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- *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:	An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets

Phase: II

Compound Number: SK&F-101468

Effective Date: 11-FEB-2008

Description:
This study employed an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and was conducted in Parkinson's disease subjects. The study was designed to demonstrate dose proportionality for an extended release (PR/CR) formulation of ropinirole over the dose range 4-12 mg, to determine the effect of food on the absorption of PR/CR at 12 mg (highest tablet strength), and to determine dosage strength equivalence for PR/CR administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets. Subjects received ropinirole PR/CR once daily starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and 12 mg dose levels administered). The 12 mg dose level incorporated three dosing regimens: 1 x 12 mg tablet for three days including steady state pharmacokinetic (PK) profile (fasted), 1 x 12 mg tablet for three days including steady state PK profile (Food and Drug Administration "high fat" breakfast) and 3 x 4 mg for three days including steady state PK profile (fasted).

The study was conducted at two clinical pharmacology units.

The PK's of ropinirole were dose proportional over the dose range 4 to 12 mg PR/CR.

Under fed conditions, ropinirole AUC(0-24) and Cmax were increased on average by 20% and 44% respectively and tmax was delayed by 3 hours, compared to the fasted state.

Dosage strength equivalence was demonstrated for 1 x 12 mg PR/CR ropinirole tablet and the 3 x 4 mg PR/CR ropinirole tablets.

The different dose regimens of ropinirole PR/CR were well tolerated. No unknown or unexpected adverse event (AE) occurred during the study. The most common AEs were headache, dizziness and nausea. There was one serious adverse event which was unrelated to ropinirole (gastric atony which led to hospitalisation). One subject withdrew due to a moderate AE of postural hypotension (4mg dose level) which was considered drug-related. A lower incidence of AEs was reported in the 12mg ropinirole PR/CR high fat fed group compared to the fasted group; number of subjects that reported AEs was 16% vs 44% respectively.

Subject: SK&F-101468, prolonged release for Parkinson's disease, pharmacokinetics, food effect, safety

Author(s): [redacted]

Indication Studied: Parkinson's disease

Initiation Date: 16 April 2007

Completion Date: 29 August 2007

Date of Report: February 2008

Sponsor Signatory:
(and Medical Officer) [redacted]

Director, Clinical Pharmacology and Discovery Medicine, Neurology, 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

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
AUC(0-24)	Area under the steady-state plasma concentration time curve from 0 to 24 hours
BID	Bis in die (Lat.), twice daily
Cmax	Maximum observed steady-state plasma concentration
Cmin	Minimum observed steady-state plasma concentration
CI	Confidence interval
CR	Controlled release
CRF	Case Report Form
CVb%	Between subject coefficient of variation
CVw%	Within subject coefficient of variation
CTC	Common toxicity criteria
CVA	Cerebrovascular accident
CYP1A2	Cytochrome P-450 1A2 enzyme
DB	Discovery Biometrics
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
FDA	Food and drug administration
FSH/LH	Follicle stimulating hormone/luteinising hormone
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GSK	GlaxoSmithKline
h	Hour
Hb	haemoglobin
HIV	Human Immunodeficiency Virus
HLQ	Higher Limit of Quantification
ICH	International Conference of Harmonisation
IR	Immediate release
LLQ	Lower limit of quantification
LSM	Least Square Mean
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MedDRA	Medical dictionary for regulatory activities
NDA	New drug application
NQ	Not quantifiable
NRH	Normal Range High
NRL	Normal Range Low
OD	Once daily
OTC	Over-the-counter
PCI	Potential Clinical Importance

PD	Parkinson's disease
PGx	Pharmacogenetics
PK	Pharmacokinetic
PR	Prolonged release
QA	Quality assurance
QC	Quality control
RAP	Reporting and Analysis Plan
RBC	Red blood cell count
SAE	Serious adverse event
SBP	Systolic blood pressure
SCA	Standard Clarification Agreement
SD	Standard deviation
SNP	Single nucleotide polymorphisms
SOC	System organ class
TID	Ter in die (Lat.), 3 times daily
Tmax	Time to attain maximal plasma concentration
UPDRS	Unified Parkinson's Disease Rating Scale
vs.	versus
WBC	White blood cell count

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1 INVESTIGATOR INFORMATION AND STUDY ADMINISTRATION

1.1 List of Investigators

Investigator	Investigator/ Site/Centre Number.	Hospital/ Institution and Address
[redacted] PhD	[redacted]	[redacted] Germany
[redacted] MD	[redacted]	[redacted] South Africa.

1.2 Study Administration

For details of Study administration refer to Attachment 1, Study Administration.

2 ETHICAL CONDUCT OF THE STUDY

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board.

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, 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. Case report forms were provided for each subject's data to be recorded.

3 OBJECTIVES & ENDPOINTS

3.1 Objectives

Primary

- To demonstrate dose proportionality for ropinirole using an extended release (PR/CR) formulation of ropinirole over the dose range 4-12 mg when administered to subjects with a diagnosis of idiopathic PD.
- To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PR/CR at 12 mg (highest tablet strength).
- To determine dosage strength equivalence for ropinirole PR/CR administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets.

Secondary

- To further confirm the safety and tolerability of ropinirole PR/CR over a dose range of 2-12 mg when administered to subjects with a diagnosis of idiopathic PD.

3.2 Endpoints

Primary

- Ropinirole AUC(0-24), the area under the steady-state plasma concentration-time curve over the dosing interval
- Ropinirole Cmax: the maximum observed steady-state plasma concentration

Secondary

- Ropinirole tmax, the time to attain ropinirole Cmax
- Cmax and AUC(0-24) for the metabolites of ropinirole, SKF-104557 and SKF-89124
- Incidence of adverse events (AEs)
- Vital signs, electrocardiogram (ECG) and clinical laboratory data

Additional Endpoint

- Ropinirole Cmin, minimum observed steady-state plasma concentration

This endpoint was not listed as an endpoint in the protocol, however, it was added as an secondary endpoint in the Reporting and Analysis Plan (RAP) (Attachment3).

4 STUDY RATIONALE AND DESIGN

4.1 Study Rationale

PD is one of the most common neurological disorders in elderly people. It is caused by a loss of dopaminergic nerve cells in certain areas of the brain. The mainstay in the treatment of PD is the administration of dopaminergic agents.

Ropinirole, 4 [2 (dipropylamino) ethyl] 1,3 dihydro 2H indol 2 one, is a non ergoline dopamine agonist acting both centrally [SK&F Report Number PW019BA; SK&F Report Number PW023BA; SK&F Report Number PP011BA; SK&F Report Number PH/0001/SKF-101468] and peripherally [Steinsland, 1978; SK&F Report Number PP 002 BA] at D2/D3 receptors. It has been developed as a therapeutic agent for the treatment of the signs and symptoms of PD.

Ropinirole immediate release (IR) is registered in more than 60 countries worldwide for the treatment of PD at dose of up to 24mg/day (administered as 8 mg three times daily).

In order to minimise peripheral dopaminergic side effects, dosing is gradually increased in multiple steps to total daily doses of 3 mg/day or higher, according to the subject's therapeutic response. Titration may require 8 weeks or longer, depending on a given subject's responsiveness and tolerance.

A prolonged-release tablet of ropinirole called prolonged release tablets (PR) in Europe and XL in USA, has been developed.[1] This tablet formulation was formerly termed ropinirole controlled release (CR). The PR/CR tablet was developed to allow once-daily dosing of ropinirole, to provide a simpler dose-titration regimen and to improve the tolerability profile by slowing the rate of absorption of ropinirole.

Administration of ropinirole PR also results in fewer fluctuations in drug plasma levels throughout the day. Compliance would also be expected to be improved with a once daily regimen versus a three-times daily regimen.

Currently, tablet strengths of 2, 3, 4 and 8 mg PR/CR ropinirole are registered. A 12 mg tablet is under development in order to reduce tablet burden for subjects taking higher doses of ropinirole PR/CR.

Across all PD studies in the PR/CR development programme, 220 subjects received the PR/CR formulation at a dose of >16 mg (29% of the safety population in these studies) of whom 117 subjects received >16 mg for 52 weeks; 234 subjects received a dose between >8 and <16 mg, 110 for >52 weeks. The mean dose of the ropinirole PR/CR formulation in the pivotal efficacy studies was around 18 mg/day.

This study was part of the phase III plans and was designed in order to address the following pharmacokinetic(PK) objectives to support registration of the 12 mg PR/CR tablet:

(i) definitive food effect for ropinirole PR/CR at a clinically relevant dose (12 mg),
(ii) dosage strength equivalence for a 3 tablet combination (3 x 4 mg vs. 1 x 12 mg),
(iii) Dose proportionality of the ropinirole PR/CR tablet over the therapeutic dose range 4-12 mg.

PD subjects were selected as the appropriate population for this study as healthy volunteers may not tolerate ropinirole PR/CR doses of up to 12 mg as well as a dopamine deficient population.

[1] In this study report the investigational drug formulation is called ropinirole PR/CR, however in the PK-report, source tables and listings the term ropinirole PR/XL is used. PR/CR and PR/XL both refer to the investigational product.

4.2 Study Design

This study consisted of an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and was conducted in PD subjects. Approximately 36 male and female subjects were planned to participate in the study. Subjects received ropinirole PR/CR once daily (OD) starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and 12 mg administered). During the 2 mg to 8 mg dosing sessions, subjects generally took their study medication at home and completed diary cards apart from PK study days. During the 12 mg dosing session subjects remained resident in the clinic for logistical reasons.

For the 2 mg dose level subjects attended the unit for dosing and safety assessments only.

For the 4 and 8 mg dose levels, subjects attended the clinic for 24-hour PK and safety evaluations after they had received at least 5 sequential days of dosing at these dose levels. At these PK clinic visits, ropinirole PR/CR was administered in the fasted state.

For the 6 mg dose level, subjects continued taking their medication at home and attended the clinic for safety evaluations; however, PK assessments were not taken.

Once subjects were titrated to 12 mg, they remained at this dose for the remainder of the study. At the 12 mg dose, subjects were randomised to one of three treatments according to six possible treatment sequences (EFG, EGF, FEG, FGE, GEF, GFE) in accordance with treatments defined in Table 1.

Table 1 Dose Levels and PK Assessment Days

Dose Level	Dosing Days	PR/CR Dose (mg)	PK Assessments
1	1 - 7	2	-
2	8 - 14	4	Any day between Days 12-14, 4 mg steady state (fasted) (Treatment B)
3	15 - 21	6	-
4	22 - 28	8	Any day between Days 26-28, 8 mg steady state (fasted) (Treatment D)
5	29 - 37	12	Assessments on Days 31, 34 and 37. Randomised, 12 mg steady state: (i) Ropinirole PR/CR 1 x 12 mg tablet (fasted) (E) (ii) Ropinirole PR/CR 1 x 12 mg tablet (fed : standard high fat FDA breakfast) (F) (iii)Ropinirole PR/CR 3 x 4 mg tablets (fasted) (G)
	38-44	Down-titration	-

On all PK assessment days, ropinirole PR/CR was administered in the fasted state except for treatment sequence F, where dosing occurred approximately 30 minutes after commencing a standardised high fat Food and Drug Administration (FDA) breakfast. On non-PK dosing days, the daily ropinirole dose was taken after a normal breakfast.
The normal breakfast usually consisted of bread rolls, butter, jam or low-fat sausage. The

FDA high fat breakfast (approximately 1000 kcal) consisted of two slices of toasted white bread with butter, two eggs fried in butter, two slices of bacon (15 g), four ounces (114 g) hash-browned potatoes and eight fluid ounces (227 ml) whole milk. Following completion of the 12 mg dosing regimen, subjects were down-titrated according to the down titration schedule in Table 2.

Lastly, subjects attended the clinic for a follow up visit 7-14 days after completion of last administration of the study drug.

Detailed descriptions of the measurements taken are presented in Section 7 "Study Assessments and Procedures".

4.2.1 Stopping Criteria for Up-Titration

During the study a number of measures were put in place to ensure subject safety.

For each individual subject, continuation of up-titration of the study medication was based on satisfactory tolerability at the current dose level, based upon review of the safety. Dosing with ropinirole PR/CR was to be discontinued in the following circumstances:

1. Clinically significant adverse effects considered related to administration of the study drug (see guidelines Table 2).
2. If the systolic or diastolic blood pressure changes were of clinical concern.
3. If the ECG showed any changes from baseline which were of clinical concern.
4. Subjects did not wish to continue with the study for any reason, e.g. unavailability, intolerance of the study procedures.

If subjects were withdrawn from the study, then, where possible, the follow up procedures were carried out within 7-14 days of last dose of study medication.

Table 2 Guideline for Investigator-Initiated Premature Termination of Dosing

Symptom	Definition
Hypotension	The subject reports orthostatic symptoms such as feeling faint or dizzy that fulfil criteria common toxicity (CTC) grade 2 or greater for hypotension. CTC grade 2 hypotension = requiring brief fluid replacement or other therapy; no physiologic consequences; CTC grade 3 hypotension = requiring therapy and sustained medical attention, but resolves without persistent physiologic consequences; CTC grade 4 hypotension = shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion) Or Clinically significant symptomatic orthostatic hypotension
Nausea	Oral intake significantly decreased (equivalent to CTC grade 2). Or No significant oral intake, requiring (i.v.) fluids (equivalent to CTC grade 3). Or Clinically significant nausea last for longer than 24 hours
Vomiting	2-5 episodes in 24 h (equivalent to CTC grade 2) Or ≥6 episodes in 24 h; or need for intravenous fluids (equivalent to CTC grade 3). Or Requiring parenteral nutrition; physiologic consequences requiring intensive care; or hemodynamic collapse (equivalent to CTC grade 4).

