS1:t_ECG_ABNORM.DEPO_CCC)
[D8] ☐ ST elevation
(MAPPINGS1:t_ECG_ABNORM.DEPO_DDD)
[D21] ☐ ST-elevation - pericarditis
(MAPPINGS1:t_ECG_ABNORM.DEPO_EEE)
[D9] ☐ ST depression
(MAPPINGS1:t_ECG_ABNORM.DEPO_FFF)
[D10] ☐ U waves abnormal
(MAPPINGS1:t_ECG_ABNORM.DEPO_GGG)
[D11] ☐ T wave inversion
(MAPPINGS1:t_ECG_ABNORM.DEPO_HHH)
[D12] ☐ T wave peaked
(MAPPINGS1:t_ECG_ABNORM.DEPO_III)
[D15] ☐ T waves flat
(MAPPINGS1:t_ECG_ABNORM.DEPO_JJJ)
[D16] ☐ T waves biphasic
(MAPPINGS1:t_ECG_ABNORM.DEPO_KKK)
[D18] ☐ Notched T-waves
(MAPPINGS1:t_ECG_ABNORM.DEPO_LLL)

[D13] ☐ Low QRS voltage
(MAPPINGS1:t_ECG_ABNORM.DEPO_MMM)
[D17] ☐ T-wave flattening/inversion
(MAPPINGS1:t_ECG_ABNORM.DEPO_NNN)
[D99] ☐ Other depolarisation/repolarisation, enter comment (MAPPINGS1:t_ECG_ABNORM.EGFOTHE)

A200

Other abnormalities
(MAPPINGS1:t_ECG_ABNORM.OTHER_AAA)
[E99] ☐ Enter comment (MAPPINGS1:t_ECG_ABNORM.EGFOTHO)

A200

CDD: MAPPINGS1 Table: t_ECG_ABNORM Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
EGDTTM	DATE - DDMONYYYY HHMM	
RHYTHM1_AAA	STRING(255)	
RHYTHM1_BBB	STRING(255)	
RHYTHM1_CCC	STRING(255)	
RHYTHM1_DDD	STRING(255)	
RHYTHM1_EEE	STRING(255)	
RHYTHM1_FFF	STRING(255)	
RHYTHM1_GGG	STRING(255)	
RHYTHM1_HHH	STRING(255)	
RHYTHM1_III	STRING(255)	
RHYTHM1_JJJ	STRING(255)	
RHYTHM1_KKK	STRING(255)	
RHYTHM1_LLL	STRING(255)	
RHYTHM1_MMM	STRING(255)	
RHYTHM1_NNN	STRING(255)	
RHYTHM1_OOO	STRING(255)	
RHYTHM1_PPP	STRING(255)	
RHYTHM1_QQQ	STRING(255)	
RHYTHM1_RRR	STRING(255)	
RHYTHM1_SSS	STRING(255)	
RHYTHM1_TTT	STRING(255)	
RHYTHM1_UUU	STRING(255)	
RHYTHM1_VVV	STRING(255)	
RHYTHM1_WWW	STRING(255)	
RHYTHM1_XXX	STRING(255)	
RHYTHM1_YYY	STRING(255)	
RHYTHM1_ZZZ	STRING(255)	
RHYTHM2_GGG	STRING(255)	
RHYTHM2_AAA	STRING(255)	
RHYTHM2_BBB	STRING(255)	
RHYTHM2_CCC	STRING(255)	

RHYTHM2_DDD	STRING(255)	
RHYTHM2_EEE	STRING(255)	
RHYTHM2_FFF	STRING(255)	
EGFOTHA	STRING(200) - A200	
MORPHOLOGY_AAA	STRING(255)	
MORPHOLOGY_BBB	STRING(255)	
MORPHOLOGY_CCC	STRING(255)	
MORPHOLOGY_DDD	STRING(255)	
MORPHOLOGY_EEE	STRING(255)	
MORPHOLOGY_FFF	STRING(255)	
EGFOTHB	STRING(200) - A200	
CONDUCTION_AAA	STRING(255)	
CONDUCTION_TTT	STRING(255)	
CONDUCTION_BBB	STRING(255)	
CONDUCTION_CCC	STRING(255)	
CONDUCTION_DDD	STRING(255)	
CONDUCTION_EEE	STRING(255)	
CONDUCTION_FFF	STRING(255)	
CONDUCTION_GGG	STRING(255)	
CONDUCTION_HHH	STRING(255)	
CONDUCTION_III	STRING(255)	
CONDUCTION_JJJ	STRING(255)	
CONDUCTION_KKK	STRING(255)	
CONDUCTION_LLL	STRING(255)	
CONDUCTION_MMM	STRING(255)	
CONDUCTION_NNN	STRING(255)	
CONDUCTION_OOO	STRING(255)	
CONDUCTION_PPP	STRING(255)	
CONDUCTION_UUU	STRING(255)	
CONDUCTION_QQQ	STRING(255)	
CONDUCTION_RRR	STRING(255)	
CONDUCTION_SSS	STRING(255)	
EGFOTHC	STRING(200) - A200	
MI_AAA	STRING(255)	
MI_BBB	STRING(255)	
MI_CCC	STRING(255)	
MI_DDD	STRING(255)	
MI_EEE	STRING(255)	
MI_FFF	STRING(255)	
MI_GGG	STRING(255)	
MI_HHH	STRING(255)	
EGFOTHD	STRING(200) - A200	
DEPO_AAA	STRING(255)	
DEPO_BBB	STRING(255)	
DEPO_CCC	STRING(255)	
DEPO_DDD	STRING(255)	

DEPO_EEE	STRING(255)	
DEPO_FFF	STRING(255)	
DEPO_GGG	STRING(255)	
DEPO_HHH	STRING(255)	
DEPO_III	STRING(255)	
DEPO_JJJ	STRING(255)	
DEPO_KKK	STRING(255)	
DEPO_LLL	STRING(255)	
DEPO_MMM	STRING(255)	
DEPO_NNN	STRING(255)	
EGFOTHE	STRING(200) - A200	
OTHER_AAA	STRING(255)	
EGFOTHO	STRING(200) - A200	

lpl112498_128 : REPEAT PHARMACOKINETICS BLOOD - SB-480848, M4, M10, M3 (PK Rpt) - Repeating Form			
#		Actual date/time	
1			

REPEAT PHARMACOKINETICS BLOOD		
1.	Actual date/time	Req / Req / Req (2008-2009) (MAPPINGS1:t_PK_RPT.PKSTDTTM) Req : Req *24-hour clock*

Form Design Note:
Repeat PK

CDD: MAPPINGS1 Table: t_PK_RPT Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
PKSTDTTM	DATE - DDMONYYYY HHMM	

lpl112498_128 : REPEAT PHARMACODYNAMICS - Lp-PLA2 (BLOOD) (PD Rpt) - Repeating Form

#		Date/time of sample	
1			

REPEAT PHARMACODYNAMICS

1.	Date/time of sample	Req / Req / Req (2008-2009) (MAPPINGS1:t_PD_RPT.PDACTDTTM) Req : Req *24-hour clock*

Form Design Note:
Rpt PD

CDD: MAPPINGS1 Table: t_PD_RPT Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
PDACTDTTM	DATE - DDMONYYYY HHMM	

lpl112498_128 : VISIT REPORTS (VRP)		
VISIT REPORTS		
1.*	This section is not implemented for your study	(MAPPINGS1:t_VISITREPORT.NOTAVAIL_CC)

* Item is not required

CDD: MAPPINGS1 Table: t_VISITREPORT Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
NOTAVAIL_CC	STRING(255)	

lpl112498_128 : Reg Docs (REG)		
Reg Docs		
1.	This section is not implemented for your study	(MAPPINGS1:t_REGDOCS.NOTAVAIL_CC)

CDD: MAPPINGS1 Table: t_REGDOCS Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
NOTAVAIL_CC	STRING(255)	

lpl112498_128 : LIVER EVENTS (LIVER EVENTS)

1.	Which liver chemistry result reached or exceeded protocol-defined investigational product stopping criteria? Check all that apply	(MAPPINGS1:t_RUCAM.RUORRSCD1A) *[1]* ☐ ALT (alanine aminotransferase) (MAPPINGS1:t_RUCAM.RUORRSCD2A) *[2]* ☐ AST (aspartate aminotransferase) (MAPPINGS1:t_RUCAM.RUORRSCD3A) *[3]* ☐ Total bilirubin (MAPPINGS1:t_RUCAM.RUORRSCD4A) *[4]* ☐ Alkaline phosphatase (MAPPINGS1:t_RUCAM.RUORRSCD5A) *[5]* ☐ 5` nucleotidase (MAPPINGS1:t_RUCAM.RUORRSCD6A) *[6]* ☐ Gammaglutamyltranspeptidase (MAPPINGS1:t_RUCAM.RUORRSCDOT1) *[OT]* ☐ Other

Record the details of any Adverse Events or exacerbations of Adverse Events on the Non-Serious Adverse Event Form or the Serious Adverse Event form. Exacerbations of Adverse Events include increases in frequency and severity.

It is particularly important to record any significant hypotension immediately prior to or concomitant with ALT elevation.

It is particularly important to record any gallbladder or biliary disease, or pancreatitis, that occurred during the study.

2.	Is the subject age 55 or older?	(MAPPINGS1:t_RUCAM.RUORRSCD2) *[Y]* ◯ Yes *[N]* ◯ No
3.	If female, is the subject pregnant?	(MAPPINGS1:t_RUCAM.RUORRSCD3) *[Y]* ◯ Yes ensure Pregnancy Notification Form has been completed. *[N]* ◯ No *[X]* ◯ Not applicable
4.	Were any diagnostic imaging tests of the liver or hepatobiliary system performed (such as liver ultrasound, computerised tomography or CAT scan, magnetic resonance imaging or MRI, or endoscopic retrograde cholangiopancreatography, or other)?	(MAPPINGS1:t_RUCAM.RUORRSCD4) **[Y]** ◯ Yes. If Yes, were the results normal? (MAPPINGS1:t_RUCAM.RUORRSCD5) *[Y]* ◯ Yes *[N]* ◯ No If No, record the details on the Non-Serious Adverse Events form or Serious Adverse Event form. *[N]* ◯ No
5.	Were any liver biopsies performed?	(MAPPINGS1:t_RUCAM.RUORRSCD6) *[Y]* ◯ Yes complete Liver Biopsy form. *[N]* ◯ No
6.	Does the subject use herbals, complementary or alternative medicines, food supplements (vitamins) or illicit drugs?	(MAPPINGS1:t_RUCAM.RUORRSCD7) *[Y]* ◯ Yes record on the appropriate Concomitant Medication form. *[N]* ◯ No
7.	Did the subject fast or undergo significant dietary change in the past week?	(MAPPINGS1:t_RUCAM.RUORRSCD8) *[Y]* ◯ Yes *[N]* ◯ No
	Evaluation interval code [*hidden*]	(MAPPINGS1:t_RUCAM.EVLINTCD)

Form Design Note:
IDSL Version 01.02A 24 AUG 06

Item Design Notes:	
Item No.	**Design Note**
1.	Codes 5 and 6 are conditional
itmEVLINTCD1L	Item will be calculated by InForm.