4.2.2 Postural Hypotension

During the study, if symptomatic or asymptomatic postural hypotension, or significant bradycardia on standing was observed, then subjects were required to remain in a sitting or lying position until supine and erect blood pressure and pulse were able to be re-measured and subsequently returned to normal.

4.2.3 Extended Time at Dose Level

Additional time at a specific dose level was permitted to allow for further desensitisation of peripheral dopamine receptors. In previous ropinirole IR studies, this had been seen to be an important factor for improved tolerability.

If necessary, 1 or 2 days of additional dosing was permitted at the start of each new dose level to improve tolerability.

If at any dose level, poor tolerability was observed on the day prior to dose escalation, dose escalation did not occur. Subjects were permitted 1 or 2 additional days of dosing at the current dose level and dose escalation occurred only if that dose level was well tolerated.

4.2.4 Bed-Rest Following First Dose at New Dose Level and on PK Assessment Days

Following the first dose of study medication at each dose level, subjects remained supine or semi-supine (bed-rest) for 2 hours post-dose (excluding vital signs recordings when subjects were required to sit and then stand). Subjects remained in the clinic for at least 2 hours post dose on dose escalation days.

Subjects also remained in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing on PK assessment days.

5 DIAGNOSIS AND CRITERIA FOR INCLUSION

5.1 Inclusion Criteria

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

1. Male or female subjects aged between 30 and 85 years of age inclusive at screening.
2. Body mass index of 18 to 32 kg/m^2, with a body weight of at least 50 kg.
3. Diagnosis of idiopathic PD graded according to modified Hoehn & Yahr Stage I-III.
4. Subjects must have given written informed consent prior to performing any screening assessments, including any washout of concomitant medications in preparation for this study.
5. QTc interval of < 450 ms at screening (or QTc < 480 ms in subjects with Bundle Branch Block).
6. Female subject was either of:
   a) non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was post-menopausal or any female who was surgically sterilized (via documented hysterectomy or bilateral tubal ligation). (For purposes of this study, postmenopausal was defined as one year without menses) **OR**
   b) child-bearing potential, had a negative urine/serum pregnancy test at the Screening Visit (prior to investigational product administration), and agreed to use acceptable contraception from one month prior to study Day 1 until one month after completion of the study (i.e. one month after the follow-up visit). All hormonal birth control had to be administered for at least one monthly cycle prior to the Screening Visit.

GlaxoSmithKline (GSK) acceptable contraception methods, when used consistently and in accordance with both the product label and the instructions of a physician, were as follows:

- complete abstinence
- sterilisation of subjects's male partner prior to female subject's entry into study
- oral contraceptive (either combined or progestogen only)
- any intra-uterine device with a documented failure rate of less than 1% per year
- systemic contraception (e.g. Norplant system)

- double barrier method if comprised of a spermicide with either a condom or diaphragm

5.2 Exclusion Criteria

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

1. Subjects who had an abnormality on physical examination. A subject with clinical abnormality could be included only if the investigator considered that the abnormality did not introduce additional risk factors and did not interfere with the study procedures.

2. Subjects who, in the opinion of the investigator, had medical conditions which may have presented a safety concern. These included, but were not limited to, the following disorders: diabetes, peripheral neuropathy, rheumatoid arthritis, fibromyalgia syndrome, symptomatic orthostatic hypotension, hepatic or renal failure, pleuro-pulmonary fibrosis, significant and/or uncontrolled psychiatric, haematological, endocrinological, neurological (other than PD), or cardiovascular disease (including myocardial infarction, unstable angina pectoris, cardiac arrhythmias, cerebrovascular accident (CVA)), or subjects who were known to have malignancy, were being treated for malignancy or had treatment for malignancy within the last year (other than basal cell cancer).

3. Subjects had a clinically significant abnormal laboratory value, ECG, or physical examination findings not resolved by the time of the baseline examinations. Abnormal 12-lead ECG findings included, but were not limited to, the following: myocardial ischemia, clinically significant conduction abnormalities, or clinically significant arrhythmias.

4. Positive result for Hepatitis B surface antigen, Hepatitis C antibody or Human Immunodeficiency Virus (HIV) antibody at screening.

5. Positive alcohol test result and / or urine test for undeclared drugs at screening.

6. Recent history of moderate to severe dizziness, syncope, or orthostatic hypotension, defined as a fall in blood pressure, after rising from the supine to erect posture, of >30 mmHg for systolic pressure and >20 mmHg for diastolic pressure.

7. Significant sleep disorder or Epworth Sleep Score ≥9 at screening.

8. Subjects had a lying/sitting diastolic blood pressure ≥110 mmHg or ≤50 mmHg or a systolic blood pressure ≥180 mmHg or ≤90 mmHg at the Screening or Baseline Visit.

9. History of any dopaminergic treatments (other than ropinirole IR and L-dopa) within 2 weeks prior to first dose:

    - Subjects on dopaminergic agonists other than ropinirole PR/CR may have been enrolled if the agent was stopped for a 2-week wash-out period prior to first dose.

- Subjects taking ropinirole IR or L-dopa were allowed to be switched to ropinirole PR/CR 2 mg on study day 1, providing they had first followed the manufacturers down-titration guidelines.
- Subjects taking ropinirole IR >4 mg/day had to be down-titrated according to the manufacturer's guidelines prior to study day 1.
- Subjects taking ropinirole IR or L-dopa had to have been on a stable dose for at least 4 weeks prior to screening; doses of ropinirole IR or L-dopa were allowed to be adjusted prior to or during the study.
- Subjects on selegiline, amantadine, or anticholinergics were allowed to be enrolled but had to have been on a stable dose for at least one month prior to study enrolment and had to remain on that dose throughout the treatment phase of the study;

10. Withdrawal, introduction, or change in dose of hormone replacement therapy and/or any drug known to substantially inhibit cytochrome P-450 1A2 enzyme (CYP1A2) (e.g., cimetidine, ciprofloxacin, fluvoxamine) or induce CYP1A2 (e.g., tobacco, or omeprazole) within 7 days prior to study enrolment. Subjects already on these agents may have been enrolled but had to remain on stable doses of the agent for at least one month prior to enrolment and throughout the treatment phase of the study.

11. Subjects who smoked >20 cigarettes per day and were unwilling or unable to maintain a constant smoking habit for the duration of the study.

12. Blood donation or significant blood loss less than 90 days before Day 1 of this study.

13. Definite or suspected personal history, or family history, of adverse reactions or hypersensitivity to ropinirole or to drugs with a similar chemical structure.

14. Use of any investigational drug (with the exception of ropinirole PR/CR) within 30 days or 5 half-lives (whichever is longer) before the start of dosing with study medication.

15. Subjects who had received over-the-counter (OTC) medicine within 48 h before the first dose of study drug. Subjects who had taken OTC medication were allowed to be entered in the study, if in the opinion of the investigator; the medication received did not interfere with the study procedures or compromise safety.

16. Recent history, or suspicion, of drug dependence or abuse of alcohol (with alcohol abuse defined as an average weekly intake of greater than 21 units or an average daily intake of greater than 3 units for men; greater than 14 units per week or greater than 2 units per day for women. One unit was equivalent to half a pint of beer, one measure of spirits, or one glass of wine).

17. Significant concern, or likelihood, that the subjects would have dropped out of the study prematurely, would have required new or prohibited concomitant medications during the study period, or would not have been compliant with study procedures.

18. Women who were pregnant or breast-feeding.

19. Subjects with prior or current major psychosis (e.g., schizophrenia or psychotic depression). E.g., scoring 3 or 4 on Unified Parkinson's Disease Rating Scale (UPDRS) item 2 (thought disorder) or item 3 (depression).

5.3 Permitted Medications

Specified medications (e.g., paracetamol for headache) could be taken with the prior knowledge and approval of the investigator, but only if they were not expected to interfere with the PK assessments or to compromise the subjects' safety in this study.

All concomitant medications taken during the study were recorded in the CRF.

5.4 Prohibited Medications

The following medications were not permitted during the clinical phase of the study;

Dopaminergic agonists other than ropinirole IR and L-dopa were prohibited within 2 weeks prior to first dose and during the clinical phase.

Dopamine antagonists such as metoclopramide and domperidone (although domperidone could be given for nausea, but had to be discontinued 48 h before a PK day).

Withdrawal, introduction, or change in dose of any drug known to substantially inhibit[2] or induce[3] CYP1A2 was prohibited within 7 days prior to first dose. Subjects already on these agents could be enrolled but had to remain on stable doses of the agent from 7 days prior to enrolment through to the end of the study.

6 TREATMENT ADMINISTRATION

6.1 Treatments Administered

Subjects received ropinirole PR/CR once daily (OD) starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8, and 12 mg dose levels administered). The 12 mg/day dose level incorporated three dosing regimens; 1 x 12 mg tablet for three days including steady state PK profile (fasted), 1 x 12 mg tablet for three days including steady state PK profile (high fat fed) and 3 x 4 mg for three days including steady state PK profile (fasted). Subjects were dosed once daily with ropinirole PR/CR in the morning from Day 1 to Day 37 in accordance with the following treatments:

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[2] 1A2 Inhibitors (examples): amiodarone, cimetidine, fluoroquinolones, fluvoxamine, furafylline, interferon, methoxsalen, mibefradil, ticlopidine

[3] 1A2 Inducers (examples): broccoli, Brussels sprouts, char-grilled meat, insulin, methyl cholanthrene, modafinil, nafcillin, beta-naphthoflavone, omeprazole, tobacco

Table 3 Dosage and Administration Details

Dosing Days	Dose (mg/day)	Administration
1-7	2	1 x Ropinirole PR/CR 2 mg tablet/day for 7 days
8-14	4	1 x Ropinirole PR/CR 4 mg tablet/day for 7 days
15-21	6	1 x Ropinirole PR/CR 4 mg tablet/day and 1 x Ropinirole PR/CR 2 mg tablet/day for 7 days
22-28	8	1 x Ropinirole PR/CR 8 mg tablet/day for 7 days
29-37	12	On Days 29, 32 and 35 subjects were randomised to take either: 1 x Ropinirole PR/CR 12mg tablet for 3 days (fasted) *or* 1 x Ropinirole PR/CR 12mg tablet for 3 days (high fat fed) *or* 3 x Ropinirole PR/CR 4mg tablets for 3 days (fasted)
38-44	Down titration	Refer to Table 4

During the study, study medication was taken with approximately 240 ml of room temperature water.

Subjects who completed the study or withdrew from the study prematurely and had received study medication were down-titrated over a 4-7 day period, consisting of a reduction in the daily dose for 4 days and a further reduction as necessary for the next 3 days. Subjects who ceased study participation whilst at the 2 mg dose level could stop taking their study medication without the need for down-titration.

Table 4 Down-Titration Schedule

PR/CR Daily Dose (mg) at the end of the treatment phase	Down Titration Schedule	
	4 Days	3 Days
2	Not applicable	Not applicable
4	2	Not applicable
6	4	2
8	6	4
12	8	4

6.1.1 Time of Dosing

Dosing was conducted in the morning throughout the entire study. The FDA definition of fasted is that study drug should be administered at least 10 h after food and no food should be taken for 4 h after dosing – this is best achieved when following a morning dosing regimen and therefore this was followed in this study. In addition, in clinical practice it is more likely that subjects would take their once daily dose in the morning. For the fed state dosing occurred approximately 30 minutes after commencing a standardised high fat FDA breakfast

6.1.2 Treatment Assignment

Subjects were assigned to study treatment in accordance with the randomisation schedule which was created by the Discovery Biometrics Department (DB) at GSK, using RandAll, prior to study start.

All eligible subjects were randomised to receive one of six treatment sequences, ABCD**EFG**, ABCD**EGF**, ABCD**FEG**, ABCD**FGE**, ABCD**GEF**, ABCD**GFE**. The regimens were as follows:

Table 5 Treatment Assignment

A:	2 mg PR/CR
B:	4 mg PR/CR
C:	6 mg PR/CR (1x4 mg PR/CR + 1x2 mg PR/CR)
D:	8 mg PR/CR
E:	1 x 12 mg PR/CR (fasted)
F:	1 x 12 mg PR/CR (high fat fed)
G:	3 x 4 mg PR/CR (fasted)

6.2 Identity of Investigational Product (s)

Table 6 Description of the Investigational Products

Drug	Daily Dose/Form/Route	Dosing Days	Batch Number
Ropinirole PR/CR	2 mg/tablet/oral	1-7	[redacted]
Ropinirole PR/CR	4 mg/tablet/oral	8-14	
Ropinirole PR/CR	6 mg/tablet/oral (1x4 mg PR/CR + 1x2 mg PR/CR)	15-21	See above
Ropinirole PR/CR	8 mg/tablet/oral	22-28	[redacted]
Ropinirole PR/CR	12 mg/tablet/oral	29-37	
Down titration	See Table 4		

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Safety Assessments

7.1.1 Adverse Events and Serious Adverse Events

Adverse event (AE) and serious adverse event (SAE) data were collected and recorded on the CRF starting on screening day and continuing until the follow up day. The investigator or site staff 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.

In the event that an AE or SAE occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics

reports) relative to the event and attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. 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, they were to report the information to GSK within 24 hours and provide an assessment of causality.

7.1.2 Clinical Laboratory Evaluations

For all subjects, standard assessment for haematology, clinical chemistry and urinalysis was performed at screening and at follow-up (see Attachment 2 Time and Event Schedule for information on timing of assessments).

Table 7 presents the clinical laboratory assessments performed during the study.