CDD: MAPPINGS1	Table: t_RUCAM	Key Type: PATIENTVISIT
Column Name	**Column Data Type**	**Design Note**
RUORRSCD1A	STRING(255)	
RUORRSCD2A	STRING(255)	
RUORRSCD3A	STRING(255)	
RUORRSCD4A	STRING(255)	
RUORRSCD5A	STRING(255)	
RUORRSCD6A	STRING(255)	
RUORRSCDOT1	STRING(255)	
RUORRSCD2	STRING(1)	
RUORRSCD3	STRING(1)	
RUORRSCD4	STRING(1)	
RUORRSCD5	STRING(1)	
RUORRSCD6	STRING(1)	
RUORRSCD7	STRING(1)	
RUORRSCD8	STRING(1)	
EVLINTCD	STRING(255)	

lpl112498_128 : INVESTIGATIONAL PRODUCT (LIVER) (LIVER IP)

Time period to the onset of ALT >= 2x Upper Limit Normal (ULN)

Notes:
- Although stopping criteria is ALT >= 3x ULN, GSK are interested in capturing ALT >= 2x ULN to assess the probabilty of drug relatedness of liver event.
- Only complete dates for the treatment period applicable to the onset of ALT >= 2x ULN.

If the liver event occurred during treatment period record start and stop date of investigational product for that treatment period.

1.	Start Date Investigational Product	(MAPPINGS1:t_EXPOSURE_LIVER.rdcEXSTDT) **[-99]** ○ Req/Unk / Req/Unk / Req/Unk (2008- 2016) (MAPPINGS1:t_EXPOSURE_LIVER.EXSTDT) *[-98]* ○ Not applicable
2.	End Date Investigational Product	(MAPPINGS1:t_EXPOSURE_LIVER.rdcEXENDT) **[-99]** ○ Req/Unk / Req/Unk / Req/Unk (2008- 2016) (MAPPINGS1:t_EXPOSURE_LIVER.EXENDT) *[-98]* ○ Not applicable

If the liver event occurred after treatment period record start and stop date of investigational product for the most recent period prior to the liver event.

3.	Start Date Investigational Product	(MAPPINGS1:t_EXPOSURE_LIVER.rdcEXSTD1) **[-99]** ○ Req/Unk / Req/Unk / Req/Unk (2008- 2016) (MAPPINGS1:t_EXPOSURE_LIVER.EXSTD1) *[-98]* ○ Not applicable
4.	End Date Investigational Product	(MAPPINGS1:t_EXPOSURE_LIVER.rdcEXEND1) **[-99]** ○ Req/Unk / Req/Unk / Req/Unk (2008- 2016) (MAPPINGS1:t_EXPOSURE_LIVER.EXEND1) *[-98]* ○ Not applicable

Form Design Note:
IDSL Version 01.03A - 11Jan07

CDD: MAPPINGS1 Table: t_EXPOSURE_LIVER Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
rdcEXSTDT	STRING(3)	
EXSTDT	DATE - DDMONYYYY	
rdcEXENDT	STRING(3)	
EXENDT	DATE - DDMONYYYY	
rdcEXSTD1	STRING(3)	
EXSTD1	DATE - DDMONYYYY	
rdcEXEND1	STRING(3)	
EXEND1	DATE - DDMONYYYY	

lpl112498_128 : PHARMACOKINETICS (LIVER PK)

An unscheduled PK blood sample must be obtained within 24 hours of last dose (or 3x the investigational product half-life or t1/2; protocol specified longer value to be inserted).

1.	Was a pharmacokinetic blood sample obtained?	(MAPPINGS1:t_PK_LIVER.rdcPKLIVER) **[Y]** ○ Yes, date and time sample taken Req / Req / Req (2008-2016) (MAPPINGS1:t_PK_LIVER.PKSTDTTM2) Req : Req *24-hour clock* If Yes, date and time of last investigational product dose prior to PK sample: Req / Req / Req (2008-2016) (MAPPINGS1:t_PK_LIVER.EXSTDTTM1) Req : Req *24-hour clock* Sample Identifier/Sample Number: A17 (MAPPINGS1:t_PK_LIVER.PKSMPID) *[N]* ○ No

Form Design Note:
IDSL Version 02.00A 16 JAN 07

Section Design Notes:

Title	Design Note
An unscheduled PK blood sample must be obtained within 24 hours of last dose (or 3x the investigational product half-life or t1/2; protocol specified longer value to be inserted).	The following text 'protocol specified longer value to be inserted' is a prompt for the eCRF designer and should be replaced with the relevant text from the protocol.

Item Design Notes:

Item No.	Design Note
1.	Sample Identifier and Sample Number are conditional. The study team must choose one for inclusion on the eCRF form.

CDD: MAPPINGS1 Table: t_PK_LIVER Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
rdcPKLIVER	STRING(1)	
PKSTDTTM2	DATE - DDMONYYYY HHMM	
EXSTDTTM1	DATE - DDMONYYYY HHMM	
PKSMPID	STRING(17) - A17	

lpl112498_128 : MEDICAL CONDITIONS (LIVER MEDHX)

LIVER DISEASE MEDICAL CONDITIONS

1.	Acute Viral Hepatitis A	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD2) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
2.	Chronic Hepatitis B	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD1) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
3.	Chronic Hepatitis C	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD3) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
4.	Cytomegalovirus Hepatitis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD4) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
5.	Epstein Barr Virus Infectious Mononucleosis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD5) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
6.	Herpes Simplex Hepatitis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD6) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
7.	Alcoholic Liver Disease	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD7) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
8.	Non-alcoholic Steatohepatitis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD8) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
9.	Fatty Liver	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATCD9) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
10.	Hepatic Cirrhosis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC10) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
11.	Hemochromatosis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC11) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
12.	Autoimmune Hepatitis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC12) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
13.	Gallbladder disease or biliary disease	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC13) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition

DRUG RELATED LIVER DISEASE CONDITIONS (All drugs including Investigational Product)		
14.	Drug related liver disease	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC14) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition

	Sequence Number	Specific Condition	Modified Term	MedDRA Synonym	MedDRA lower level term code	Failed coding	Status
15.	[*hidden*]		[*hidden*]	[*hidden*]	[*hidden*]	[*hidden*]	

OTHER LIVER DISEASE CONDITIONS Entry		
15.a*	Sequence Number [*hidden*]	xxxx (MAPPINGS1:t_MEDHIST_A_LIVER.MHSEQ)
15.b	Specific Condition	A100 (MAPPINGS1:t_MEDHIST_A_LIVER.MHTERM)
15.c*	Modified Term [*hidden*]	A100 (MAPPINGS1:t_MEDHIST_A_LIVER.MHMODIFY)
	MedDRA Synonym [*hidden*]	(MAPPINGS1:t_MEDHIST_A_LIVER.MHMEDSYN)
	MedDRA lower level term code [*hidden*]	(MAPPINGS1:t_MEDHIST_A_LIVER.MHLLTCD)
	Failed coding [*hidden*]	(MAPPINGS1:t_MEDHIST_A_LIVER.calMH_FAILED)
15.d	Status	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC15) *[1]* ◯ Current *[2]* ◯ Past

OTHER MEDICAL CONDITIONS		
16.	Drug Allergies	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC16) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
17.	Rheumatoid Arthritis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC17) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
18.	Psoriasis	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC18) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
19.	Thyroid Disease	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC19) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
20.	Inflammatory Bowel Disease	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC20) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
21.	Lupus	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC21) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition
22.	Sjogren's Syndrome	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC22) *[1]* ◯ Current

		[2] ◯ Past *[5]* ◯ No Medical Condition
23.	Vitiligo	(MAPPINGS1:t_MEDHIST_A_LIVER.MHSTATC23) *[1]* ◯ Current *[2]* ◯ Past *[5]* ◯ No Medical Condition

* Item is not required

Form Design Note:
IDSL Version 01.01A 07 AUG 06

CDD: MAPPINGS1 Table: t_MEDHIST_A_LIVER Key Type: PATIENTVISIT

Column Name	Column Data Type	Design Note
MHSTATCD2	STRING(1)	
MHSTATCD1	STRING(1)	
MHSTATCD3	STRING(1)	
MHSTATCD4	STRING(1)	
MHSTATCD5	STRING(1)	
MHSTATCD6	STRING(1)	
MHSTATCD7	STRING(1)	
MHSTATCD8	STRING(1)	
MHSTATCD9	STRING(1)	
MHSTATC10	STRING(1)	
MHSTATC11	STRING(1)	
MHSTATC12	STRING(1)	
MHSTATC13	STRING(1)	
MHSTATC14	STRING(1)	
MHSEQ	NUMERIC - N4	
MHTERM	STRING(100) - A100	
MHMODIFY	STRING(100) - A100	
MHMEDSYN	STRING(255)	
MHLLTCD	STRING(255)	
calMH_FAILED	STRING(255)	
MHSTATC15	STRING(1)	
MHSTATC16	STRING(1)	
MHSTATC17	STRING(1)	
MHSTATC18	STRING(1)	
MHSTATC19	STRING(1)	
MHSTATC20	STRING(1)	
MHSTATC21	STRING(1)	
MHSTATC22	STRING(1)	
MHSTATC23	STRING(1)	

lpl112498_128 : ALCOHOL INTAKE (LIVER ALCOHOL)		
ALCOHOL INTAKE		
1.	Does the subject consume alcohol?	(MAPPINGS1:t_SUBUSE_AL_LIVER.SUAL1) *[N]* ○ No **[Y]** ○ Yes, record the average number of units of alcohol consumed per week xxx.xx (MAPPINGS1:t_SUBUSE_AL_LIVER.SUALUNWK1)
	Substance Use Type [*hidden*]	(MAPPINGS1:t_SUBUSE_AL_LIVER.SUTYPCD1)

Form Design Note:
IDSL Version 01.02A 18 OCT 06

Item Design Notes:	
Item No.	**Design Note**
itmSUTYPCD1	This item will be calculated by InForm.

CDD: MAPPINGS1 Table: t_SUBUSE_AL_LIVER Key Type: PATIENTVISIT		
Column Name	**Column Data Type**	**Design Note**
SUAL1	STRING(1)	
SUALUNWK1	FLOAT - F6.2	
SUTYPCD1	STRING(255)	

lpl112498_128 : LIVER IMAGING (IMAGING) - Repeating Form

#		Date of hepatic or liver imaging test	What method was used for this imaging test?	Are images technically adequate?	Indicate the liver size	Indicate the liver texture	Grade the diffuse and/or geographic fatty infiltrate of the liver	Ascites present	Are Focal Hepatic Lesions characterisable?	Gallstones or gallbladder lesions?	Biliary ductal lesions?	Po ab
1												

Date of hepatic or liver imaging test

1.	Date of hepatic or liver imaging test	Req / Req / Req (2008-2016) (MAPPINGS1:t_LIMAGING.LIDT)

What method was used for this imaging test?