Table 7 Clinical Laboratory Assessments

Test	Assessment
Clinical Chemistry	sodium, potassium, urea, creatinine, total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transferase (GGT), calcium, phosphate, cholesterol, triglycerides, glucose, creatine phosphokinase, chloride, follicle stimulating hormone/luteinising hormone (FSH/LH) (screen only, female subjects only, for confirmation of post-menopausal status if required).
Haematology	haemoglobin (Hb), haematocrit, mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), red blood cell count (RBC), white blood cell count (WBC), platelets, differential WBC count.
Urinalysis	pH, protein, glucose, bilirubin, blood, microscopy for cells and casts, specific gravity.
Other Tests	HIV I/II antibodies, Hepatitis B surface antigen, Hepatitis C antibodies, urine drug screen including alcohol, women of child-bearing potential underwent urine/serum pregnancy tests.

Abnormal laboratory findings that were judged by the investigator as clinically significant were recorded as AEs or SAEs if they met the definition of an AE or SAE as provided in the study protocol.

7.1.3 Other Safety Assessments

7.1.3.1 Vital signs and ambulatory blood pressure monitoring (ABPM)

Blood pressure and pulse rate measurements were recorded in both the supine and standing position at the time points indicated in the Time and Events Schedule (Attachment 2).

At the time-point of pre-dose Day 1, to establish a stable baseline, a minimum of 3 sets (and a maximum of 6 sets) of supine and standing blood pressure and pulse rate

measurements were measured. In this instance 'stable' was defined as each supine diastolic measurement being within 15 mmHg of the lowest measurement. This rule also applied for the supine systolic and standing systolic and diastolic measurements.

On the first day at each new dose level, subjects had their blood pressure taken hourly for 12 hours post dose, using an appropriate portable ABPM device after discharge from the unit.

7.1.3.2 ECG

All measurement timings are detailed in the Time and Events Schedule (Attachment 2). ECGs were measured in triplicate (10 minutes apart) at baseline and as single recordings at all other time-points.

All ECGs were obtained after the subject had rested in a supine position for at least 15 minutes. Hot and cold drinks and food had to be avoided 30 minutes before each scheduled ECG recording time-point. If asleep, subjects were to be woken at least 15 minutes before a scheduled ECG recording time-point.

If QTc was > 500 msec (or > 530 msec in subjects with Bundle Branch Block) or uncorrected QT was > 600 msec, three further ECGs were to be obtained at 5 minute intervals. If the mean of the QTc on the three ECGs met these criteria then the subject was to be withdrawn.

7.1.3.3 Physical examination

All measurement timings are detailed in the Time and Events Schedule (Attachment 2).

A physical examination was performed to ensure suitability according to the inclusion and exclusion criteria at screening, including bodyweight, and a medical history was also recorded. A physical examination was also performed at the Follow-up visit or at early termination, as appropriate, to document the health status at study completion.

7.2 Pharmacokinetic Assessments

7.2.1 Collection and Preparation of Samples

Pharmacokinetic blood samples were collected on the PK assessment days outlined in Table 1. On PK sampling days, serial blood samples were collected for PK analysis of ropinirole and its metabolites SKF-104557 and SKF-89124 at pre-dose and at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose.

Blood samples were taken via an indwelling cannula (or by direct venepuncture), collected into a 4 ml tube containing lithium heparin and immediately placed on water ice. Samples were centrifuged for 15 minutes at 1500 g at approximately 4°C and transferred into appropriate labelled polypropylene tube (s) prior to freezing. Supernatant plasma was transferred to a 3.6 ml Nunc tube and stored at approximately -20°C before

shipment. Samples were shipped frozen on dry ice at agreed time points throughout the study to GSK Bioanalysis group, Upper Merion, USA.

7.2.2 Assay Methodology

Plasma samples were analysed for ropinirole (SKF-101468), SKF-104557 and SKF-89124 at GSK in Upper Merion PA using a validated analytical method based on solid phase extraction followed by HPLC-MS/MS analysis using an Atmospheric Pressure Chemical Ionization interface and multiple reaction monitoring in the positive ion mode. The method had a lower limit of quantification (LLQ) for SKF-101468 and SKF-89124 of 20 pg/mL and 50 pg/mL for SKF-104557, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification (HLQ) of 5000 pg/mL [GSK Document ID: CD2004/01194/00].

Quality Control samples (QC), prepared at 4 to 5 different analyte concentrations and stored with study samples, were analysed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration should be within 15% of nominal. The applicable analytical runs met all predefined run acceptance criteria. All data are stored in the Archive at GSK Upper Merion USA.

7.3 Pharmacogenetic Assessments

7.3.1 Collection and Preparation of Samples

In addition to any blood samples taken for the clinical study, a whole blood sample (~10 ml) was collected for the pharmacogenetic (PGx) research using a tube containing ethylene diamine tetra-acetic acid (EDTA). The PGx sample was labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples did not carry personal identifiers (such as name or social security number). The blood sample was taken on a single occasion unless a duplicate sample was required due to inability to utilize the original sample.

7.3.2 Pharmacogenetics Analyses

All assessments are ongoing.

8 METHODS

8.1 Data Quality Assurance

At the clinical study sites, the investigator or their designee recorded all required subject data in paper CRFs and Diary cards. A screening log with GSK required information, created by the investigator at site, tracked subjects who were screened prior to entry into the study but were not randomized.

An initiation meeting was held on 16 March 2007 where the CRF and CRF completion guidelines were presented. Site Staff was additionally trained in using the Ambulatory Blood Pressure Set on 25 April 2007 by Spacelab Company. Monitoring took place at several times by an independent monitor commissioned and authorised by GSK.

The completed original CRFs and laboratory data were returned to [redacted] in [redacted] for scanning and tracking. The scanned CRF, Diary card and laboratory data images were used by [redacted] South Africa for processing. The investigator retained copies of the CRFs.

Data entry applications were designed and validated using a data entry screen software system (ClinTrial4). Data values recorded on the CRF were entered using double data entry.

Manual data validation was performed on CRF data using ClinTrial validation checks and study-specific data validation checks. Validation discrepancies, if not covered by a Standard Clarification Agreement (SCA), were queried using the documented data query process for review and resolution by investigators, and if appropriate with reference to the clinical Study Team members. Any necessary changes were made to both the CRF and the database by data management staff.

Quality Control (QC) tasks were conducted in accordance with existing data management standard operating procedures to ensure database accuracy against the data collected in the CRF. QC procedures are in alignment with the International Conference on Harmonisation of Good Clinical Practice (ICH GCP). AEs were coded using the industry standard Dictionary MedDRA. Concomitant medications were coded using a GSK in-house dictionary GSKDrug.

SAE data, consistent with the data collected for other AEs, were entered onto the database and quality assured, including reconciliation with the Global Clinical Safety and Pharmacovigilance database.

After all data management QC/QA procedures were completed the database was released on 26 October 2007. The database was frozen on 09 November 2007 at which time access to the data was also restricted (database lock).

The raw data (CRFs, etc.) will be archived according to company standard procedures.

8.2 Data Analysis Methods

Full details of the data analysis methods are provided in the RAP (Attachment 3).

The final statistical analysis was carried out using SAS v8.2 or higher on a UNIX platform, and the final outputs were generated using the HARP system.

8.2.1 Sample Size Considerations

Twenty-eight male and female subjects between 30-85 years of age were enrolled to ensure evaluable data was obtained from a minimum of 25 subjects completing the study. Subjects who withdrew would have been replaced if the number of evaluable subjects had fallen below 25. Full details of the sample size considerations are provided in the RAP (Attachment 3).

8.2.2 Drug Concentration Data

Plasma ropinirole (SKF-101468) and metabolites (SKF-104557, SKF-89124) concentrations, along with the actual blood sampling dates and times were listed by subject, treatment and planned sampling time. Plasma ropinirole (SKF-101468) and metabolites (SKF-104557, SKF-89124) concentrations were summarised by planned sampling time and treatment. Figures of individual and mean/median plasma ropinirole (SKF-101468) and metabolites (SKF-104557, SKF-89124) concentration-time profiles were produced on both semi-log and linear scales.

For the calculation of individual PK parameters, 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 Pharmacokinetic Parameters

PK analysis was conducted by SGS Aster (Poitiers, France), under the direction of Clinical Pharmacokinetics/Modeling and Simulation, CPDM, GSK. The statistical analyses of PK data were the responsibility of Clinical Pharmacology Statistics and Programming (CPSP), GSK.

PK analyses of plasma ropinirole (SKF-101468) and metabolites (SKF-104557, SKF-89124) concentration-time data were conducted using noncompartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.01 (Pharsight Corporation, Mountain View, CA) according to the standard operating procedures described in Standard Methods for the Non-Compartmental Analysis of Pharmacokinetic Data (SOP-CPK-0001 v01, 29-Aug-03). Actual elapsed time from dosing was used to

estimate all individual plasma PK parameters for evaluable subjects. The following PK parameters were estimated.

- The steady-state maximum observed plasma concentration (Cmax) and the time of first occurrence of Cmax (tmax) were the actual observed values.
- The steady-state area under the plasma concentration-time curve over the time of the dosing interval of 24 hours (AUC(0-24)) was 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.
- The steady-state trough concentration (Cmin) was the average of actual observed pre-dose and 24 hours concentration for each subject.

Plasma ropinirole (SKF-101468) and metabolites (SKF-104557, SKF-89124) PK parameter estimates were listed by subject. Plasma ropinirole (SKF-101468) and metabolites (SKF-104557, SKF-89124) PK parameter values were summarised by treatment.

The two metabolites of ropinirole (SKF-104557 and SKF-89124) do not contribute to the pharmacological activity of ropinirole. However, PK parameters for the metabolites were derived for completeness.

In accordance with GSK SOP-NPD-0003 v01, Management of the Sponsor's Clinical Study Documents (Sponsor Study Records)**,** all PK analyses were stored in the Archive, GSK, Research and Development under protocol ROP109087

8.2.4 Pharmacokinetic Analyses

Dose proportionality assessment

Dose proportionality of ropinirole was assessed by fitting the loge-transformed parameters AUC (0-24) and Cmax for ropinirole PR/CR 1 x 4 mg (fasted), 1 x 8 mg (fasted) and 1 x 12 mg (fasted) to the Power Model:

$$parameter = e^{a} (dose)^{b}$$

$$\text{ie :} \quad \log(parameter) = a + (b * \log(dose))$$

(Where a was the intercept, depending on subjects, and b was the slope, measuring the extent of dose proportionality).

Dose proportionality was demonstrated if the 90% confidence interval of the estimated mean slope of AUC (0-24) and Cmax were completely contained within the range 0.797 to 1.203. In addition, Cmin was analysed using similar methods to the primary endpoints (AUC (0-24) and Cmax).

Effect of food

The effect of food of ropinirole PR/CR on the highest tablet strength (1 x 12 mg (high fat fed) vs 1 x 12 mg (fasted)) was assessed separately by fitting the loge-transformed parameters AUC (0-24) and Cmax to a mixed model analysis of variance (ANOVA). Back-transformed point estimates and 90% confidence intervals were derived for the ratio of fed : fasted. In addition, Cmin was analysed using similar methods to the primary endpoints (AUC(0-24) and Cmax).

The parameter tmax was analysed using the Wilcoxon Signed Rank Test.

Dosage strength equivalence

The effect of dosage strength equivalence of 1 x 12 mg ropinirole PR/CR (fasted) and 3 x 4 mg ropinirole PR/CR (fasted) was assessed separately by fitting the loge-transformed parameters AUC (0-24) and Cmax to a mixed model analysis of variance (ANOVA). Back-transformed point estimates and 90% confidence intervals for the ratio 1 x 12 mg fasted : 3 x 4 mg fasted were presented. Dosage strength equivalence was demonstrated if the 90% confidence intervals for the ratios of AUC(0-24) and Cmax were completely contained within the range 0.80 to 1.25. In addition, Cmin was analysed using similar methods to the primary endpoints (AUC(0-24) and Cmax).

The parameter tmax was analysed using the Wilcoxon Signed Rank Test.

8.2.5 Safety Analyses

No formal statistical analysis of safety data was planned. All safety data are listed and summarised by regimen and time-point where appropriate.

Any values that fell outside the potential clinical importance (PCI) ranges were summarised by treatment group.

The criteria for PCI of clinical laboratory, ECG, vital sign and ABPM values are listed in Table 8 to Table 11. The clinical concern ranges were defined for Europe and the US separately.

Table 8 Laboratory Values of Potential Clinical Importance

Lab Parameter (units)	Clinical Importance Range	
	FDA	Europe
Sodium (mmol/L)	≤ 127, ≥ 151	≤ 130, ≥ 150
Potassium (mmol/L)	≤ 3.0, ≥ 6.0	≤ 3, ≥ 5.5
Chloride (mmol/L)	≤ 90, ≥ 112	≤ 80% NRL, ≥ 120% NRH
Glucose (mmol/L)	≤ 2.8, ≥ 11.1	≤ 2.8, ≥ 9.7
Phosphate (mmol/L)	≤ 0.6, ≥ 1.9	≤ 0.5, ≥ 1.7
Calcium (mmol/L)	≤ 1.9, ≥ 2.7	≤ 1.8, ≥ 3.0
Albumin (G/L)	≤ 26	-
Cholesterol (mmol/L)	≥ 6.5	-
Serum Creatinine (µmol/L)	≥ 177	≤ 50% NRL, > 125% NRH
GGT (U/L)	≥ 3.0 x NRH:	≥ 250% NRH
Alkaline Phosphatase (U/L)	≥ 3.0 x NRH	-
AST (U/L)	≥ 3.0 x NRH	≥ 250% NRH
ALT (U/L)	≥ 3.0 x NRH	≥ 250% NRH
Total Bilirubin (µmol/L)	≥ 2.0 x NRH	≥ 150% NRH
Red Blood Cell Count (Tl/L)	-	≤ 80% NRL, ≥ 120% NRH
Haemoglobin (G/L)	≤ 85 % NRL ≥ 115% NRH	≤ 75% NRL, ≥ 115% NRH
Haematocrit (%)	≤ 85 % NRL ≥ 115% NRH:	≤ 80% NRL, ≥ 120% NRH
White Blood Cell Count	≤ 3, ≥ 16	≤ 3, ≥ 15
Neutrophils (%)	-	≤ 75% NRL, ≥ 150% NRH
Neurophils (Seg) Absolute	≤ 1.5	-
Lymphocytes (%)		≤ 75% NRL, ≥ 150% NRH (%)
Lymphocytes Absolute (10^9	≤ 0.6, ≥ 5.0	-
Eosinophils (%)	≥ 10 %	≥ 200% NRH
Eosinophils Absolute (10^9 /	≥ 1.0	-
Platelets (10^9 / L)	≤ 100, ≥ 600	≤ 100, ≥ 500
Basophils (%)	≥ 5.0	≥ 200% NRH
Basophils Absolute (10^9 / L)	≥ 0.4	-
Monocytes (%)	≥ 20.0	≥ 200% NRH
Monocytes Absolute (10^9 /	≥ 2.0	-
Serum Protein (G/L)	-	≤ 80% NRL, ≥ 110% NRH

NRL = Normal Range Low, NRH = Normal Range High
Source: RAP (Attachment 3)

Table 9 ECG Values of Potential Clinical Importance

ECG Parameter	Values of Potential Clinical Importance	
	FDA	Europe
PR Interval	>300 msec OR Increase from baseline of > 25% when Baseline PR > 0.2 sec OR Increase of > 50% when Baseline PR ≤0.2 sec	>300 msec OR Increase from baseline of >25% when baseline PR > 0.2 sec OR Increase of >50% when baseline PR ≤ 0.2 sec
QRS Interval	>200 msec OR Increase from baseline of > 25% when Baseline QRS > 100 msec OR Increase from baseline of > 50% when Baseline QRS ≤ 100 msec	>200 msec OR Increase from baseline of > 25% when Baseline QRS > 100 msec OR Increase from baseline of > 50% when Baseline QRS ≤ 100 msec
QT Interval (QT, QTcB and QTcF)	>500 msec OR >60 msec increase from Baseline	>0.5 sec OR Increase from baseline of > 15% when Baseline QTc > 440 msec OR Increase from baseline of > 30% when Baseline QTc ≤ 440 msec

Source: RAP (Attachment 3)

Table 10 Vital Sign Values of Potential Clinical Importance

Vital Sign	Clinical Importance Range	Increase from Original Baseline	Decrease from original Baseline	Units
Europe				
Systolic Blood Pressure	90-180	>30	>30	mmHg
Diastolic Blood Pressure	50-115	>20	>20	mmHg
Pulse	50-120	-	-	bpm
FDA				
Systolic Blood Pressure	-	≥20	≥20	mmHg
Diastolic Blood Pressure	-	≥10	≥10	mmHg
Pulse	-	≥15	≥15	bpm

Source: RAP (Attachment 3)

Table 11 ABPM Values of Potential Clinical Importance

Ambulatory reading	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<80 and >190	mmHg
Diastolic Blood Pressure	<50 and >120	mmHg

Source: RAP (Attachment 3)

8.2.6 Changes in Conduct of the Study or Planned Analyses

Cmin was not listed as an endpoint in the protocol, however, it was added as a secondary endpoint in the RAP (Attachment 3). Details of the analysis of Cmin have been outlined in the RAP. Cmin and tmax for the metabolites of ropinirole, SKF-104557 and SKF-89124 were not listed as secondary endpoints in the protocol or RAP, however, both endpoints were derived for the metabolites and so have been included in the summaries and listings.

9 STUDY POPULATION RESULTS

9.1 Subject Disposition and Demographics

A total of 28 subjects were enrolled into the study, 14 males and 14 females subjects. [redacted] None of the subjects were replaced. Twenty-five subjects completed the study. A summary of subject disposition and demographics is presented in Table 12.

Table 12 Summary of Subject Disposition and Demographic Characteristics

Number of Subjects	Total
Number of subjects planned, N	36
Number of subjects randomised, N	28
Number of subjects included in the Safety population, n (%)	28 (100)
Number of subjects included in the PK population, n (%)	27 (96)
Number of subjects completed as planned, n (%)	25 (89)
Number of subjects withdrawn (any reason), n (%):	3 (11)
Reasons for subject withdrawal	
Adverse Event, n (%):	1 (4)
Other –n (%)	2 (7)
Demographics	
Age in years, Mean (SD; Range)	64.5 (8.56; 47-81)
Sex, n (%)	
Female:	14 (50)
Male:	14 (50)
BMI, Mean (SD; Range)	25.53 (3.326; 20 – 32)
Weight (kg), Mean (SD; Range)	73.4 (13.20; 54 – 96)
Height (cm), Mean (SD; Range)	169.3 (10.31; 145 – 186)
Race, n(%)	
White – White/Caucasian/European Heritage	27 (96)
White – Arabic/North Africa	1 (4)
Ethnicity, n(%)	0
Hispanic or Latino	0
Not Hispanic or Latino	28 (100)

Source data: Table 9.01 - Table 9.03

9.2 Protocol Deviations

There were no protocol deviations or protocol violations, documented in the file notes that lead to exclusion from statistical analysis.

One protocol violation was noted with respect to protocol exclusion criteria 6:

[redacted]
Despite this event, the subject was included in the study (Table 10.29).

Protocol violations with respect to ropinirole regimens during the down titration period:

[redacted]
When reviewing their medication and diary card, it became clear that they had – in error – used the back-up medication during the down titration period.

These 4 subjects received 4 x 8 mg and 3 x 4 mg tablets as well as 1 x 8 mg (back-up) and 1 x 4 (back-up) tablets prior to discharge on Day 38; and received the first dose of 8 mg at the clinic. Subjects were instructed on use of the down-titration medication and to use the back-up medication only in the event of a tablet being lost. However, these subjects had not completely understood the instructions.

[redacted] They were instructed during down-titration period by investigator to check on general well-being; and were instructed not to use the back-up of 4 mg tablet. Consequently, the last intake of investigational product was 17th August 2007; and not 16 August 2007 as planned.

[redacted] Consequently, the last intake of investigational product was 18 August 2007; and not 16th August as planned.

None of these protocol violations affected the PK analysis.

The other protocol deviations were of minor relevance and did not compromise the results of the study.

9.3 Populations of Interest

The following populations were analysed:

- **Safety Population**: All subjects who received at least one dose of study medication. All subjects who entered the study were included in this population.
- **PK Concentration Population**: Twenty-eight subjects were enrolled into the study. [redacted]
- **PK Parameter Population**: All subjects with evaluable PK data from at least one session were included in the PK listings and summaries. [redacted] For the assessments of dosage strength

equivalence of 3 x 4 mg (fasted) and 1 x 12 mg (fasted) ropinirole PR/CR, food effect 1 x 12 mg (fed) versus 1 x 12 mg (fasted) and dose proportionality for 1 x 4 mg (fasted), 1 x 8 mg (fasted) and 1 x 12 mg (fasted), all subjects with evaluable PK data from at least one of the sessions of interest was included in the statistical analysis. [redacted]

9.4 Concomitant Medications

Concomitant medications are presented in Source Table 9.04.

Most of the subjects required concomitant medication because of their PD and other pre-existing diseases.

The subjects who are shown in Source Table 9.04 as taking REQUIP™ (approved ropinirole IR) during the study switched back to IR during the down titration phase or shortly afterwards. [redacted]

10 SAFETY RESULTS

10.1 Extent of Exposure

Of the 28 subjects participating in this study, 28 subjects received 2 mg and 4 mg, 26 subjects received 6 mg, and 25 subjects received 8 mg, 1 x 12 mg (fasted), 1 x 12 mg (high fat fed), and 3 x 4 mg (fasted).

Subjects received the 2 mg, 4 mg and 6 mg ropinirole PR/CR doses for 7 days, and the 12 mg dose regimens for 3 days each. Subjects were dosed once daily with ropinirole PR/CR in the morning from Day 1 to Day 37.

[redacted]

A summary of exposure to study drug is presented in Table 13.

Table 13 Summary of Exposure to Study Drug

		2 mg PR/CR (N=28)	4 mg PR/CR (N=28)	6 mg PR/CR (N=26)	8 mg PR/CR (N=25)	1 x 12 mg PR/CR (fasted) (N=25)	1 x 12 mg PR/CR (high fat fed) (N=25)	3 x 4 mg PR/CR (fasted) (N=25)
Cumulative Dose (mg) at Each dose Level	N	28	28	26	25	25	25	25
	Mean	14.0	27.6	41.5	56.0	36.0	36.0	36.0
	SD	0.00	2.27	2.35	0.00	0.00	0.00	0.00
	Median	14.0	28.0	42.0	56.0	36.0	36.0	36.0
	Min.	14	16	30	56	36	36	36
	Max.	14	28	42	56	36	36	36

Source Data: Table 10.01

10.2 Adverse Events

10.2.1 Brief Summary of Adverse Events

All 28 subjects who were enrolled and received at least one dose of study drug were included in the safety evaluation.

During the treatment period, 22 (79%) of 28 subjects experienced a total of 79 treatment emergent AEs, and 15 subjects (54%) experienced a total of 44 AEs that were judged by the investigator to be related to the study drug. Most of the AEs were mild or moderate in intensity. Three subjects experienced 5 AEs that were of severe intensity (2 x nausea, 1 x abdominal pain upper; 1 x syncope; 1 x diarrhoea). The most frequently reported adverse events were headache, nausea and dizziness. No subjects died during the study. One subject had an SAE (gastric atony), which was considered by the investigator to be unrelated to study

drug. One subject discontinued from the study due to an AE (orthostatic hypotension, which was drug-related).

Table 14 provides an overview of AEs for the safety population.

Table 14 Summary of All Adverse Events

		Total (N=28)
Number of Subjects with AEs		22 (79%)
Number of treatment emergent AEs		79[a]
Number of Subjects with Drug-Related AEs		15 (54%)
Number of Drug-Related AEs		44
Number of Subjects with AEs by Maximum Intensity	Mild	10 (36%)
	Moderate	9 (32%)
	Severe	3 (11%)

Source Data: Table 10.07
a. excludes pre-treatment AEs and multiple episodes within a single treatment period

10.2.2 Details of All Adverse Events

All AEs are summarised and listed by dose regimens according to MedDRA coding dictionary in Data Source Table 10.02.

AEs are summarised by system organ class and preferred term in Table 15.

The most common AEs occurred in the System Organ Classes (SOCs) Nervous System Disorders and Gastrointestinal Disorders. Overall, the incidence of AEs during the treatment phase was comparable across the doses. The most frequently reported AEs across all the dose levels were headache, nausea and dizziness, however the incidence of each of these AEs was low with only 1 to 5 subjects (4-18%) reporting each one across the different dose levels. Although there was no clear trend in the total incident of AEs for any dose, dizziness was more frequent in the higher doses (8 and 12 mg ropinirole PR/CR) compared to the lower doses of 2, 4 and 6 mg ropinirole PR/CR. There was a lower incidence of AEs following 12 mg ropinirole PR/CR high fat fed compared to 12mg fasted group; the proportion of subjects that reported AEs was 16% vs 44% respectively.

The intensity of AEs was mild in 10 (36%) subjects, moderate in 9 (32%) subjects and severe in 3 (11%) subjects. [redacted]

All AEs were resolved by the end of the study.

Overall, the incidence of AEs was low and generally comparable across all doses. No obvious relationship between severity of AEs and individual dose was observed.