2.	What method was used for this imaging test?	(MAPPINGS1:t_LIMAGING.LIMETHCD1) *[1]* Ultrasound - transabdominal *[2]* Ultrasound - endoscopic *[3]* Magnetic Resonance Imaging (MRI) *[4]* Computerised Tomography (CT) *[5]* Endoscopic Retrograde Cholangiopancreatography (ERCP) *[6]* Positron Emission Tomography (PET) *[7]* Positron Emission Tomography/Computerised Tomography (PET/CT) **[OT]** Other, specify: A200 (MAPPINGS1:t_LIMAGING.LIM

Are images technically adequate?

3.	Are images technically adequate?	(MAPPINGS1:t_LIMAGING.IMGADQCD1) *[1]* Optimal *[2]* Readable, but not optimal *[3]* Not readable **[OT]** Other, specify: A200 (MAPPINGS1:t_LIMAGING.IM

Indicate the liver size

4.	Indicate the liver size	(MAPPINGS1:t_LIMAGING.LIORRSCDA1) *[A1]* Normal size *[A2]* Hypertrophy (or enlarged) *[A3]* Atrophy (or smaller than normal) *[A4]* Segmental hypertrophy **[A99]** Other, specify: A200 (MAPPINGS1:t_LIMAGING.L

Indicate the liver texture

5.	Indicate the liver texture	(MAPPINGS1:t_LIMAGING.LIORRSCDB1) *[B1]* Normal *[B2]* Heterogenous *[B3]* Suggestive of fibrosis *[B4]* Nodular or suggestive of cirrhosis **[B99]** Other, specify: A200 (MAPPINGS1:t_LIMAGING.L

Grade the diffuse and/or geographic fatty infiltrate of the liver

6.	Grade the diffuse and/or geographic fatty infiltrate of the liver	(MAPPINGS1:t_LIMAGING.LIORRSCDC1) *[C1]* Not applicable - no fatty infiltration *[C2]* Mild (<=25%) *[C3]* Moderate (>25% to <75%) *[C4]* Severe (>=75%) **[C99]** Other, specify: A200 (MAPPINGS1:t_LIMAGING.L

Ascites present

7.	Ascites present	(MAPPINGS1:t_LIMAGING.LIORRSCDD1) None present

		[D1] ○ *[D2]* ○ Yes - small amount *[D3]* ○ Yes - moderate or severe amount **[D99]** ○ Other, specify: A200 (MAPPINGS1:t_LIMAGING.L
Are Focal Hepatic Lesions characterisable?		
8.	Are Focal Hepatic Lesions characterisable?	(MAPPINGS1:t_LIMAGING.LIORRSCDE0) *[E0]* ○ Not applicable - no hepatic lesions **[E]** ○ Check all that apply (MAPPINGS1:t_LIMAGING.LIORRSCDE1) *[E1]* ☐ Solid (MAPPINGS1:t_LIMAGING.LIORRSCDE2) *[E2]* ☐ Cystic (MAPPINGS1:t_LIMAGING.LIORRSCDE3) *[E3]* ☐ Hemangioma (MAPPINGS1:t_LIMAGING.LIORRSCDE4) *[E4]* ☐ Focal Nodular Hyperplasia (MAPPINGS1:t_LIMAGING.LIORRSCDE99) **[E99]** ☐ Other, specify: A200 (MAPPINGS1:t_LIMAGING.
Gallstones or gallbladder lesions?		
9.	Gallstones or gallbladder lesions?	(MAPPINGS1:t_LIMAGING.LIORRSCDF0) *[F0]* ○ None **[F]** ○ Check all that apply (MAPPINGS1:t_LIMAGING.LIORRSCDF1) *[F1]* ☐ Gallstones (MAPPINGS1:t_LIMAGING.LIORRSCDF2) *[F2]* ☐ Gallbladder polyp(s) (MAPPINGS1:t_LIMAGING.LIORRSCDF3) *[F3]* ☐ Sludge (MAPPINGS1:t_LIMAGING.LIORRSCDF4) *[F4]* ☐ Gallbladder wall thickening/oedema (MAPPINGS1:t_LIMAGING.LIORRSCDF5) *[F5]* ☐ Gallbladder wall gas (MAPPINGS1:t_LIMAGING.LIORRSCDF6) *[F6]* ☐ Cholecystitis (MAPPINGS1:t_LIMAGING.LIORRSCDF7) *[F7]* ☐ Gallbladder wall calcification (MAPPINGS1:t_LIMAGING.LIORRSCDF8) *[F8]* ☐ Gallbladder mass (MAPPINGS1:t_LIMAGING.LIORRSCDF99) **[F99]** ☐ Other, specify: A200 (MAPPINGS1:t_LIMAGING.
Biliary ductal lesions?		
10.	Biliary ductal lesions?	(MAPPINGS1:t_LIMAGING.LIORRSCDG0) *[G0]* ○ None **[G]** ○ Check all that apply (MAPPINGS1:t_LIMAGING.LIORRSCDG1) *[G1]* ☐ Intrahepatic ductal dilation (focal involving the right hepatic lobe) (MAPPINGS1:t_LIMAGING.LIORRSCDG2) *[G2]* ☐ Intrahepatic ductal dilation (focal involving the left hepatic lobe) (MAPPINGS1:t_LIMAGING.LIORRSCDG3) *[G3]* ☐ Intrahepatic ductal dilation (focal involving both right and left hepatic (MAPPINGS1:t_LIMAGING.LIORRSCDG4) *[G4]* ☐ Extrahepatic ductal dilation (MAPPINGS1:t_LIMAGING.LIORRSCDG5) *[G5]* ☐ Diffuse ductal dilation (involving both intrahepatic and extrahepatic du (MAPPINGS1:t_LIMAGING.LIORRSCDG6) *[G6]* ☐ Acute Cholangitis (MAPPINGS1:t_LIMAGING.LIORRSCDG7) *[G7]* ☐ Primary sclerosing cholangitis

		(MAPPINGS1:t_LIMAGING.LIORRSCDG8) *[G8]* ☐ Choledocholithiasis (gallstone in duct) (MAPPINGS1:t_LIMAGING.LIORRSCDG9) *[G9]* ☐ Ductal filling defect(s), other than gallstone (MAPPINGS1:t_LIMAGING.LIORRSCDG10) *[G10]* ☐ Ductal wall thickening or oedema (MAPPINGS1:t_LIMAGING.LIORRSCDG11) *[G11]* ☐ Choledochal cyst (MAPPINGS1:t_LIMAGING.LIORRSCDG12) *[G12]* ☐ Ductal mass (MAPPINGS1:t_LIMAGING.LIORRSCDG13) *[G13]* ☐ Extrinsic mass compressing bile duct(s) (MAPPINGS1:t_LIMAGING.LIORRSCDG99) **[G99]** ☐ Other, specify: | A200 | (MAPPINGS1:t_LIMAGING.
Portal/Hepatic vein abnormalities?		
11.	Portal/Hepatic vein abnormalities?	(MAPPINGS1:t_LIMAGING.LIORRSCDH0) *[H0]* ○ None **[H]** ○ Check all that apply (MAPPINGS1:t_LIMAGING.LIORRSCDH1) *[H1]* ☐ Portal vein enlargement (MAPPINGS1:t_LIMAGING.LIORRSCDH2) *[H2]* ☐ Hepatic vein enlargement (MAPPINGS1:t_LIMAGING.LIORRSCDH3) *[H3]* ☐ Nonocclusive portal vein thrombosis (MAPPINGS1:t_LIMAGING.LIORRSCDH4) *[H4]* ☐ Occlusive portal vein thrombosis - bland (MAPPINGS1:t_LIMAGING.LIORRSCDH5) *[H5]* ☐ Hepatic vein thrombosis - bland (MAPPINGS1:t_LIMAGING.LIORRSCDH6) *[H6]* ☐ Occlusive portal vein thrombosis - malignant (MAPPINGS1:t_LIMAGING.LIORRSCDH7) *[H7]* ☐ Hepatic vein thrombosis - malignant (MAPPINGS1:t_LIMAGING.LIORRSCDH8) *[H8]* ☐ Involvement of the main portal vein (MAPPINGS1:t_LIMAGING.LIORRSCDH9) *[H9]* ☐ Involvement of the right portal vein (MAPPINGS1:t_LIMAGING.LIORRSCDH10) *[H10]* ☐ Involvement of the left portal vein (MAPPINGS1:t_LIMAGING.LIORRSCDH11) *[H11]* ☐ Budd-Chiari syndrome (MAPPINGS1:t_LIMAGING.LIORRSCDH99) **[H99]** ☐ Other, specify: | A200 | (MAPPINGS1:t_LIMAGING.

Form Design Note:
IDSL Version 01.02A 05 OCT 06

CDD: MAPPINGS1	**Table: t_LIMAGING**	**Key Type: PATIENTVISIT**
Column Name	**Column Data Type**	**Design Note**
LIDT	DATE - DDMONYYYY	
LIMETHCD1	STRING(2)	
LIMETHSP	STRING(200) - A200	
IMGADQCD1	STRING(2)	
IMGADQSP	STRING(200) - A200	
LIORRSCDA1	STRING(3)	

LIORRSSPA99	STRING(200) - A200	
LIORRSCDB1	STRING(3)	
LIORRSSPB99	STRING(200) - A200	
LIORRSCDC1	STRING(3)	
LIORRSSPC99	STRING(200) - A200	
LIORRSCDD1	STRING(3)	
LIORRSSPD99	STRING(200) - A200	
LIORRSCDE0	STRING(2)	
LIORRSCDE1	STRING(255)	
LIORRSCDE2	STRING(255)	
LIORRSCDE3	STRING(255)	
LIORRSCDE4	STRING(255)	
LIORRSCDE99	STRING(255)	
LIORRSSPE99	STRING(200) - A200	
LIORRSCDF0	STRING(2)	
LIORRSCDF1	STRING(255)	
LIORRSCDF2	STRING(255)	
LIORRSCDF3	STRING(255)	
LIORRSCDF4	STRING(255)	
LIORRSCDF5	STRING(255)	
LIORRSCDF6	STRING(255)	
LIORRSCDF7	STRING(255)	
LIORRSCDF8	STRING(255)	
LIORRSCDF99	STRING(255)	
LIORRSSPF99	STRING(200) - A200	
LIORRSCDG0	STRING(2)	
LIORRSCDG1	STRING(255)	
LIORRSCDG2	STRING(255)	
LIORRSCDG3	STRING(255)	
LIORRSCDG4	STRING(255)	
LIORRSCDG5	STRING(255)	
LIORRSCDG6	STRING(255)	
LIORRSCDG7	STRING(255)	
LIORRSCDG8	STRING(255)	
LIORRSCDG9	STRING(255)	
LIORRSCDG10	STRING(255)	
LIORRSCDG11	STRING(255)	
LIORRSCDG12	STRING(255)	
LIORRSCDG13	STRING(255)	
LIORRSCDG99	STRING(255)	
LIORRSSPG99	STRING(200) - A200	
LIORRSCDH0	STRING(2)	
LIORRSCDH1	STRING(255)	
LIORRSCDH2	STRING(255)	
LIORRSCDH3	STRING(255)	
LIORRSCDH4	STRING(255)	