Table 15 Summary of All Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	2 mg PR/CR (N=28)	4 mg PR/CR (N=28)	6 mg PR/CR (N=26)	8 mg PR/CR (N=25)	1 x 12 mg PR/CR (fasted) (N=25)	1 x 12 mg PR/CR (high fat fed) (N=25)	3 x 4 mg PR/CR (fasted) (N=25)
ANY EVENT	7 (25%)	11 (39%)	2 (8%)	8 (32%)	11 (44%)	4 (16%)	9 (36%)
Nervous system disorders							
Any event	2 (7%)	6 (21%)	-	5 (20%)	7 (28%)	3 (12%)	5 (20%)
Headache	1 (4%)	5 (18%)	-	3 (12%)	2 (8%)	1 (4%)	3 (12%)
Dizziness	-	1 (4%)	-	2 (8%)	3 (12%)	2 (8%)	-
Somnolence	-	-	-	-	1 (4%)	-	2 (8%)
Convulsion	-	-	-	-	1 (4%)	-	-
Depressed level of consciousness	-	-	-	-	-	-	1 (4%)
Disturbance in attention	-	-	-	-	-	-	1 (4%)
Restless legs syndrome	-	1 (4%)	-	-	-	-	-
Syncope	1 (4%)	-	-	-	-	-	-
Tremor	-	-	-	-	1 (4%)	-	-
Gastrointestinal disorders							
Any event	4 (14%)	4 (14%)	1 (4%)	1 (4%)	5 (20%)	1 (4%)	3 (12%)
Nausea	2 (7%)	2 (7%)	-	1 (4%)	2 (8%)	-	2 (8%)
Constipation	1 (4%)	2 (7%)	-	-	1 (4%)	-	-
Abdominal pain upper	-	1 (4%)	-	-	1 (4%)	-	1 (4%)
Diarrhoea	-	-	1 (4%)	-	1 (4%)	-	1 (4%)
Gastric atony	-	-	1 (4%)	1 (4%)	-	-	-
Abdominal pain	-	-	-	-	-	1 (4%)	-
Dry mouth	1 (4%)	-	-	-	-	-	-
Dyspepsia	-	-	-	-	1 (4%)	-	-
Infections and infestations							
Any event	2 (7%)	-	-	2 (8%)	1 (4%)	-	1 (4%)
Influenza	-	-	-	-	1 (4%)	-	1 (4%)
Rhinitis	2 (7%)	-	-	-	-	-	-
Nasopharyngitis	-	-	-	1 (4%)	-	-	-
Oral herpes	-	-	-	1 (4%)	-	-	-

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Table 15 Summary of All Adverse Events by System Organ Class and Preferred Term (continued)

System Organ Class Preferred Term	2 mg PR/CR (N=28)	4 mg PR/CR (N=28)	6 mg PR/CR (N=26)	8 mg PR/CR (N=25)	1 x 12 mg PR/CR (fasted) (N=25)	1 x 12 mg PR/CR (high fat fed) (N=25)	3 x 4 mg PR/CR (fasted) (N=25)
General Disorders and administration site conditions							
Any event	-	2 (7%)	-	-	-	-	1 (4%)
Fatigue	-	2 (7%)	-	-	-	-	-
Feeling abnormal	-	-	-	-	-	-	1 (4%)
Eye disorders							
Any event	-	-	-	1 (4%)	-	-	1 (4%)
Eye inflammation	-	-	-	1 (4%)	-	-	-
Vision blurred	-	-	-	-	-	-	1 (4%)
Injury, poisoning and procedural complications							
Any event	-	-	1 (4%)	1 (4%)	-	-	-
Joint sprain	-	-	1 (4%)	-	-	-	-
Ligament Sprain	-	-	-	1 (4%)	-	-	-
Respiratory, thoracic and mediastinal disorders							
Any event	1 (4%)	1 (4%)	-	-	-	1 (4%)	-
Nasal congestion	1 (4%)	-	-	-	-	1 (4%)	-
Cough	-	1 (4%)	-	-	-	-	-
Skin and subcutaneous tissue disorders							
Any event	-	1 (4%)	-	-	1 (4%)	1 (4%)	-
Dermatitis contact	-	-	-	-	1 (4%)	1 (4%)	-
Pruritus	-	1 (4%)	-	-	-	-	-
Cardiac Disorders							
Any event	-	-	-	1 (4%)	-	-	-
Tachycardia	-	-	-	1 (4%)	-	-	-
Musculoskeletal and connective tissue disorders							
Any event	1 (4%)	-	-	-	-	-	-
Back pain	1 (4%)	-	-	-	-	-	-
Vascular disorders							
Any event	-	1 (4%)	-	-	-	-	-
Orthostatic hypotension	-	1 (4%)	-	-	-	-	-

Source Data: Table 10.02

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10.3 Drug-Related Adverse Events

All drug-related AEs are summarised and listed by treatment regimen according to MedDRA coding dictionary in Data Source Table 10.03.

AEs judged by the investigator to be related to study drug are summarised by body system and preferred term in Table 16.

The most common drug-related AEs occurred in the SOCs Nervous System Disorders and Gastrointestinal Disorders. Overall, the incidence of drug-related AEs during the treatment phase was slightly higher at the lower doses of 2 and 4 mg/day ropinirole PR/CR. The most frequently reported drug-related AEs across all the doses were nausea, headache and dizziness. However the incidence of each of these AEs was low with only up to 3 subjects (11%) reporting each one across the different dose levels.

Table 16 Summary of Drug-related Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	2 mg PR/CR (N=28)	4 mg PR/CR (N=28)	6 mg PR/CR (N=26)	8 mg PR/CR (N=25)	1 x 12 mg PR/CR (fasted) (N=25)	1 x 12 mg PR/CR (high fat fed) (N=25)	3 x 4 mg PR/CR (fasted) (N=25)
ANY EVENT	6 (21%)	8 (29%)	1 (4%)	3 (12%)	4 (16%)	2 (8%)	4 (16%)
Nervous system disorders							
Any event	2 (7%)	5 (18%)	-	3 (12%)	2 (8%)	2 (8%)	2 (8%)
Headache	1 (4%)	3 (11%)	-	1 (4%)	-	1 (4%)	1 (4%)
Dizziness	-	1 (4%)	-	2 (8%)	1 (4%)	1 (4%)	-
Somnolence	-	-	-	-	1 (4%)	-	1 (4%)
Depressed level of consciousness	-	-	-	-	-	-	1 (4%)
Restless legs	-	1 (4%)	-	-	-	-	-
Syncope	1 (4%)	-	-	-	-	-	-
Gastrointestinal disorders							
Any event	4 (14%)	4 (14%)	1 (4%)	-	4 (16%)	1 (4%)	2 (8%)
Nausea	2 (7%)	2 (7%)	-	-	2 (8%)	-	2 (8%)
Constipation	1 (4%)	2 (7%)	-	-	1 (4%)	-	-
Diarrhoea	-	-	1 (4%)	-	1 (4%)	-	1 (4%)
Abdominal pain	-	-	-	-	-	1 (4%)	-
Abdominal pain upper	-	1 (4%)	-	-	-	-	-
Dry mouth	1 (4%)	-	-	-	-	-	-
Dyspepsia	-	-	-	-	1 (4%)	-	-
General Disorders and administration site conditions							
Any event	-	1 (4%)	-	-	-	-	1 (4%)
Fatigue	-	1 (4%)	-	-	-	-	-
Feeling abnormal	-	-	-	-	-	-	1 (4%)
Eye disorders							
Any event	-	-	-	-	-	-	1 (4%)
Vision blurred	-	-	-	-	-	-	1 (4%)
Respiratory, thoracic and mediastinal disorders							
Any event	1 (4%)	-	-	-	-	1 (4%)	-
Nasal congestion	1 (4%)	-	-	-	-	1 (4%)	-
Vascular disorders							
Any event	-	1 (4%)	-	-	-	-	-
Orthostatic	-	1 (4%)	-	-	-	-	-

Source Data: Table 10.03

10.4 Serious Adverse Events

One subject experienced a non-fatal SAE during the study. Further details of the SAE are presented in Section 10.4.2. A case narrative for the SAE is presented in Section 15

10.4.1 Fatal Events

There were no fatal events in this study.

10.4.2 Non-Fatal Events

[redacted]

The subject completed all study periods.

See also case narrative in Section 15.

10.5 Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

[redacted] See also case narrative in Section 15

10.6 Other Relevant Adverse Events

In addition to the standard summaries of AEs, a summary and listing of AEs of special interest was created. AEs of special interest were identified via a list of pre-selected preferred terms categorized into "topics".

In this study there were 9 AEs of special interest in 8 subjects within the topic "hypotension"; 2 AEs in 2 subjects within the topic "fall/injury", and 1 AE within the topic "syncope". With the exception of the syncope which was classified as a severe event, all of these AEs were of mild to moderate intensity. The syncope, orthostatic hypotension and 5 of 8 reported cases of dizziness were judged by the investigator to be drug-related.

Narratives of these subjects are presented in Section 15.

A summary of all adverse events of special interest are presented in Table 17.

Table 17 Summary of All Adverse Events of Special Interest

Topic / Preferred Term	2 mg PR/CR (N=28)	4 mg PR/CR (N=28)	6 mg PR/CR (N=26)	8 mg PR/CR (N=25)	1 x 12 mg PR/CR (fasted) (N=25)	1 x 12 mg PR/CR (high fat fed) (N=25)
Any Event	1 (4%)	2 (7%)	1 (4%)	3 (12%)	3 (12%)	2 (8%)
Hypotension						
Any Event	-	2 (7%)	-	2 (8%)	3 (12%)	2 (8%)
Dizziness	-	1 (4%)	-	2 (8%)	3 (12%)	2 (8%)
Orthostatic Hypotension	-	1 (4%)	-	-	-	-
Fall/ Injury						
Any Event	-	-	1 (4%)	1 (4%)	-	-
Joint sprain	-	-	1 (4%)	-	-	-
Ligament sprain	-	-	-	1 (4%)	-	-
Syncope						
Any Event	1 (4%)	-	-	-	-	-
Syncope	1 (4%)	-	-	-	-	-

Source Data: Table 10.06

10.7 Pregnancies

No female subject became pregnant during this study.

10.8 Clinical Laboratory Evaluations

As chemistry and haematology parameters were only collected at screening and follow-up visit, only listings were produced.

Laboratory values of PCI are provided in Source Table 10.21 to Table 10.24.

In total, 7 subjects had laboratory values of PCI. Five subjects had high serum cholesterol; 4 of whom had high cholesterol levels at screening and 1 at both screening and follow-up, based on FDA specified clinical concern range. [redacted]

None of these values were reported as an AE.

10.9 Vital Signs

Heart rate and blood pressure measurements were taken in the different dose regimens throughout the study. For the 4, 8, and 12 mg dose levels, measurements were taken pre-dose, and 4 h, 6 h, 12 h and 24 h after study drug administration on PK assessment days.

Summaries of values of vital signs and their changes from baseline are listed in Source Table 10.11, and Table 10.12. Source Table 10.13, Table 10.14 and Table 10.20 summarise the change from baseline vital signs outside the range of PCI.

10.9.1 Individual Subject Changes

Table 18 summarises the mean change from baseline (three pre-dose measurements on Day 1) for supine and standing systolic (SBP) and diastolic blood pressure (DBP) on PK days.

Mean systolic and diastolic blood pressure were reduced compared to the mean pre-dose baseline on Day 1 in both the standing and supine positions. The maximum SBP and DBP reduction generally occurred at four or six hours after study drug administration.

Mean heart rate was slightly higher compared to the mean pre-dose baseline at most post-dose time points, especially in the standing position. (Source Table 10.12)

Table 18 Summary of Mean Changes from Baseline for Supine and Standing Blood Pressure on PK Days

		Systolic Blood Pressure mmHg				Diastolic Blood Pressure mmHg			
		Supine		Standing		Supine		Standing	
	Planned Relative Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD
4 mg PR/CR	pre-Dose	-4.89	10.070	-2.94	12.383	-0.78	6.770	-0.67	7.222
	4h	-7.74	13.795	-9.53	14.741	-1.70	8.260	-0.93	9.134
	6h	-13.78	15.620	-12.20	18.963	-6.70	8.351	-6.96	10.049
	12h	-11.41	14.782	-12.01	19.927	-6.44	7.247	-4.74	9.436
	24h	-2.56	13.642	-2.64	15.002	-1.59	7.579	-0.56	6.886
8 mg PR/CR	pre-Dose	-3.72	15.571	-0.31	14.087	0.07	7.518	1.47	9.996
	4h	-7.40	10.741	-8.03	14.439	0.39	6.533	-0.65	8.854
	6h	-10.16	15.311	-9.63	18.730	-4.69	8.658	-2.77	11.212
	12h	-7.44	11.962	-8.67	17.281	-0.93	8.340	-2.69	13.237
	24h	-0.92	11.289	-3.99	16.200	0.15	7.140	0.71	9.125
1 x12 mg PR/CR (fasted) Day 31	pre-Dose	-7.17	19.982	-6.08	19.747	-1.83	5.828	-1.46	7.402
	4h	-14.04	17.058	-16.58	16.831	-1.71	6.883	-1.83	7.165
	6h	-15.04	20.721	-11.21	13.240	-5.21	6.705	-1.83	5.300
	12h	-12.17	23.142	-10.71	12.060	-2.08	4.556	1.79	7.699
	24h	0.71	19.763	-1.58	11.818	2.92	3.753	3.42	4.793
Day 34	pre-Dose	-3.19	16.650	-4.93	24.615	-0.67	9.037	1.41	11.248
	4h	-5.52	21.850	-13.48	23.557	-2.33	11.158	-4.93	14.145
	6h	-4.41	28.264	-11.81	23.643	-3.33	12.826	-4.15	14.668
	12h	-2.96	24.476	-15.15	33.794	-1.67	12.131	-4.37	15.420
	24h	-5.74	17.316	-18.26	19.268	-2.33	10.165	0.07	11.944
Day 37	pre-Dose	-4.88	10.101	-2.08	6.849	0.42	8.759	2.71	9.221
	4h	-6.38	10.844	-4.08	10.518	0.79	10.046	4.33	8.524
	6h	-12.63	13.085	-5.46	19.507	-3.33	9.342	-0.17	12.891
	12h	-1.38	15.766	-5.96	18.914	-0.33	8.599	0.21	10.820
	24h	-5.50	10.954	4.42	16.399	-0.58	6.630	7.46	15.053

Source data: Table 10.12

Table 18 Summary of Mean Changes from Baseline for Supine and Standing Blood Pressure on PK Days (continued)

	Planned Relative Time	Systolic Blood Pressure mmHg				Diastolic Blood Pressure mmHg			
		Supine		Standing		Supine		Standing	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1 x12 mg PR/CR (high fat fed) Day 31	pre-Dose	-1.96	9.164	-2.46	11.048	0.92	6.281	3.71	5.664
	4h	-10.71	21.531	-5.46	18.196	-1.96	12.872	-4.17	6.547
	6h	-10.08	17.884	-6.08	18.482	-4.46	10.439	-1.42	6.104
	12h	-5.71	11.203	0.17	12.151	-1.33	7.010	-1.42	7.510
	24h	-2.58	10.120	-3.83	21.131	-0.83	8.591	3.33	14.203
Day 34	pre-Dose	-5.67	18.483	-2.46	11.521	-0.29	8.418	1.29	5.144
	4h	-7.04	14.931	-4.58	12.312	-1.67	7.492	-2.71	8.901
	6h	-8.17	22.322	-9.21	14.748	-2.04	8.201	-3.71	9.169
	12h	-7.92	17.233	-7.46	11.987	-1.67	9.583	3.04	5.788
	24h	-6.04	19.076	-7.58	11.425	-1.04	5.138	-1.33	7.807
Day 37	pre-Dose	-9.67	27.060	-15.81	31.205	-5.81	12.274	-7.15	14.366
	4h	-17.78	29.961	-21.81	20.526	-9.26	12.869	-10.70	10.715
	6h	-8.00	27.775	-23.81	25.439	-5.26	14.069	-7.48	15.426
	12h	-8.00	9.100	-19.37	21.295	-2.81	8.300	-7.70	7.273
	24h	-1.78	16.711	-5.93	18.124	-0.15	8.349	-1.70	9.091
3 x 4 mg PR/CR (fasted) Day 31	pre-Dose	-5.89	9.677	-16.93	25.028	-2.78	5.528	-4.93	11.536
	4h	-7.11	11.250	-14.26	20.624	-3.11	6.896	-7.59	11.652
	6h	-14.00	13.473	-25.26	23.696	-5.56	9.272	-11.37	13.264
	12h	-3.44	14.360	-9.48	17.112	-3.56	6.700	-2.48	8.007
	24h	-6.44	11.364	-12.37	15.716	-3.33	5.790	-1.59	8.348
Day 34	pre-Dose	-8.25	10.093	-8.58	7.657	0.00	3.324	-0.04	6.552
	4h	-9.87	14.164	-8.71	7.258	2.13	5.339	2.08	4.911
	6h	-14.37	8.224	-12.46	12.953	-2.50	4.231	-1.79	8.643
	12h	-16.62	13.083	-17.58	22.574	-4.88	6.854	-6.92	8.288
	24h	-10.00	8.300	-8.96	14.240	0.50	6.928	-1.29	10.018
Day 37	pre-Dose	-7.12	25.648	-7.33	21.899	0.33	8.552	1.42	10.732
	4h	-10.63	21.575	-8,96	19.042	-3.04	11.509	-0.46	10.073
	6h	-10.00	28.132	-4,96	18.630	-3.79	12.616	-3.21	8.599
	12h	-4.87	16.920	-4,71	12,525	-0,92	8.681	1.17	6.852
	24h	-6.50	15.552	-7,21	16,002	0,58	9.036	5.79	10.016

Source data: Table 10.12

10.9.2 Abnormalities of Potential Clinical Importance

Vital sign values, which fell outside the PCI ranges, separated according to the FDA and the European classification, are summarised and listed in Source Table 10.13, Table 10.14, Table 10.20, Table 10.25, Table 10.26 and Table 10.27.

Considering the European reference ranges of systolic 90-180 mmHg, diastolic 50-115 mmHg and heart rate 50-120 bpm, 21 subjects had vital sign values of PCI in at least one of the measurements during the study period.

A SBP of PCI (below 90mmHg) was the most frequent vital sign value of PCI, followed by low values for DBP and HR.

Considering the FDA and European threshold values of potential clinical concerns for SBP (Europe: >30 mmHg, FDA ≥20 mmHg for increase and decrease from original baseline value) and DBP (Europe >20 mmHg, FDA ≥10 mmHg for increase and decrease from original baseline value), both increases and decreases from baseline were observed; however, more decreases were observed than increases, particular when the changes of larger magnitude were considered. Blood pressure reduction of potential clinical concern was most frequent in the 12 mg ropinirole PR/CR dose groups 4-12 hrs after dosing.



All vital signs measured for this subject are presented in Section 15.2.

10.9.3 Ambulatory Blood Pressure Monitoring

Summaries of ABPM are provided in Source Table 10.17 and their changes from baseline are provided in Source Table 10.18. Values outside clinical concern ranges are provided in Source Table 10.19. Plots are presented in Source Figure 10.01 to Figure 10.06.

Ambulatory blood pressure was monitored over 12 hours on Day 1 (first day of 2 mg dose), Day 8 (dose increase day, 4 mg), Day 15 (dose increase day, 6 mg dose), Day 22 (dose increase day, 8 mg dose) and Day 29 (dose increase day, 12 mg dose).

The following describes the mean changes from baseline at different time points in the different treatment groups:

A drop in mean SBP was observed at the 2 mg, 4 mg and 6 mg doses with maximum mean decrease of -9.7 mmHg, -10.6 mmHg, -9.8 mmHg, respectively, after 5 to 6 hours.

The drop in mean SBP was less pronounced at the 8 mg dose level with a maximum mean decrease of -2.0 mmHg 5 hours after dosing.

The largest mean drop in SBP was observed at the 12 mg dose levels, with the exception of 1 x 12 mg (fasted) that showed similar decreases in mean SBP as seen in the 2, 4 and 6 mg dose levels. The largest mean drop in SBP was -15.5 mmHg 5 hours after dosing with 1 x 12 mg (high fat fed) and following the 3 x 4mg dose, the largest mean drop in SBP was -11.9 mmHg at 3 hours.

The changes in mean DBP were different across the doses. Trends towards decreases in mean DBP were only seen in the 2 mg and 4 mg dose levels. The maximum drop in mean DBP was -7.2 mmHg at the 4 mg dose level. No trend in any direction could be observed in the higher dose levels of 6 mg, 8 mg, and 12 mg ropinirole PR/CR.

The mean heart rates did not show any clinically significant changes during ABPM measurements.

During the ABPM recording, 10 subjects had SBP/DBP values flagged of PCI: 7 subjects had low DBP values, 4 subjects had low SBP values and 3 subjects had high SBP flagged of potential clinical concern (defined as SBP <80 mmHg or >190mmHg, and DBP <50 mmHg or >120mmHg).(Table 10.19)

10.10 ECGs

Summaries of ECG findings and values and the change from baseline are provided in Source Table 10.08 to Table 10.10.

All 12-lead ECGs were judged by the study physician to be within normal limits or not clinically significant. No clinically significant abnormal ECGs were observed.

The mean and median values of the different ECG variables PR interval, QRS duration and QT interval did not show any clinically relevant changes across the ropinirole doses.

11 PHARMACODYNAMIC RESULTS

Not Applicable

12 PHARMACOKINETIC RESULTS

12.1 Concentration Data

12.1.1 Ropinirole Concentration Data

Individual plasma ropinirole concentration-time profiles are displayed with actual time on both semi logarithmic and linear scales by subject and treatment in Source Figure 12.08 and Figure 12.09. Descriptive statistics for plasma ropinirole concentration data at each planned relative time are presented by treatment in Source Table 12.01. Mean and median steady-state plasma ropinirole concentration-time profiles for all treatments are displayed with scheduled time and are presented on both semi-logarithmic and linear scales in Source Figure 12.01 to Figure 12.07.

No plasma ropinirole concentrations were excluded from the PK analysis.

At steady-state plasma ropinirole concentrations increased with increasing dose and the concentration-time profiles for ropinirole were similar in shape for each PR/CR formulation under fasted condition with concentrations of ropinirole measurable at all time points over the dosing interval of 24 h for all subjects and treatments. The concentration-time profiles were quite superimposable for the 1 x 12 mg (fasted) and 3 x 4 mg (fasted) regimens. Under fasted condition the mean concentration-time profiles for ropinirole were fairly flat with a low peak to trough ratio (~ 1.5-fold to ~1.7-fold range of concentrations). Under fed conditions, the PK profile had a higher and delayed peak and a more rapid decrease in concentrations following Cmax relative to the fasted regimens (peak to trough ratio of ~ 2.3-fold).

12.1.2 Metabolite Concentration Data

12.1.2.1 SKF-104557 Plasma Concentrations

Individual plasma SKF-104557 concentration-time profiles are displayed with actual time on both semi logarithmic and linear scales by subject and treatment (Source Figure 12.12 and Figure 12.13). Descriptive statistics for plasma SKF-104557 concentration data at each planned relative time are presented by treatment (Source Table 12.02). Mean and median steady-state plasma concentration-time profiles for all treatments are displayed with scheduled time and are presented on both semi-logarithmic and linear scales (Source Figure 12.10 and Figure 12.11).

No plasma SKF-104557 concentrations were excluded from the PK analysis.

At steady-state the concentrations for SKF-104557 were in the range to those of the parent drug with concentrations of SKF-104557 measurable at all time points over the dosing interval of 24 h for all subjects and treatments. Plasma SKF-104557 concentrations increased with increasing dose of the parent drug and concentration-time profiles were quite super-imposable for the 1 x 12 mg (fasted) and 3 x 4 mg (fasted) regimens. Under fasted condition, the mean PK profiles were similar in shape over the

dosing interval (24 h) for each PR/CR treatment in the fasted state and depicted an apparent mono-exponential decline following the peak. As observed for parent drug under fed condition there was a higher peak and a more rapid decrease of concentration.

12.1.2.2 SKF-89124 Plasma Concentrations

Individual plasma SKF-89124 concentration-time profiles are displayed with actual time on both semi logarithmic and linear scales by subject and treatment (Source Figure 12.16 and Figure 12.17). Descriptive statistics for plasma SKF-89124 concentration data at each planned relative time are presented by treatment (Source Table 12.03). Mean and median steady-state plasma concentration-time profiles for all treatments are displayed with scheduled time and are presented on both semi-logarithmic and linear scales (Source Figure 12.14 to Figure 12.15).

No plasma SKF-89124 concentrations were excluded from the PK analysis.

At steady-state the concentrations for SKF-89124 were lower than those of the parent drug but were measurable at all time points over the dosing interval of 24 h for all subjects but two (at pre-dose in the 4 mg dose group and 8 mg dose group). Plasma SKF-89124 concentrations increased with increasing dose of the parent drug and plasma concentration-time profiles were quite superimposable for the 1 x 12 mg (fasted) and 3 x 4 mg (fasted) regimens. Under fasted condition, over the dosing interval (24h) SKF-89124 PK profiles were similar in shape for each PR/CR regimen and the concentration-time profiles depicted an apparent mono-exponential decline following the peak. As observed for parent drug under fed condition there was a higher peak and more rapid decrease of concentration.

12.2 Pharmacokinetic Parameters

12.2.1 Ropinirole (SKF-101468) PK parameters

Individual plasma ropinirole PK parameters are presented in Source Table 12.06 and are summarised in Source Table 12.04 and Table 12.05. Selected PK parameters are also summarised in Table 19.

Table 19 Summary (geometric mean (CVb%)) of Ropinirole Pharmacokinetic Parameters by Regimen

Regimen	Ropinirole PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/CR (fasted)	27	57.1 (59.3)	3.36 (48.9)	6.00 (2.03 – 14.00)	1.64 (71.5)
1 x 8mg ropinirole PR/CR (fasted)	25	118 (46.8)	6.63 (44.6)	4.03 (2.00 – 10.00)	3.58 (58.1)
1 x 12mg ropinirole PR/CR (fasted)	25	164 (52.3)	9.06 (48.5)	4.02 (2.00 – 16.00)	4.74 (64.5)
1 x 12mg ropinirole PR/CR (fed)	25	197 (51.6)	13.1 (49.7)	10.00 (4.00 – 12.00)	4.57 (81.2)
3 x 4mg ropinirole PR/CR (fasted)	25	173 (53.8)	9.57 (52.4)	6.00 (2.00 – 14.00)	5.07 (60.9)

Source Data: Table 12.04 and Table 12.05

a. Median (range)

Median tmax values were similar between all dosing regimens under fasted conditions (4 to 6 h). However under fed conditions, median tmax was delayed until 10 h after dosing.

The CVb% for AUC(0-24) and Cmax ranged from 45% to 59% for all regimens.

12.2.2 SKF-104557 PK parameters

Individual plasma SKF-104557 PK parameters are presented in Source Table 12.09 and are summarised in Source Table 12.07 and Table 12.08. Selected PK parameters are also summarised in Table 20.

Table 20 Summary (geometric mean (CVb%)) of SKF-104557 Pharmacokinetic Parameters by Regimen

Regimen	SKF-104557 PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/CR (fasted)	27	78.8 (32.7)	4.02 (30.0)	9.98 (3.80 – 14.05)	2.66 (36.7)
1 x 8mg ropinirole PR/CR (fasted)	25	155 (32.8)	7.75 (37.2)	8.00 (0.00 – 14.00)	5.38 (35.5)
1 x 12mg ropinirole PR/CR (fasted)	25	219 (34.9)	10.8 (33.7)	8.00 (4.00 – 16.00)	7.60 (36.3)
1 x 12mg ropinirole PR/CR (fed)	25	250 (32.3)	13.7 (35.4)	10.00 (6.00 – 12.00)	7.70 (38.0)
3 x 4mg ropinirole PR/CR (fasted)	25	230 (24.6)	11.2 (25.5)	8.00 (2.00 – 14.00)	7.97 (26.4)

Source Data: Table 12.07 and Table 12.08
a. Median (range)

Median tmax values were similar between all dosing regimens under fasted and fed conditions (8 to 10 h).

The CVb% for AUC(0-24) and Cmax ranged from 25% to 37% for all regimens.

12.2.3 SKF-89124 PK parameters

Individual plasma SKF-89124 PK parameters are presented in Source Table 12.12 and are summarised in Source Table 12.10 and Table 12.11. Selected PK parameters are also summarised in Table 21.

Table 21 Summary (geometric mean (CVb%)) of SKF-89124 Pharmacokinetic Parameters by Regimen

Regimen	SKF-89124 PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/CR (fasted)	27	2.78 (49.5)	0.156 (49.6)	8.00 (1.80 – 20.00)	0.092 (47.2)
1 x 8mg ropinirole PR/CR (fasted)	25	5.72 (43.3)	0.305 (49.3)	6.00 (0.00 – 20.00)	0.200 (44.7)
1 x 12mg ropinirole PR/CR (fasted)	25	8.61 (44.7)	0.463 (45.3)	6.00 (2.00 – 20.02)	0.286 (41.5)
1 x 12mg ropinirole PR/CR (fed)	25	10.2 (44.6)	0.584 (48.0)	10.00 (2.00 – 16.00)	0.315 (47.5)
3 x 4mg ropinirole PR/CR (fasted)	25	9.19 (38.5)	0.494 (40.4)	6.00 (2.00 – 20.00)	0.314 (35.0)

Source Data: Table 12.10 and Table 12.11
a. Median (range)

Median tmax values were similar between all dosing regimens under fasted conditions (6 to 8 h). However under fed conditions, median tmax was delayed until 10 h after dosing.