LIORRSCDH5	STRING(255)	
LIORRSCDH6	STRING(255)	
LIORRSCDH7	STRING(255)	
LIORRSCDH8	STRING(255)	
LIORRSCDH9	STRING(255)	
LIORRSCDH10	STRING(255)	
LIORRSCDH11	STRING(255)	
LIORRSCDH99	STRING(255)	
LIORRSSPH99	STRING(200) - A200	

lpl112498_128 : LIVER BIOPSY (BIOPSY) - Repeating Form

#		Date of liver biopsy	Biopsy size	Final Diagnosis	Liver Architecture	Description of Liver Cells or Hepatocytes	Liver Cell or Hepatocyte Inclusions or Vacuoles	Hepatocyte or Liver Cell Nuclear Abnormalities	Liver or Lobular Infiltrates	Portal Tract Inflammation	Bile Ducts
1											

Date of liver biopsy

1.	Date of liver biopsy	Req / Req / Req (2008-2016) (MAPPINGS1:t

Biopsy size

2.	Approximate size of liver biopsy	xx mm (MAPPINGS1:t_LBIOPSY.BIOPSZ)
3.*	Biopsy size unit [*hidden*]	MM

Final Diagnosis

4.	Final Diagnosis	(MAPPINGS1:t_LBIOPSY.LPORRSCDA0NOR) *[A0]* ○ Normal **[AAA]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDA1) *[A1]* ☐ Acute hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA2) *[A2]* ☐ Chronic hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA3) *[A3]* ☐ Cholestatic hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA4) *[A4]* ☐ Drug-induced cholestasis (MAPPINGS1:t_LBIOPSY.LPORRSCDA5) *[A5]* ☐ Acute viral hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA6) *[A6]* ☐ Chronic viral hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA7) *[A7]* ☐ Drug-induced hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA8) *[A8]* ☐ Autoimmune hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA9) *[A9]* ☐ Bridging necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA10) *[A10]* ☐ Submassive hepatic necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA11) *[A11]* ☐ Massive hepatic necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA12) *[A12]* ☐ Steatosis - microvesicular (MAPPINGS1:t_LBIOPSY.LPORRSCDA13) *[A13]* ☐ Steatosis - macrovesicular (MAPPINGS1:t_LBIOPSY.LPORRSCDA14) *[A14]* ☐ Steatosis - mixed (MAPPINGS1:t_LBIOPSY.LPORRSCDA15) *[A15]* ☐ Non-alcoholic steatohepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA16) *[A16]* ☐ Alcoholic hepatitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA17) *[A17]* ☐ Hepatic granulomas (MAPPINGS1:t_LBIOPSY.LPORRSCDA18) *[A18]* ☐ Sarcoidosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA19) *[A19]* ☐ Fibrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA20) *[A20]* ☐ Cirrhosis

		(MAPPINGS1:t_LBIOPSY.LPORRSCDA21) *[A21]* ☐ Primary biliary cirrhosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA22) *[A22]* ☐ Primary sclerosing cholangitis (MAPPINGS1:t_LBIOPSY.LPORRSCDA23) *[A23]* ☐ Autoimmune overlap syndrome (MAPPINGS1:t_LBIOPSY.LPORRSCDA24) *[A24]* ☐ Hemochromatosis (MAPPINGS1:t_LBIOPSY.LPORRSCDA25) *[A25]* ☐ Alpha-1-antitrypsin deficiency (MAPPINGS1:t_LBIOPSY.LPORRSCDA26) *[A26]* ☐ Wilson's disease (MAPPINGS1:t_LBIOPSY.LPORRSCDA27) *[A27]* ☐ Veno-occlusive disease (MAPPINGS1:t_LBIOPSY.LPORRSCDA28) *[A28]* ☐ Budd-Chiari syndrome (MAPPINGS1:t_LBIOPSY.LPORRSCDA29) *[A29]* ☐ Neoplasia (MAPPINGS1:t_LBIOPSY.LPORRSCDA99) **[A99]** ☐ Other, specify: | A200
Liver Architecture		
5.	Liver Architecture	(MAPPINGS1:t_LBIOPSY.LPORRSCDB1NORM) *[B1]* ○ Normal **[BBB]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDB2) *[B2]* ☐ Bridging fibrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB3) *[B3]* ☐ Diffuse fibrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB4) *[B4]* ☐ Nodular regenerative hyperplasia (MAPPINGS1:t_LBIOPSY.LPORRSCDB5) *[B5]* ☐ Congenital hepatic fibrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB6) *[B6]* ☐ Cirrhosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB7) *[B7]* ☐ Centrilobular congestion (MAPPINGS1:t_LBIOPSY.LPORRSCDB8) *[B8]* ☐ Endophlebitis (MAPPINGS1:t_LBIOPSY.LPORRSCDB9) *[B9]* ☐ Veno-occlusive disease (MAPPINGS1:t_LBIOPSY.LPORRSCDB10) *[B10]* ☐ Canalicular cholestasis (MAPPINGS1:t_LBIOPSY.LPORRSCDB11) *[B11]* ☐ Apoptosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB12) *[B12]* ☐ Focal (or spotty or mild) hepatocellu (MAPPINGS1:t_LBIOPSY.LPORRSCDB13) *[B13]* ☐ Interface hepatitis (periportal hepat (MAPPINGS1:t_LBIOPSY.LPORRSCDB14) *[B14]* ☐ Ischaemic necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB15) *[B15]* ☐ Centrolobular (Zone 3) necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB16) *[B16]* ☐ Focal coagulative necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB17) *[B17]* ☐ Centrolobular (Zone 3) coagulative (MAPPINGS1:t_LBIOPSY.LPORRSCDB18) *[B18]* ☐ Bridging hepatocellular necrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDB19) *[B19]* ☐ Massive or panlobular hepatocellula (MAPPINGS1:t_LBIOPSY.LPORRSCDB20) *[B20]* ☐ Dysplasia

		(MAPPINGS1:t_LBIOPSY.LPORRSCDB21) *[B21]* ☐ Neoplasia (MAPPINGS1:t_LBIOPSY.LPORRSCDB99) **[B99]** ☐ Other, specify: | A200
Description of Liver Cells or Hepatocytes		
6.	Description of Liver Cells or Hepatocytes	(MAPPINGS1:t_LBIOPSY.LPORRSCDC0NOR) *[C0]* ○ Normal **[CCC]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDC1) *[C1]* ☐ Ballooning (MAPPINGS1:t_LBIOPSY.LPORRSCDC2) *[C2]* ☐ Acidophilic (MAPPINGS1:t_LBIOPSY.LPORRSCDC3) *[C3]* ☐ Pseudoxanthomatous (MAPPINGS1:t_LBIOPSY.LPORRSCDC4) *[C4]* ☐ Multinucleated giant hepatocytes (MAPPINGS1:t_LBIOPSY.LPORRSCDC99) **[C99]** ☐ Other, specify: | A200
Liver Cell or Hepatocyte Inclusions or Vacuoles		
7.	Liver Cell or Hepatocyte Inclusions or Vacuoles	(MAPPINGS1:t_LBIOPSY.LPORRSCDDONOINC) *[D0]* ○ No inclusions **[DDD]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDD1) *[D1]* ☐ Macrovesicular steatosis (MAPPINGS1:t_LBIOPSY.LPORRSCDD2) *[D2]* ☐ Microvesicular steatosis (MAPPINGS1:t_LBIOPSY.LPORRSCDD3) *[D3]* ☐ Bile accumulation (MAPPINGS1:t_LBIOPSY.LPORRSCDD4) *[D4]* ☐ Diastase-resistant, PAS-positive cyto (MAPPINGS1:t_LBIOPSY.LPORRSCDD5) *[D5]* ☐ Alpha-1-antitrypsin inclusions (MAPPINGS1:t_LBIOPSY.LPORRSCDD6) *[D6]* ☐ Megamitochondria (MAPPINGS1:t_LBIOPSY.LPORRSCDD7) *[D7]* ☐ Mallory bodies (MAPPINGS1:t_LBIOPSY.LPORRSCDD8) *[D8]* ☐ "Ground Glass" inclusions (MAPPINGS1:t_LBIOPSY.LPORRSCDD9) *[D9]* ☐ Lipofuscin pigment (MAPPINGS1:t_LBIOPSY.LPORRSCDD10) *[D10]* ☐ Hemosiderin granules (MAPPINGS1:t_LBIOPSY.LPORRSCDD11) *[D11]* ☐ Orcein-positive cytoplasmin granule (MAPPINGS1:t_LBIOPSY.LPORRSCDD12) *[D12]* ☐ Protoporphyrin crystals (birefringen (MAPPINGS1:t_LBIOPSY.LPORRSCDD13) *[D13]* ☐ Uroporphyrin crystals (red fluoresce (MAPPINGS1:t_LBIOPSY.LPORRSCDD99) **[D99]** ☐ Other, specify: | A200
Hepatocyte or Liver Cell Nuclear Abnormalities		
8.	Hepatocyte or Liver Cell Nuclear Abnormalities	(MAPPINGS1:t_LBIOPSY.LPORRSCDE0NONE) *[E0]* ○ None **[EEE]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDE1) *[E1]* ☐ Hepatocellular mitosis (MAPPINGS1:t_LBIOPSY.LPORRSCDE2) *[E2]* Binucleated or multinucleated hepatoc