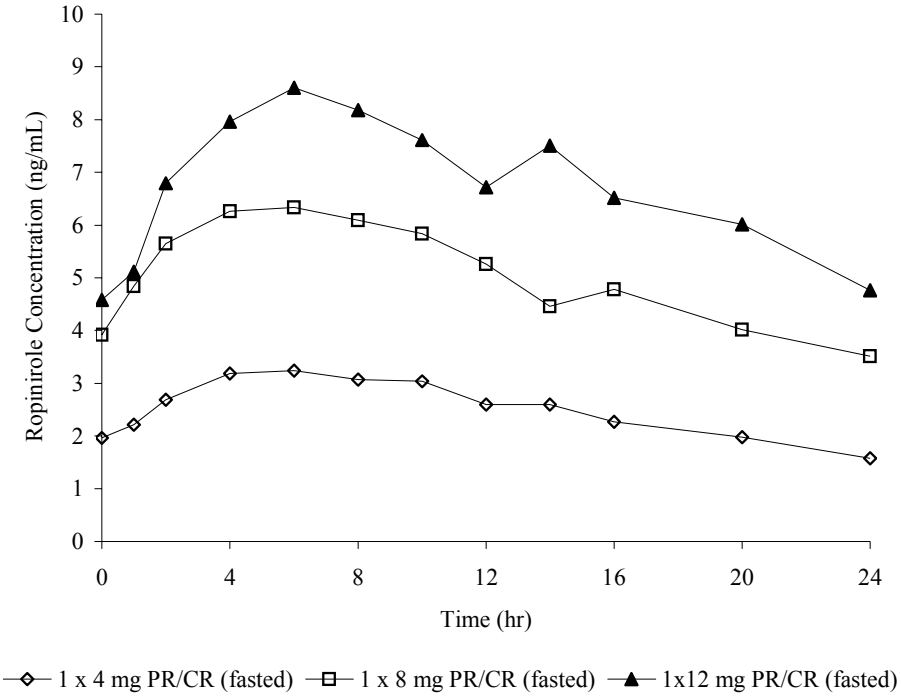
The CVb% for AUC(0-24) and Cmax ranged from 39% to 50% for all regimens.

[redacted]

12.3 Statistical Analyses of Pharmacokinetic Parameters

12.3.1 Dose proportionality Assessment

Figure 1 Median Ropinirole Plasma Concentrations for Regimens Used in the Assessment of Dose Proportionality



Source Data: Figure 12.05

Results of the ANOVA output for the dose proportionality assessment for ropinirole AUC(0-24), Cmax and Cmin for ropinirole over the dose range 4-12 mg are summarised in Table 22.

Table 22 Summary of the Slope and 90% Confidence Intervals for Ropinirole AUC(0-24), Cmax and Cmin from the Power Model

Parameter	Slope	Standard error	CVw%	90% CI
AUC(0-24) (hr*ng/mL)	0.970	0.0455	18.06%	(0.893,1.046)
Cmax (ng/mL)	0.905	0.0415	16.45%	(0.835,0.974)
Cmin (ng/mL)	0.986	0.0639	25.61%	(0.878,1.093)

Source Data: Table 12.17, Table 12.18, Table 12.19
CVw% = % within-subject coefficient of variation

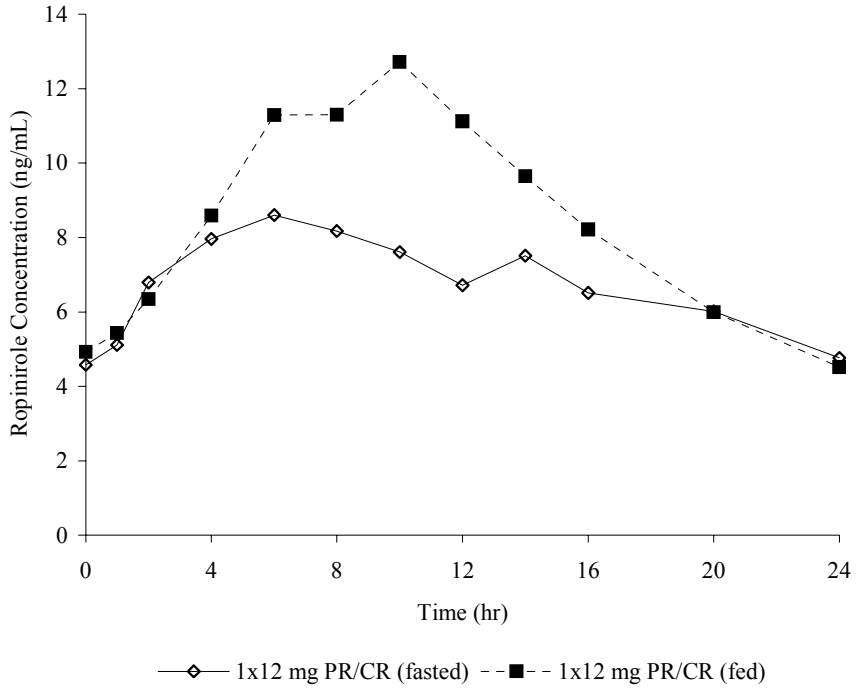
For the primary endpoints AUC(0-24) and Cmax, the PKs of ropinirole were dose proportional over the ropinirole PR/CR dose range 4 mg (fasted) to 12 mg (fasted) based on the estimated mean slopes being close to unity and the 90% confidence intervals within the pre-specified limits of (0.797, 1.203).

In addition, the estimated mean slope of the secondary endpoint Cmin was close to unity and the 90% confidence interval was within the limits of (0.797, 1.203).

For AUC(0-24), Cmax and Cmin, the calculated within subject variabilities (CVw%) were 18%, 16% and 26% respectively.

12.3.2 Effect of Food

Figure 2 Median Ropinirole Plasma Concentrations for Regimens Used in the Assessment of Effect of Food



Source data: Figure 12.06

Results of the analysis of variance output for the food effect for AUC(0-24), Cmax and Cmin for ropinirole 1 x 12 mg PR/CR (fasted) and 1 x 12 mg PR/CR (fed) are summarised in Table 23.

Table 23 Summary of Point Estimates and 90% Confidence Intervals for Ropinirole PK Parameters for the Comparison 1 x 12 mg PR/CR (Fed) Versus 1 x 12 mg PR/CR (Fasted)

Parameter	Geometric LS Mean		Ratio	90% CI	CVw%
	Test 1 x 12 m g PR/CR (Fed)	Ref 1 x 12 m g PR/CR (Fasted)			
AUC(0-24) (hr*ng/mL)	196.59	163.85	1.20	(1.12, 1.28)	14.08
Cmax (ng/mL)	13.03	9.02	1.44	(1.34, 1.56)	15.85
Cmin (ng/mL)	4.54	4.72	0.96	(0.86, 1.08)	24.51
tmax[a] (hr)	10.00	4.02	3.01	(2.00, 4.01)	-

Source Data: Table 12.20, Table 12.21, Table 12.22, Table 12.26
a. median along with estimated median difference between treatments and 90% CI
CVw% = % within-subject coefficient of variation

On average AUC(0-24) was 20% higher, and Cmax was 44% higher, when the 1 x 12 mg PR/CR 24h formulation was administered in the fed state compared to the fasted state. The secondary endpoint Cmin, was similar in the fed and fasted states.

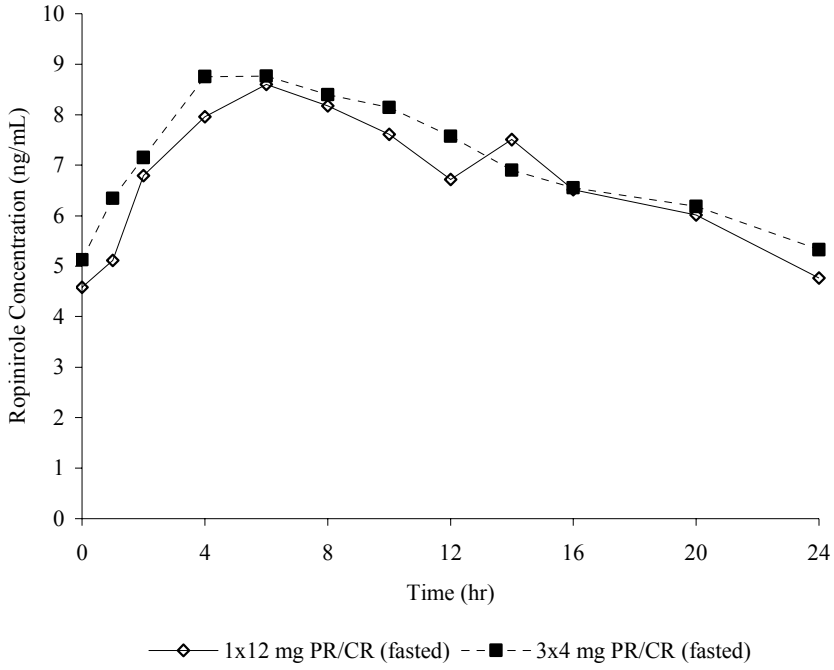
Statistical analysis indicated that tmax occurred, on average, 3 hours later following dosing in the fed state compared to the fasted state.

There was a statistically significant period effect at the 5% level in the ANOVA model for the PK parameter AUC(0-24). For AUC(0-24) the back transformed least squares means (LSMs) for periods 5, 6 and 7 were 166.97, 182.07 and 183.51, respectively. A model was fitted with an interaction term between treatment and period (outputs with LSMs are on file), and there was no evidence of a period treatment interaction. The effect of period was accounted for in the analysis.

For AUC(0-24), Cmax and Cmin, the calculated within subject variabilities (CVw%) were 14%, 16% and 25% respectively.

12.3.3 Dosage Strength Equivalence

Figure 3 Median Ropinirole Plasma Concentrations for Regimens used in the Assessment of Dosage Strength Equivalence



Source data: Figure 12.07

Results of the analysis of variance output for the dosage strength comparison of 1 x 12 mg PR/CR (fasted) and 3 x 4 mg PR/CR (fasted) for AUC(0-24), Cmax and Cmin are summarised in Table 24.

Table 24 Summary of Point Estimates and 90% Confidence Intervals for Ropinirole PK Parameters for the Comparison of 1 x 12 mg PR/CR (Fasted) Versus 3 x 4 mg PR/CR (Fasted)

Parameter	Geometric LS Mean		Ratio	90% CI	CVw%
	Test 1 x 12 mg PR/CR	Ref 3x4 mg PR/CR			
AUC(0-24) (hr*ng/mL)	163.85	173.18	0.95	(0.89, 1.01)	14.08
Cmax (ng/mL)	9.02	9.56	0.94	(0.88, 1.02)	15.85
Cmin (ng/mL)	4.72	5.07	0.93	(0.83, 1.04)	24.51
Tmax[a] (h)	4.02	6.00	0.00	(-1.00, 1.00)	-

Source data: Table 12.23, Table 12.24, Table 12.25, Table 12.27
a median along with estimated median difference between treatments and 90% CI
CVw% = % within-subject coefficient of variation

The primary endpoints AUC(0-24) and Cmax for the 1 x 12 mg PR/CR (fasted) regimen and the 3 x 4 mg PR/CR (fasted) regimen were bioequivalent since the 90% confidence intervals were within the pre-specified limits of (0.80, 1.25).

In addition, for the secondary endpoint Cmin, the 90% confidence interval was within the limits of (0.80, 1.25), also indicating bioequivalence.

For tmax, there was no statistically significant difference between 1 x 12 mg and 3 x 4 mg PR/CR (fasted).

There was a statistically significant period effect at the 5% level in the ANOVA model for the PK parameter AUC(0-24). For AUC(0-24) the back transformed least squares means (LSMs) for periods 5, 6 and 7 were 166.97, 182.07 and 183.51, respectively. A model was fitted with an interaction term between treatment and period (outputs with LSMs are on file), and there was no evidence of a period treatment interaction. The effect of period was accounted for in the analysis.

For AUC(0-24), Cmax and Cmin the calculated within subject variabilities (CVw%) were 14%, 16% and 25%, respectively.

13 DISCUSSION AND CONCLUSIONS

13.1 Discussion

This was an open label, repeat dose, dose escalation study conducted in Parkinson's disease subjects to characterise the PKs and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets.

PD is one of the most common neurological disorders in elderly people. It is caused by a loss of dopaminergic nerve cells in brain area of the brain. Ropinirole is a selective non-ergot dopamine agonist which acts at the D2/D3 receptors and is active both peripherally and centrally.

Ropinirole immediate release (IR) is registered in more than 60 countries worldwide for the treatment of PD at dose of up to 24mg/day (administered as 8 mg three times daily). A prolonged-release (PR) tablet of ropinirole has been developed to allow once-daily dosing of ropinirole, to provide a simpler dose-titration regimen and to improve the tolerability profile by slowing the rate of absorption of ropinirole.

A 12 mg tablet is under development in order to reduce tablet burden for subjects taking higher doses of ropinirole PR/CR. This study was designed to demonstrate dose proportionality for the extended release (PR/CR) formulations of ropinirole over the dose range 4-12 mg, to determine the effect of food on the absorption of PR/CR at 12 mg (highest tablet strength), and to determine dosage strength equivalence for PR/CR administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets.