		☐ (MAPPINGS1:t_LBIOPSY.LPORRSCDE3) *[E3]* ☐ CMV inclusion bodies (MAPPINGS1:t_LBIOPSY.LPORRSCDE4) *[E4]* ☐ HSV inclusions (MAPPINGS1:t_LBIOPSY.LPORRSCDE5) *[E5]* ☐ Varicella inclusions (MAPPINGS1:t_LBIOPSY.LPORRSCDE99) **[E99]** ☐ Other, specify: | A200
Liver or Lobular Infiltrates		
9.	Liver or Lobular Infiltrates	(MAPPINGS1:t_LBIOPSY.LPORRSCDF0NONE) *[F0]* ○ None **[FFF]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDF1) *[F1]* ☐ Eosinophils (MAPPINGS1:t_LBIOPSY.LPORRSCDF2) *[F2]* ☐ Lymphocytes (MAPPINGS1:t_LBIOPSY.LPORRSCDF3) *[F3]* ☐ Plasma cells (MAPPINGS1:t_LBIOPSY.LPORRSCDF4) *[F4]* ☐ Neutrophils (MAPPINGS1:t_LBIOPSY.LPORRSCDF5) *[F5]* ☐ Macrophages and proliferating Kupffer (MAPPINGS1:t_LBIOPSY.LPORRSCDF6) *[F6]* ☐ Granulomas (MAPPINGS1:t_LBIOPSY.LPORRSCDF99) **[F99]** ☐ Other, specify: | A200
Portal Tract Inflammation		
10.	Portal Tract Inflammation	(MAPPINGS1:t_LBIOPSY.LPORRSCDG0NONE) *[G0]* ○ None **[GGG]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDG1) *[G1]* ☐ Eosinophils (MAPPINGS1:t_LBIOPSY.LPORRSCDG2) *[G2]* ☐ Lymphoid aggregates and/or follicles (MAPPINGS1:t_LBIOPSY.LPORRSCDG3) *[G3]* ☐ Plasma cells (MAPPINGS1:t_LBIOPSY.LPORRSCDG4) *[G4]* ☐ Neutrophils (MAPPINGS1:t_LBIOPSY.LPORRSCDG5) *[G5]* ☐ Histocytes and macrophages (MAPPINGS1:t_LBIOPSY.LPORRSCDG99) **[G99]** ☐ Other, specify | A200
Bile Ducts		
11.	Bile Ducts	(MAPPINGS1:t_LBIOPSY.LPORRSCDH0NOR) *[H0]* ○ Normal **[HHH]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDH1) *[H1]* ☐ Proliferation of bile ducts (bile ductul (MAPPINGS1:t_LBIOPSY.LPORRSCDH2) *[H2]* ☐ Dilation, degeneration or disruption (MAPPINGS1:t_LBIOPSY.LPORRSCDH3) *[H3]* ☐ Paucity of bile ducts (MAPPINGS1:t_LBIOPSY.LPORRSCDH4) *[H4]* ☐ Periductal fibrosis (MAPPINGS1:t_LBIOPSY.LPORRSCDH99) **[H99]** ☐ Other, | A200

		specify:
Portal Veins		
12.	Portal Veins	(MAPPINGS1:t_LBIOPSY.LPORRSCDI0NOR) *[I0]* ○ Normal **[III]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDI1) *[I1]* ☐ Pyelophlebitis (MAPPINGS1:t_LBIOPSY.LPORRSCDI2) *[I2]* ☐ Thrombosis, sclerosis or occlusion of pc (MAPPINGS1:t_LBIOPSY.LPORRSCDI3) *[I3]* ☐ Neoplastic invasion of portal vein (MAPPINGS1:t_LBIOPSY.LPORRSCDI4) *[I4]* ☐ Granulomatous compression of portal v (MAPPINGS1:t_LBIOPSY.LPORRSCDI99) **[I99]** ☐ Other, specify: | A200
Liver Infections		
13.	Liver Infections	(MAPPINGS1:t_LBIOPSY.LPORRSCDJ0NOR) *[J0]* ○ Normal **[JJJ]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDJ1) *[J1]* ☐ Leishmaniasis donovani (MAPPINGS1:t_LBIOPSY.LPORRSCDJ2) *[J2]* ☐ Plasmodium falciparum (MAPPINGS1:t_LBIOPSY.LPORRSCDJ3) *[J3]* ☐ Toxoplasmosis (MAPPINGS1:t_LBIOPSY.LPORRSCDJ4) *[J4]* ☐ Cryptococcus neoformans (MAPPINGS1:t_LBIOPSY.LPORRSCDJ5) *[J5]* ☐ Histoplasma capsulatum (MAPPINGS1:t_LBIOPSY.LPORRSCDJ6) *[J6]* ☐ Mycobacterium tuberculois (MAPPINGS1:t_LBIOPSY.LPORRSCDJ7) *[J7]* ☐ Other mycobacterial species (MAPPINGS1:t_LBIOPSY.LPORRSCDJ99) **[J99]** ☐ Other, specify: | A200
Parasites or Ova		
14.	Parasites or Ova	(MAPPINGS1:t_LBIOPSY.LPORRSCDK0NONE) *[K0]* ○ None **[KKK]** ○ Check all that apply (MAPPINGS1:t_LBIOPSY.LPORRSCDK1) *[K1]* ☐ Schistosome and/or ova (MAPPINGS1:t_LBIOPSY.LPORRSCDK2) *[K2]* ☐ Ascaris and/or ova (MAPPINGS1:t_LBIOPSY.LPORRSCDK3) *[K3]* ☐ Toxocara and/or ova (MAPPINGS1:t_LBIOPSY.LPORRSCDK4) *[K4]* ☐ Echinococcus cysts (MAPPINGS1:t_LBIOPSY.LPORRSCDK5) *[K5]* ☐ Hepatic capillariasis worms and/or ov (MAPPINGS1:t_LBIOPSY.LPORRSCDK99) **[K99]** ☐ Other, specify: | A200
Histologic Staining or Additional Studies Obtained		
15.	Histologic Staining or Additional Studies Obtained	(MAPPINGS1:t_LBIOPSY.LPORRSCDL1) *[L1]* ☐ Haematoxylin and eosin (or H & E) (MAPPINGS1:t_LBIOPSY.LPORRSCDL2) *[L2]* ☐ Masson

		(MAPPINGS1:t_LBIOPSY.LPORRSCDL3) *[L3]* ☐ Toluidine blue or Giemsa (MAPPINGS1:t_LBIOPSY.LPORRSCDL4) *[L4]* ☐ Prussian blue (MAPPINGS1:t_LBIOPSY.LPORRSCDL5) *[L5]* ☐ Periodic Acidic Schiff (PAS), with or without diast (MAPPINGS1:t_LBIOPSY.LPORRSCDL6) *[L6]* ☐ Oil red O (MAPPINGS1:t_LBIOPSY.LPORRSCDL7) *[L7]* ☐ Congo red (MAPPINGS1:t_LBIOPSY.LPORRSCDL8) *[L8]* ☐ Hall's stain (MAPPINGS1:t_LBIOPSY.LPORRSCDL9) *[L9]* ☐ Gridley's stain (MAPPINGS1:t_LBIOPSY.LPORRSCDL10) *[L10]* ☐ Rhodanine (copper) (MAPPINGS1:t_LBIOPSY.LPORRSCDL11) *[L11]* ☐ Rubeanic acid (copper) (MAPPINGS1:t_LBIOPSY.LPORRSCDL12) *[L12]* ☐ Orcein, aldehyde fuchsin or Victoria blue (MAPPINGS1:t_LBIOPSY.LPORRSCDL13) *[L13]* ☐ Electron microscopy (MAPPINGS1:t_LBIOPSY.LPORRSCDL14) *[L14]* ☐ Hepatitis A immunostains positive (MAPPINGS1:t_LBIOPSY.LPORRSCDL15) *[L15]* ☐ Hepatitis B core antigen or hepatitis B surface a (MAPPINGS1:t_LBIOPSY.LPORRSCDL16) *[L16]* ☐ Hepatitis D immunostains (MAPPINGS1:t_LBIOPSY.LPORRSCDL17) *[L17]* ☐ Other immunostains (MAPPINGS1:t_LBIOPSY.LPORRSCDL99) **[L99]** ☐ Other, specify: A200

* Item is not required

Form Design Note:
IDSL Version 01.02A 05 OCT 06

CDD: MAPPINGS1 Table: t_LBIOPSY Key Type: PATIENTVISIT		
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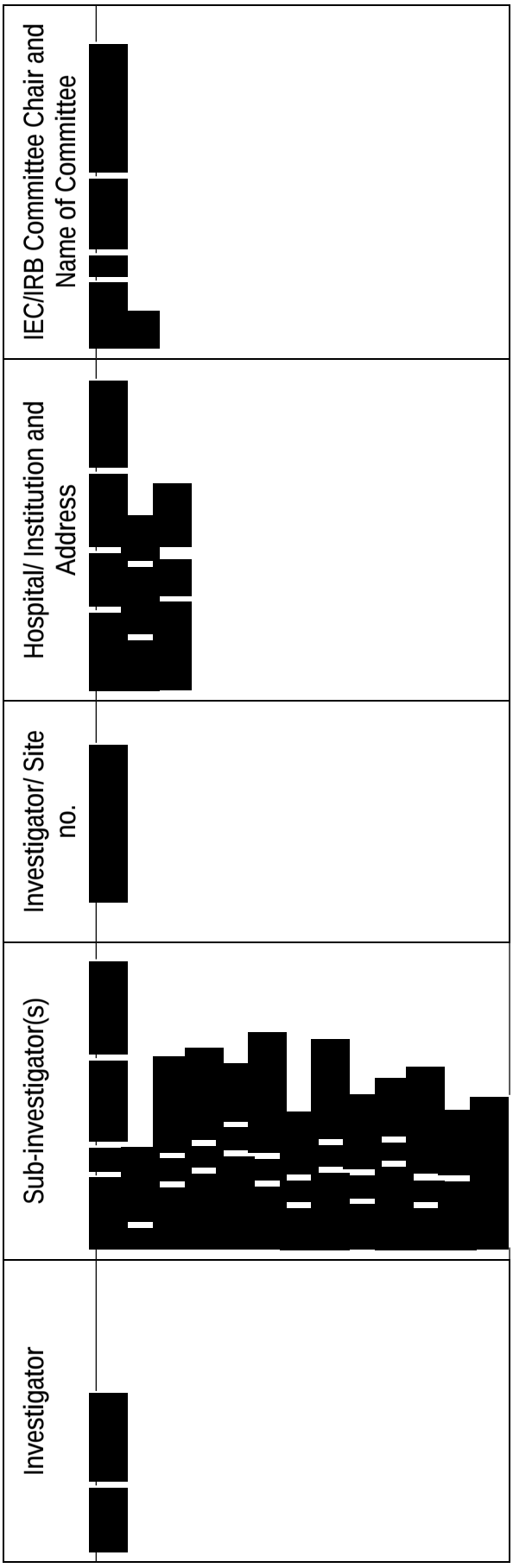
LIST OF INVESTIGATORS AND IECS/IRBS FOR LPL112498 (ZM2009/00013/00)



This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

INFORMED CONSENT AND AUTHORIZATION TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE:	A Study to Evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of Darapladib and its Metabolites in Healthy Volunteers
PROTOCOL #:	LPL112498 August 26, 2008
SPONSOR:	GlaxoSmithKline
STUDY DOCTOR:	[redacted] M.D.
[redacted] **ADDRESS:**	[redacted]
MAIN TELEPHONE #:	[redacted]
RECRUITERS TELEPHONE #:	[redacted]
24-HOUR PHYSICIAN CONTACT #:	[redacted]
[redacted] **STUDY #:**	[redacted]

Participant Name:

PURPOSE OF THE VOLUNTEER INFORMATION AND CONSENT FORM

Please read this form carefully before you sign it. This form describes the purpose, procedures, benefits, risks, discomforts, and precautions of the research study. Ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand. Ask as many questions as needed. You should not sign this form if you have any questions that have not been answered to your satisfaction.

The sponsor, GSK, will pay the study doctor to conduct this research.

NATURE AND PURPOSE OF THE STUDY

Darapladib is an investigational drug that is being developed to treat atherosclerosis, a build up of plaque (cholesterol and other substances) in arteries that can lead to heart disease or stroke. "Investigational" means the drug being tested has not been approved by the U.S. Food and Drug Administration (FDA) for sale in the U.S.

The purpose of this study is to test:

- How quickly darapladib enters the bloodstream, how it is distributed in the body, broken down and removed, in healthy subjects.
- The safety and side effects of single and repeat oral doses of darapladib when taken with food.

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INFORMED CONSENT AND AUTHORIZATION TO PARTICIPATE IN A RESEARCH STUDY

This study is being done for research purposes only. It is not intended to treat any medical condition.

VOLUNTEER SELECTION

You are invited to take part in this study if you are from 18 to 65 years of age and in good health. Women must be unable to become pregnant, or willing to use an acceptable method of birth control. The study doctor can discuss with you what birth control methods are allowed for this study.

About 20 volunteers will take part in this study at [redacted]

STUDY DURATION

Your part in the study will last about 2 months, not including the screening visit. The screening visit will be within 30 days before the start of the study, to see if you are qualified and want to be in the study.

The study will have 2 sessions, Session A and Session B. You will be in both sessions.

STUDY DESIGN

This study will test the following dosing regimens (a regimen is an organized plan):

- Session A:
  - You will receive a single 160 mg dose of darapladib on Day 1.

Session A (Single Dose): There will be a 3-night stay at the research clinic at the beginning of the study and 2 follow up visits on Days 4 and 5.

- Session B:
  - You will receive a 160 mg dose of darapladib daily for 28 days beginning 5 days after taking your single dose in Session A.

Session B (Repeat Dose): There will be two 2-night stays at the research clinic on Days 9-11 and 27-29. There will be 37 follow up visits to the research clinic on Days 1-8, 12-26, 30-35, 38, 41, 44, 47, 50, 53 and 56 for study related procedures. There will be a follow-up visit at the research clinic 28 days after your last dose of study drug.

You will take part in both Sessions A and B. All doses of darapladib will be taken by mouth in tablet form, with food.

The absorption and elimination of the study drug and how it affects your body will be tested by taking samples of your blood. Researchers will measure the levels of the study drug in your blood. They will also do tests to monitor your health.

INFORMED CONSENT AND AUTHORIZATION TO PARTICIPATE IN A RESEARCH STUDY

STUDY VISITS AND PROCEDURES

Screening:
For your own safety, you must tell the study medical staff all of your past and present medical problems, allergies, reactions to medications, and medications you are taking. Medications include prescription and over-the-counter medicines, herbal supplements, vitamins and anything else you are using. You must also tell the medical staff about your alcohol, drugs, and smoking history.

You must not eat or drink anything except water for at least **8** hours before this visit.

After you sign this informed consent form the following procedures will be done:

- You will be asked questions about your health and medical history. These will include questions about smoking, alcohol and drug use, and about your age and race.
- You will be asked about medications you are taking, including over-the-counter and prescription medications, vitamins, and herbal supplements.
- Your blood pressure, heart rate, temperature, and breathing rate will be checked.
- An ECG (electrocardiogram: a tracing of the electrical activity in your heart) will be done.
- Your height and weight will be measured and your BMI (body mass index) will be calculated.
- A complete physical examination will be done.
- Blood and urine will be collected for routine laboratory tests.
- If you are a woman, you will have a pregnancy test. If you are postmenopausal you will have tests for FSH and estradiol (hormones) to confirm that menopause has occurred.

Your blood will be tested for HIV, hepatitis B and hepatitis C. If you have a positive test for HIV or hepatitis you cannot be in the study. You will be informed in private. Positive HIV and hepatitis test results must be reported to the Department of Health. The law also requires that your name be reported. Although this information is expected to be private, this cannot be guaranteed. For example, it is possible for a court to get medical or study records without your permission. These results, if disclosed, may affect your employment or health insurance options.

Your urine will be tested for alcohol and drugs of abuse. If you have a positive test you cannot be in the study. If these test results are positive, you will be told in private.

Screening does not guarantee that you can be in the study. Entry into the study will depend on the results of your laboratory tests, study requirements, and the opinion of the study doctor.

Session A (Single Dose):

Day –1 ("day minus one"):
You will check in to the clinic the afternoon before the first day you receive the study drug. You must not eat or drink anything but water for 8 hours before you arrive at the clinic.

- You will be asked questions about your health and medication use.

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- You will have a physical exam.
- Your blood pressure, heart rate, temperature, and breathing rate will be checked.
- Blood and urine samples will be collected for lab tests and tests for alcohol and drugs of abuse.
- Women will have a pregnancy test.

You must not eat or drink anything (except water) from 11 PM until the morning you take your dose of study drug.

Meals will be provided during all in-house stays at scheduled times.

Days 1 to 3:
During the rest of your 3-night stay the following procedures will be done at different times

- You will have a moderate fat breakfast 1 hour before taking your dose of darapladib. You must be able to eat your breakfast as directed by study staff.
- You will take your dose of darapladib on Day 1.
- Meals will be served 6 and 10 hours after you take your dose of darapladib.
- .Blood samples will be collected 10 times on Day 1, 3 times on Day 2, and 1 time on Day 3, to measure levels of the study drug in your bloodstream.
- Blood and urine samples will be collected for lab tests on Day 3.
- Your blood pressure, heart rate, temperature, and breathing rate will be checked.
- You will be asked often how you are feeling.
- *On Day 1 and Day 2, you must not eat or drink anything (except water) from 11 pm until breakfast the next day.*
- After all study related procedures are done on Day 3, you will leave the clinic.

Follow up visits: Days 4 and 5

- You will arrive at the research clinic in the morning.
- Blood samples will be collected once.
- You will be asked questions about your health and medication use.
- You will be asked how you are feeling.
- After all study related procedures are done, you will leave the clinic.

Session B (Repeat Dose):

Day 1 of Session B will be the day after Day 5 of Session A.

Follow up Visits: Days 1-8, 12-26, 30-35, 38, 41, 44, 47, 50 and 53

- You will arrive at the research clinic in the morning.

- You will have a moderate fat breakfast 1 hour before taking your dose of darapladib. You must be able to eat your breakfast as directed by study staff.
- After Day 29, breakfast will not be provided at the clinic. You may eat breakfast at home.
- You will take your doses of study drug once daily on Days 1-8 and 12-26.
- Blood samples will be collected once on Days 26, 30-35, 38, 41, 44, 47, 50 and 53, to measure levels of the study drug in your bloodstream
- Blood samples will be collected once on Days 30-35, 38, 41, 44, 47, 50, 53, to see how the study drug affects the body.
- Your blood pressure, heart rate, temperature, and breathing rate will be checked on Day 14 only.
- You will be asked often how you are feeling.
- You will be asked often about your use of medications, dietary and herbal supplements, drugs, etc.
- After all study procedures are done, you will leave the clinic.

Overnight Stays: Days 9-11 and 27-29:

During your 2-night stays the following procedures will be done at different times.

- You will arrive at the research clinic in the morning on Day 9 and Day 27, and you will stay in the clinic until the morning of Day 11 and Day 29.
- You will have a moderate fat breakfast 1 hour before taking your dose of darapladib.
- You will take your doses of study drug once daily.
- Meals will be served 6 and 10 hours after you take your dose of darapladib.
- Blood samples will be collected 10 times on Days 10 and 28, and once on Days 11, 26, 27 and 29, to measure levels of the study drug in your bloodstream.
- Blood samples will be collected 10 times on Days 10 and 28, and once on Days 11 and 29, to see how the study drug affects the body.
- Your blood pressure, heart rate, temperature, and breathing rate will be checked on Day 28 only.
- You will be asked often how you are feeling.
- After all study related procedures are done on Days 11 and 29, you will leave the clinic.

Follow up: Day 56

- You must not eat or drink anything (except water) from 11 pm on Day 55 until after your blood and urine tests have been collected on the morning of Day 56.
- Your vital signs will be checked.
- An ECG will be done.

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- A blood sample will be collected to measure the levels of study drug in your blood stream.
- Blood and urine samples will be collected for lab tests.
- Women will have a pregnancy test.
- After all study related procedures are done, you will leave the clinic.

If the findings from these tests are not acceptable, the study doctor may ask you to return for more visits to monitor your health.

BLOOD SAMPLING

Blood samples will be taken about 54 times during the study, including at the screening and end-of-study visits. A total of about 432 mL (about 1 4/5 cups) of blood will be collected. More blood samples may be drawn during the study if the study doctor feels they are needed to monitor your health or test how your body handles the study drug. You will be informed about any such changes.

For comparison, a normal blood donation at a blood collection center is 500 mL (about 16 ounces or 2 cups) of blood, taken at one time. It is generally safe to donate that much every 8 weeks.

RESTRICTIONS

Certain foods, drinks, and activities can change how your body handles a drug and increase the chance of side effects. This may change the results of the study. To reduce these possible interactions, you are asked to make the following changes to your normal lifestyle while you are in the study:

- You must not take any prescription or over-the-counter drugs, herbal, vitamins or dietary supplements (including St. John's Wort) from 14 days before your first dose of study drug until the end of the study.
- You must not have been in any other research studies from the last 30 days before your first dose of darapladib until the end of the study.
- You must not donate blood or plasma from 56 days before your first dose of darapladib.
- You must not have anything that contains grapefruit or grapefruit juice from 7 days before your first dose of darapladib until the end of the study.
- Some drugs and supplements that have an effect on certain enzymes produced in the liver may be restricted for 14 days. The study staff can give you information about these.
- You must not be using any hormonal contraceptives (birth control pills, patches, injections).

Alcohol, Drugs of Abuse, Tobacco and Caffeine

- You must not have any alcohol, caffeine or xanthine-containing beverages beginning at 08:00 am on Day -1, until the end of the study. If you have any questions about this, ask your study staff.

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- Your alcohol use during the 6 months before the study must not have been more than 14 units per week for men, and 7 units per week for women. One unit of alcohol is the same as 12 ounces of beer, 5 ounces of wine or 1½ ounces of liquor.

Activity

- You must avoid strenuous activity, such as running, weight lifting or competitive sports from 48 hours before your admission on Day -1 until the end of the study.

RISKS AND DISCOMFORTS

This study drug may cause side effects in some people. One of the reasons for doing this study is to learn more about the possible side effects of darapladib. There may be rare and unknown side effects, including reactions that may be life threatening.

You may feel different than you normally do while in this study. Any symptom other than normal would be an "adverse event." Adverse events may be, but are not necessarily side-effects of the study drug. We will watch everyone in the study for any adverse events.

Adverse events may be mild, moderate, or severe. Sometimes an adverse event can be serious. We may give you medicine as treatment. Some side effects may go away as soon as you stop taking the study drug. In some cases, side effects can be long-lasting or permanent.

- You will be monitored very closely by the study doctor and medical staff while you are in the study. This monitoring will include measuring blood pressure, heart rate, temperature, and breathing rate, blood and urine tests, electronic monitoring of your heart, and other tests if the study doctor feels that they are needed.

It is important that you tell the study staff if you feel abnormal or unusual in anyway. If you are not completely truthful about any side effects you may increase the risk of harming yourself by taking part in this study. You will be given any new information that may affect your willingness to start or continue in the study.

DARAPLADIB

The following side effects may be likely:

- Abnormal smell of urine, stool (feces), or skin
- Change in taste
- Diarrhea

There may be other side effects that are not known now. For example, this study drug may cause allergic reactions in some people. Some medical problems can be more dangerous if not treated quickly; call your study doctor right away if you have any of these symptoms that may be evidence of liver damage:

- Feel very tired or faint
- Feel pain or sick in your stomach and do not want to eat
- Bruise easily or develop itching
- Have yellow eyes or skin, or dark urine
- Become confused

If you experience problems such as a possible allergic reaction, swelling, difficulty breathing, a bad skin rash, laboratory tests showing liver or kidney damage, changes in your heart rhythm, or other symptoms, you may be asked to return to the clinic for more assessments, which may include more blood tests. The study doctor will explain these tests to you if they are needed. You may also need to stop taking the study drug, after talking with your study doctor.

It is important for you to be aware of this information:

- You should not take part in this study if you are pregnant. Mothers should not breastfeed a baby while in this study.
- You should not become pregnant while you are in this study because it is not known whether the drug in this study may affect an unborn baby.
- If you get pregnant during this study, call the study doctor right away. You may be asked questions later about the pregnancy and the baby.
- Ask the study doctor if you have any questions about possible side effects.

Potential Risks of a Metabolite (chemical from breakdown of the study drug)
In the presence of a high level of stomach acid (such as when you are fasting), the study drug could form small amounts of a metabolite. In tests with bacteria or animal cells, one metabolite caused changes to the genetic material (DNA) of cells. This showed the potential to cause cancer or tumors.

When the metabolite was given to animals at very high doses (more than 48,000 times higher than could possibly happen in people), tumors were seen in the stomach. The exact meaning of these results regarding the risk to you is not known.

The following efforts have been made to reduce that risk:

1. You will get the study drug in a tablet that is coated to make it very unlikely to dissolve in the stomach. This means it is not likely to be exposed to stomach acid and form the metabolite.

2. You will swallow the tablet whole. You will NOT chew it. This will preserve the coating and prevent the tablet from dissolving in the stomach.

3. You will take the study drug with food, which also reduces the chances of forming the metabolite.

In the worst case, if the coating on the study drug tablet failed, only a small amount of this metabolite is likely to be formed in a person's stomach. This amount is much less than the amounts used in studies with animals that showed an increased risk of cancer or tumors.

Other Potential Risks of Study Drug

- It is possible that the study drug could make asthma symptoms or allergic reactions worse. You cannot be in this study if you have severe asthma or a history of severe allergic reactions to anything (e.g. food, medicines, latex, etc.).

- The study drug could make blood form a clot more easily by making some cells in your blood ("platelets") stickier. A blood clot could lead to heart attack, stroke, or leg pains. However, a study of darapladib in healthy people did not show that platelets become sticky either during or after taking the study drug.

- An earlier study showed a small increase in blood pressure in people taking this study drug. This was not seen in any previous studies and it is not know whether this is important.

- Studies in animals showed that fatty deposits could collect in the internal organs after higher doses of the study drug. However, there was no evidence of these changes in tests with people taking study drug for up to 1 year.

If you do not understand any part of this information about possible risks (e.g., what any of these side effects mean), please ask the study doctor or study staff to explain it to you.

Photographs

If a rash develops on your skin, a photograph may be taken to document the rash. The photo(s) will only identify you by your initials and study identification number. If a rash is on your face, your identity may be revealed by recognition. The study staff will try to conceal your identity in these photographs. The purpose of photographing this area is to help us understand what is occurring to you and to assist us in caring for this event. Also, the information will be shared with the Sponsor so that they may better understand the type of reaction and possibly give advice for treating the rash. They may share the photograph(s) of your skin rash with other doctors, researchers and regulators (e.g., the FDA). If you do not want your photograph taken, you cannot be in this study.

OTHER TESTS

After you have an ECG you may have itching, redness, blistering or bruising of the skin where the recording patches are placed.

The blood pressure cuff may cause discomfort or bruising to the upper arm.

When you have your blood drawn you may feel some minor discomfort. Possible side effects include pain, redness, bruising or bleeding at the site of the needle puncture. Some people feel lightheaded or faint when their blood is drawn. Rarely blood clots or an infection may occur. The problems at the site of the needle puncture will normally get better within a few days.

The study doctor may decide that placing an IV cannula (small plastic tube) into one of your veins for drawing blood may be helpful. The IV cannula will be flushed with a fluid called normal saline. Normal saline is sterile water with 0.9% salt to make it compatible with blood.

The study doctor may decide to flush the cannula with heparin. Heparin is a drug that can prevent blood from clotting in the cannula. The amount of heparin used is small, but in rare cases it may lower platelet counts. Platelets are cells in the blood that cause the blood to clot normally and help stop bleeding. If you are allergic to heparin or have had a side effect from heparin, you should not be in this study.

Please tell the study doctor or staff right away if you have any side effects or unusual health events, even if they don't disrupt your daily life, regardless of whether you think the study drug caused them or not.

If you are admitted to the hospital or receive care from a health care provider during this study you will be asked to sign a release form allowing the study doctor to review your medical records and discuss the matter with that health care provider.

REPRODUCTIVE RISKS AND CONTRACEPTION

Some drugs are "mutagenic". They can cause genetic changes or damage. Some are "teratogenic". They can interfere with the development of a fetus and cause birth defects. Since the teratogenic effects of darapladib are not known, and there is a potential for a possible metabolite of the study drug to be mutagenic, it is important to be sure that unborn or newborn babies are not exposed to darapladib.

Women: If you are pregnant or breastfeeding a baby [or able to become pregnant], you cannot be in this study. Unable to become pregnant means:

- Hysterectomy (uterus removal), bilateral oophorectomy (both ovaries removed), bilateral tubal ligation ("tubes tied") [documented with medical records]
- Postmenopausal (at least 1 year since last period, and an appropriate age)

If you are able to become pregnant, you must agree to use acceptable birth control from at least the first day of your last normal menstrual period before you take the study drug, and agree to continue using it until at least the final follow up visit. Acceptable birth control includes the following:

- Complete abstinence from sexual intercourse. If you are abstinent, you must agree to use an acceptable method of birth control if you become sexually active during the study.
- Having a single sexual partner who has had a vasectomy at least 3 months ago, and has had a follow-up check showing zero sperm count.
- Use of (as per protocol):
  - Male or female condom and occlusive cap plus spermicidal agent.
  - Non-hormonal IUD.

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UNKNOWN/UNFORESEEABLE RISKS
There may be other unknown, infrequent or unforeseeable risks related to the use of this study drug. Allergic reaction, uncommon side effects, or interaction with another drug may be possible. You will be told in a timely manner, both verbally and in writing, about any new information, findings or changes to the way the research will be done that might affect your willingness to continue in this study.

PHYSICIAN AVAILABILITY
A clinician will be present any time the study drug is being given at the research clinic, and on-call at all other times. If you have any type of medical emergency, a study doctor will be on call and available throughout the study. If you have a serious emergency, study staff will give first aid and call 911.

BENEFITS
You may not receive any medical benefit. Your part in this research will help provide knowledge that may lead to better treatment in the future.

ALTERNATIVE
This study is not a substitute for your usual medical care by your regular doctor. [redacted] is not a Healthcare Provider. [redacted] does not accept responsibility for your healthcare needs that are not directly related to this study. You may be advised by [redacted] staff to see your regular doctor about issues in your medical history or laboratory test results. But [redacted] does not provide this healthcare. Your alternative is to not take part in this study.

IN CASE OF INJURY
If you are injured by the investigational drug being studied or by any procedure that is done to you as specified by the study, GSK will pay for reasonable and necessary medical expenses to treat the injury that are not covered by your medical insurance. GSK is not offering to compensate you for any other expenses.

You do not give up any of your legal rights by signing this form.

Study Compensation Schedule

Period 1: $160 for the overnight stay on Day -1	$160
Period 1: $180 for the overnight stay on Day 1	$180
Period 1: $200 for the overnight stay on Day 2	$200
Period 1: $70 for each follow up visit on Days 4 and 5	$140
Period 2: $70 for each follow up visit on Days 1, 2, 3 and 4	$280
Period 2: $70 for each follow up visit on Days 5, 6, 7 and 8	$280
Period 2: $200 for the overnight stay on Day 9	$200

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Period 2: $215 for the overnight stay on Day 10	$215
Period 2: $70 for each follow up visit on Days 12, 13, 14, 15, 16	$350
Period 2: $70 for each follow up visit on Days 17, 18, 19, 20 and 21	$350
Period 2: $75 for each follow up visit on Days 22, 23, 24, 25 and 26	$375
Period 2: $220 for the overnight stay on Day 27	$220
Period 2: $220 for the overnight stay on Day 28	$220
Period 2: $75 for the follow up visit on Days 30, 31, 32, 33 and 34	$375
Period 2: $70 for each follow up visit on Days 35, 38, 41, 44 and 47	$350
Period 2: $70 for each follow up visit on Days 50, 53 and 56	$210
$75 for the final follow up visit	$75
$25 for each transportation card (there are 6)	$150
$1,010 for the completion of all visits/procedures	$1,010
Total	**$5,340**

You will receive $1,200 at Period 2 D11 discharge, $1,500 at period 2 D29 discharge, and $2,490 at the final follow up visit scheduled for the group which you are participating in.

You will receive $25 in the form of a gift card for transportation purposes at period 1 D3 visit, period 2 D4 visit, period 2 D16 visit, period 2 D21 visit, period 2 day 34 visit, period 2 day 47 visit. It will be available for pick up at [redacted]

If you miss any of the stays/visits listed in the table above, you will not be compensated for those visits and will not receive the completion bonus. You will be issued your check one week after the original compensation schedule.

If you do not finish the study or if any of your drug and alcohol tests are positive, you will be disqualified from the study. You will receive an amount based on the procedures and visits that you have completed. Your check will be issued within 3 weeks after the last visit scheduled for your study group.

If an extra visit is required by the study doctor, a $25 check will be issued within 3 weeks after you complete the visit.

If you are admitted to the research clinic, stay overnight, are qualified and willing to continue, but are not selected to receive a dose of the study drug, you will receive $125 within three weeks after the overnight visit. If, when you are admitted into the study any of your drug and alcohol tests come back positive before you are dosed, you will be disqualified and may not be compensated.

If you are qualified to admit and the study is cancelled within 7 days *before* your scheduled admission you will receive $250. Your check will be mailed to you within 3 weeks of your scheduled admission date.

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ADDITIONAL COSTS

There is no cost to you to take part in this study. The study sponsor pays all the costs. You will still be responsible for the cost of your usual ongoing medical care during this study, including procedures and medications that your regular doctor requires as part of your usual medical care. If you have any questions, please ask the study doctor, a member of the study staff, or your insurance company.

PARTICIPANT RESPONSIBILITIES

While you are in the study, you must:

- Follow the general clinic rules (House Rules).
- Follow the instructions you are given.
- Follow the study restrictions.
- Come to the study center for your visits with the study doctor.
- Tell the study doctor or study staff about any changes in your health.
- Tell the truth about your medical history and current conditions.
- Tell the study doctor if you have been in a research study in the last 30 days or are in another research study now.
- Tell the study doctor about any problems you have during the study.
- Take the study drug as directed by the study doctor and study staff.
- Use acceptable methods of birth control.
- Do not share the study drug with anyone else. Keep the study drug out of the reach of children and persons of limited capacity to read or understand.

HOW WILL MY PRIVACY BE PROTECTED?

The researchers who conduct this study will collect health information about you. Your health information can be collected, used and shared only with your permission.

By law, the researchers must protect the privacy of your health information. This form describes who will see your health information, what will be done with it and how it will be protected. The limits in this form come from a federal law called the Health Insurance Portability and Accountability Act (HIPAA).

Please read this form carefully. If you agree with it sign your name on the last page. By signing this form you show that you give your permission to use and share your health information collected during this study.

If you sign this form, health information about you will be collected, used and shared as described below.

You have a right to see and make copies of your Personal Health Information. You are agreeing, however, by signing this consent form, not to see a copy of your Personal Health Information until the sponsor has completed all work related to this study.

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What "health information" includes:
Health information about you that is created during this research study will become part of the study records. Examples of such information would be:

- Your medical history.
- Results from physical exams.
- Results of laboratory tests, blood tests, x-rays, medical tests and procedures.
- Diaries and questionnaires you might fill out.
- Your answers to questions researchers ask you.
- Observations about your health made by researchers.

Who may see this information:
Your health information will be shared with certain people and groups. These may include:

- The sponsor, GSK, and its representatives, in this country and in other countries.
- [redacted]
- [redacted] a committee that monitors the rights and welfare of research subjects.
- Other researchers when a review board approves.
- Government authorities, such as the U.S. Food and Drug Administration and others that approve new drugs and make sure research is done right.
- Companies and universities working with GSK to develop this drug.
- Regulatory authorities in other countries where GSK is doing business.
- Others, if the law requires.

How your health information may be used:
Health information about you may be:

- Used to see if the study drug works and is safe.
- Used to compare the study drug to other drugs.
- Stored and analyzed on computers to see what the study is telling us.
- Part of information published about the results of the study (this will not include information that identifies you).
- Shared as part of research with other companies and universities to further develop this drug.
- Used to plan new studies or other types of research.
- Used for other medical purposes related to development of this drug.

How your health information will be protected:

- The study doctor will abide by all the rules of the Health Insurance Portability and Accountability Act (HIPAA).
- Researchers will follow all other federal, state and local laws that govern the use of health information.
- Your health information will only be shared with others who agree to use it as described in this form.

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- If information is sent to another country, GSK will apply the same level of protection to the extent allowed by local law.
- The information that the study doctor sends to the sponsor does not include your identity. Your name, address, social security number and other identifiers are removed. The study doctor uses your initials and a code number for your records.
- Absolute privacy cannot be guaranteed. Once researchers and others who are not health care providers get your health information, the HIPAA rules may no longer apply. But other privacy protections will still apply. Laws or courts may require that your health information be disclosed to other parties.

Please note:
You do not have to sign this form. If you choose not to sign you cannot be in this study.

You can change your mind and cancel your permission at any time. If you do so you can no longer be in the study. To cancel your permission, write to:

[redacted] M.D.
[redacted]
[redacted]
[redacted]

If you cancel your permission the researchers will keep and use any information about you they have already collected. But they will not create any new information about you.

This permission does not have an expiration date.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY
Taking part in research is voluntary. You are free to withdraw from this study at any time. You agree to inform the study doctor right away if you intend to withdraw. There will be no penalty or loss of benefits to which you are otherwise entitled.

The doctor in charge of the study can withdraw you from this study without your consent for any reason, including, but not limited to:

a. His judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study.
b. Your failure to follow the instructions of the study doctor or staff.
c. If the study is stopped by the sponsor or study doctor before completion.
d. If it is found that you do not meet the study requirements.
e. If you have any side effects of concern to the study doctor.
f. If you are unavailable for follow up.

OFFER TO ANSWER ANY QUESTIONS ABOUT THIS STUDY
If you have any questions or problems during this study, or if you think that you may have had a research-related injury, you should contact the [redacted] study coordinator [redacted] at [redacted]

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If you need to speak with the study doctor, contact [redacted] **M.D.** or another Investigator, at [redacted] or after office hours at [redacted]

This study was reviewed by [redacted] (the IRB). The IRB is an ethics committee that is independent of the study doctor and the sponsor (the company that is paying for this research to be done). The purpose of the IRB is to protect the rights and welfare of people who volunteer to take part in research studies. You may call the QA & Compliance Administrator if you have questions about your rights as a research subject or if you have any concerns about taking part in this study.

[redacted] (collect calls accepted)

The information and the materials that are given to you in relation to the study are confidential information belonging to GlaxoSmithKline and should be kept private. You can discuss this information privately with your regular doctor or friends and family to decide about taking part in this study and in talking about your healthcare.

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INFORMED CONSENT AND AUTHORIZATION TO PARTICIPATE IN A RESEARCH STUDY

SIGNATURE

I have read in a language that I understand well, the above information. The content and meaning of this information has been explained to me. I hereby voluntarily consent and offer to take part in this study. I authorize the use and disclosure of my medical information.

- I have read the 17 pages of written information in the informed consent form for this study. I will be given a signed and dated copy of this form.
- The study information and procedures have been explained to me during the consent process for this study.
- I have had the opportunity to ask questions about this study. I am satisfied with the answers and explanations that have been given.
- I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in this study.
- I agree and am willing to take part in this study.

Volunteer

Print Name: Date:

Sign Name: Time:

Person Conducting the Informed Consent

Print Name: Date:

Sign Name: Time:

Person Issuing Copy of the Consent Form

Copy of signed consent form given to volunteer. Initials: Date:

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Randomization Code

Master Schedule Report

StudyID: *LPL112498*
Description: *An open label study to evaluate safety and tolerability of single and repeat oral doses of darapladib when administered in a fasted state to healthy adult subjects.*

1. Sequence and Treatment Definitions

		Treatments	
Sequence	**Code**	**Description**	**Period**
A1A2	A1	160 mg of EC micronized free-base darapladib as a single dose	1
	A2	160 mg of EC micronized free-base darapladib as repeat dose for 28 days	2

Master Schedule Report

StudyID: *LPL112498*
Description: *An open label study to evaluate safety and tolerability of single and repeat oral doses of darapladib when administered in a fasted state to healthy adult subjects.*

2. Randomisation Schedule - Treatment or Sequence Assignments

Schedule: 1
Stratum None

Main Schedule

Randomisation Number	Treatment / Sequence
[redacted]	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2

Master Schedule Report

StudyID: *LPL112498*
Description: *An open label study to evaluate safety and tolerability of single and repeat oral doses of darapladib when administered in a fasted state to healthy adult subjects.*

Main Schedule

Randomisation Number	Treatment / Sequence
[redacted]	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2
	A1A2

CONFIDENTIAL

COA No.: 081153598-03

GlaxoSmithKline

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline Research
& Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel. [redacted]
www.gsk.com

Product: Darapladib

Strength / Dose Form: 160 mg Enteric Coated Tablets

Batch Number: 081153598

Date of Manufacture: 16-Jan-2008

Site of Manufacture: GSK, GMS Ware, UK

Test	Acceptance Criteria	Results
Description	Plain, white, round, biconvex coated tablet with no markings	Conforms
Identification of Darapladib (SB-480848) by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Darapladib (SB-480848) reference material chromatogram.	Conforms
Darapladib (SB-480848) content by HPLC (% label claim)	90.0-110.0% label claim (144 mg – 176 mg)	100.3 (161 mg per tablet)
Uniformity of dosage units by HPLC (% label claim)	Complies with USP <905> and Ph. Eur. 2.9.40	Conforms Mean: 99.5 Range: 98.8 – 100.6 %RSD: 0.7 Acceptance value: 1.6
Drug-related impurities content by HPLC (% area)		
SB-553253 Any individual unspecified degradation product	Not greater than 1.0 Not greater than 0.2	0.10 <0.05
Total degradation products	Not greater than 2.0	0.10

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COA No.: 081153598-03

Test	Acceptance Criteria	Results
Dissolution (% Darapladib [SB-480848] released)	Complies with level A1 of Acceptance Table 3 of USP <711> for the acid stage. Complies with Acceptance Table 4 of USP <711> for the buffer stage, Q = 75% at 45 minutes.	Conforms Mean: 0% Range: 0 – 0% Conforms Mean: 105% Range: 102 – 106%
This material conforms to Specification S0010926/2.		

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] **Date:** 22 JUL - 2008

Qualified Person
R&D Quality Assurance
GSK, Harlow, UK.

ICH Data Listings

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Other Data Listings

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: A Study to evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of Darapladib and its Metabolites in Healthy Volunteers

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. LPL112498 ZM2009/00013/00

Name of Investigator: [redacted] MD

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 19 JUNE 2009

SIGNATORY SIGNATURE PAGE

STUDY TITLE: A Study to evaluate the Pharmacokinetics of the Enteric-Coated Micronized Free Base Formulation of Darapladib and its Metabolites in Healthy Volunteers

Study: ZM2009/00013/00 Development Phase: I

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: SVP, Drug Discovery

Signature: [redacted]

Date: 15/6/09