The study was a steady-state open, non-randomised sequential design, followed by a 3-period randomised crossover design in subjects with PD.

Over the dose range 4-12 mg PR/CR, plasma ropinirole concentrations increased with increasing doses and the ropinirole concentration-time profiles were similar in shape for all the extended-release (PR/CR) tablet strengths under fasted conditions. The results of the power model showed that the PKs of ropinirole were dose proportional over this dose range, based on the slope being close to unity (0.970 for AUC(0-24), and 0.905 for Cmax) and the 90% confidence intervals being contained within the pre-defined criteria of 0.797 to 1.203.

The dosage strengths of one, 12 mg PR/CR tablet (1x12 mg) compared with three, 4 mg PR/CR tablets were shown to be equivalent, and therefore, subjects who are receiving 3 x 4 mg tablets can be switched to a single 12 mg tablet without any expected changes in safety or efficacy.

Following administration of 1 x 12 mg PR/CR in the fed state (high fat breakfast), AUC(0-24) and Cmax values of ropinirole were on average, 20% and 44% higher than in the fasted state and tmax occurred on average, 3 h later in the fed state. Cmin was similar in both the fed and fasted state. The time lag and faster rate of rise in plasma concentration observed in the fed state relative to the fasted state, is likely to be due to delayed gastric emptying with food.

Ropinirole is highly soluble and highly permeable and is considered to be a Biopharmaceutics Classification System Class 1 drug. In-vitro dissolution data from the immediate release formulation shows that 90% of the drug is released over 15 minutes. This is reflected by the rapid absorption of ropinirole when the immediate release (IR) formulation is orally administered (median tmax generally between 1 and 2 hours post dose). In contrast, the ropinirole PR/CR formulation provides an approximate zero order delivery of ropinirole over a 24 hour period and the in-vitro release rate of ropinirole has been shown to be similar in Simulated Gastric Fluid and in pH4 and pH 7.5 citrate buffers (GSK laboratory record eE309216). Thus based on the in vitro data is SGF, following administration of PR/CR tablets, ropinirole is likely to be released in the normal controlled manner whilst in the stomach but will not available for absorption until gastric emptying has occurred. Therefore the initial time in the absorption of ropinirole observed in the fed state is likely due to a delay in gastric empting, but once in the small intestine, the ropinirole that has already dissolved in the stomach will be available for absorption, hence the faster rate of rise to Cmax. This higher rate of absorption in the fed state is unlikely to be due to dose dumping since the peak to trough ratio of ~2.3-fold is much lower than that observed following administration of ropinirole IR (~10-fold) [GSK Document Number HM2004/00489/00]).

Even though the ropinirole plasma exposures were higher after the 12 mg tablet in the fed state, this regimen was associated with a lower incidence of AEs (16% of subjects reporting an AE) compared to 12 mg fasted (44%) and 3 x 4 mg fasted (36%). The dosing regimen was reasonably well tolerated by PD subjects. During the treatment period, 22 (79%) of 28 subjects experienced a total of 79 treatment emergent AEs, and 15 subjects (54%) experienced a total of 44 AEs which were judged by the investigator to be related to the study drug. The severity of the AEs was mostly mild to moderate in intensity. Three subjects experienced a total of 5 AEs which were of severe intensity (2x nausea, 1x abdominal pain upper; 1x syncope; 1x diarrhoea). The most frequently reported adverse events were headache, nausea and dizziness. No subjects died during the study. One subject had an SAE of gastric atony, which was considered by the investigator to be unrelated to study drug. One subject discontinued from the study due to a drug-related AE (orthostatic hypotension).

Mean systolic and diastolic blood pressure was lower compared to baseline after all doses of ropinirole with a trend for lower mean systolic blood pressure following 12 mg daily doses compared to the 4 mg and 8 mg ropinirole PR/CR doses. The largest mean blood pressure reduction occurred between 4 and 6 hours after study drug administration which correlates with the time of maximum plasma concentrations. The ABPM data confirmed the blood pressure changes seen in the serial vital signs measurements. Reductions in blood pressure and postural hypotension are known adverse reactions with dopamine agonists and have been reported with ropinirole IR formulations.

Safety laboratory values and ECG variables did not show any clinically relevant changes.

Overall, the most frequently observed AEs are well-known side effects of therapy with dopamine agonists like ropinirole. No unexpected or unknown AE occurred in this study.

13.2 Conclusions

In subjects with PD

- The pharmacokinetics of ropinirole were dose proportional over the dose range 4 to 12 mg PR/CR.
- Under fed conditions ropinirole AUC(0-24) and Cmax were on average 20% and 44% higher, respectively and tmax was delayed by 3 hours compared to the fasted state.
- Dosage strength equivalence was demonstrated for 1 x 12 mg PR/CR ropinirole tablet and the 3 x 4 mg PR/CR ropinirole tablets.
- The different dose regimens of ropinirole PR/CR were well tolerated. No unknown or unexpected AEs occurred during the study.
- A lower incidence of AEs was reported following 12 mg ropinirole PR/CR in the fed state compared to the same dose fasted; the proportion of subjects that reported AEs was 16% vs 44%, respectively.

14 REFERENCES

GSK Document ID: CD2004/01194/00. The Validation of a Method for the Determination of SKF101468 (range 20 - 5000 pg/mL), SKF104557 (range 50 - 5000 pg/mL) and SKF89124 (range 20 - 5000 pg/mL) in Human Plasma using HPLC-MS/MS. Authors: [redacted]

GSK Report Number: HM2004/00489/00. A single-blind, parallel group, up-titration, Phase I study in healthy volunteers to determine a starting dose and select an uptitration regimen for an extended release formulation for ropinirole. July 2007.

SK&F Report Number PH/0001/SKF-101468. Effects of ropinirole and its major metabolites SK&F 89124 and SK&F 104557 on CNS, dopamine receptors in-vitro, assessed using D1and D2-receptor binding assays and D2-receptor regulation of acetylcholine release. [redacted] 1 July 1991.

SK&F Report Number PP 002 BA. The effect of ropinirole on the pressor responses evoked by sympathetic nerve stimulation in the perfused hind limb of the dog. [redacted] December 1986.

SK&F Report Number PP011BA. Interaction of ropinirole, SK&F 89124-A and SK&F 104557-A with central adrenergic receptors. [redacted] July 1988.

SK&F Report Number PW019BA: Receptor binding studies with ropinirole in rat and bovine brain membranes: an assessment of data provided by Nova Pharmaceutical Corporation, Baltimore, USA. [redacted] June 1988.

SK&F Report Number PW023BA. Interaction of ropinirole and other DA2 agonists with receptor binding sites. [redacted] October 1988.

Steinsland O S, Hieble J P: Dopaminergic inhibition of adrenergic neurotransmission as a model for studies on dopamine receptor mechanisms. *Science* 1978; 199:443-445.

This section contained patient narratives which are textual descriptions of medical history, treatment and outcome for individual patients who experienced a clinically important adverse event including serious adverse events during the trial. They have been excluded to protect patient privacy. This data may be made available subject to an approved research proposal and a determination of the ability to provide information from the specific narratives whilst protecting the patient's privacy. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Study Population Data Source Tables

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Table 9.01
Summary of Subject Disposition

	Total (N=28)
Completion Status	
Completed	25 (89%)
Prematurely Withdrawn	3 (11%)
Primary reason for withdrawal	
Adverse Event	1 (4%)
Lost to follow-up	0
Protocol Violation	0
Subject decided to withdraw from study	2 (7%)
Other	0

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Table 9.02
Summary of Demographic Characteristics

		Total (N=28)
Age (y)	n	28
	Mean	64.5
	SD	8.56
	Median	65.0
	Min.	47
	Max.	81
Sex	n	28
	Female	14 (50%)
	Male	14 (50%)
Ethnicity	n	28
	Hispanic/Latino	0
	Not Hispanic/Latino	28 (100%)
Race	n	28
	White - Arabic/North African Heritage	1 (4%)
	White - White/Caucasian/European Heritage	27 (96%)
Height (cm)	n	28
	Mean	169.3
	SD	10.31
	Median	168.5
	Min.	145
	Max.	186
Weight (kg)	n	28
	Mean	73.4
	SD	13.20
	Median	72.6
	Min.	54

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Table 9.02
Summary of Demographic Characteristics

		Total (N=28)
Weight (kg)	Max.	96
BMI (kg/m^2)	n	28
	Mean	25.53
	SD	3.326
	Median	26.20
	Min.	19.9
	Max.	32.3

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HM2007/00444/00
ROP109087

Table 9.03
Summary of Race and Racial Combinations Details

Race	Total (N=28)	
n	28	
African American/African Heritage	0	
American Indian or Alaska Native	0	
Asian - Central/South Asian Heritage	0	
Asian - East Asian Heritage	0	
Asian - Japanese Heritage	0	
Asian - South East Asian Heritage	0	
Native Hawaiian or other Pacific Islander	0	
White - Arabic/North African Heritage	1	(4%)
White - White/Caucasian/European Heritage	27	(96%)

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Table 9.04
Summary of Concomitant Medications by Generic Term

ATC Level 1 Ingredient	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Any medication	4 (14%)	5 (18%)	6 (23%)	4 (16%)	7 (28%)	6 (24%)	6 (24%)
No ATC assigned							
Any medication	0	0	0	0	0	0	1 (4%)
PARAFFIN	0	0	0	0	0	0	1 (4%)
NERVOUS SYSTEM							
Any medication	3 (11%)	4 (14%)	3 (12%)	1 (4%)	5 (20%)	5 (20%)	4 (16%)
ROPINIROLE HYDROCHLORIDE	0	1 (4%)	1 (4%)	0	2 (8%)	3 (12%)	3 (12%)
PARACETAMOL	2 (7%)	1 (4%)	1 (4%)	1 (4%)	0	1 (4%)	1 (4%)
IBUPROFEN	0	0	1 (4%)	1 (4%)	1 (4%)	0	2 (8%)
CARBIDOPA	1 (4%)	0	1 (4%)	0	2 (8%)	0	0
LEVODOPA	1 (4%)	0	1 (4%)	0	2 (8%)	0	0
ACETYLSALICYLIC ACID	0	1 (4%)	0	0	1 (4%)	0	0
CODEINE PHOSPHATE	0	0	1 (4%)	0	0	0	1 (4%)
BIPERIDEN	0	0	0	0	0	1 (4%)	0
ROPINIROLE	0	0	0	0	1 (4%)	0	0
ROTIGOTINE	0	1 (4%)	0	0	0	0	0
TRAMADOL HYDROCHLORIDE	0	0	0	1 (4%)	0	0	0
RESPIRATORY SYSTEM							
Any medication	1 (4%)	0	3 (12%)	2 (8%)	1 (4%)	1 (4%)	3 (12%)
CODEINE PHOSPHATE	0	0	1 (4%)	0	0	0	1 (4%)
SODIUM CHLORIDE	0	0	1 (4%)	0	0	0	1 (4%)
BETAMETHASONE SODIUM PHOSPHATE	0	0	0	1 (4%)	0	0	0
BROMHEXINE HYDROCHLORIDE	0	0	1 (4%)	0	0	0	0
CHLORPHENAMINE MALEATE	0	0	0	0	1 (4%)	0	0
CHLORPHENOXAMINE HYDROCHLORIDE	0	0	0	0	0	0	1 (4%)

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Table 9.04
Summary of Concomitant Medications by Generic Term

ATC Level 1 Ingredient	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DEXAMETHASONE	0	0	0	1 (4%)	0	0	0
DIMETINDENE	0	0	0	0	0	1 (4%)	0
LEVOMENTHOL	0	0	0	0	0	0	1 (4%)
PHENYLEPHRINE	0	0	0	0	0	1 (4%)	0
PHENYLPROPANOLAMINE HYDROCHLORIDE	1 (4%)	0	0	0	0	0	0
PHENYLTOLOXAMINE CITRATE	1 (4%)	0	0	0	0	0	0
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	0	0	1 (4%)	0	0
ALIMENTARY TRACT AND METABOLISM							
Any medication	1 (4%)	3 (11%)	2 (8%)	3 (12%)	2 (8%)	0	2 (8%)
BISACODYL	0	1 (4%)	1 (4%)	1 (4%)	0	0	0
ACETYLSALICYLIC ACID	0	1 (4%)	0	0	1 (4%)	0	0
DOMPERIDONE	1 (4%)	1 (4%)	0	0	0	0	0
SODIUM CHLORIDE	0	0	1 (4%)	0	0	0	1 (4%)
ASCORBIC ACID	0	0	0	0	1 (4%)	0	0
BETAMETHASONE ACETATE	0	0	0	1 (4%)	0	0	0
BETAMETHASONE SODIUM PHOSPHATE	0	0	0	1 (4%)	0	0	0
DEXAMETHASONE	0	0	0	1 (4%)	0	0	0
HYOSCINE BUTYLBROMIDE	0	0	1 (4%)	0	0	0	0
LOPERAMIDE HYDROCHLORIDE	0	0	0	0	1 (4%)	0	0
SYZYGIUM AROMATICUM	0	0	0	0	0	0	1 (4%)
DERMATOLOGICALS							
Any medication	0	0	0	3 (12%)	0	1 (4%)	2 (8%)
ACYCLOVIR	0	0	0	1 (4%)	0	0	0
BETAMETHASONE ACETATE	0	0	0	1 (4%)	0	0	0

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Table 9.04
Summary of Concomitant Medications by Generic Term

ATC Level 1 Ingredient	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
BETAMETHASONE SODIUM PHOSPHATE	0	0	0	1 (4%)	0	0	0
CAMPHOR	0	0	0	0	0	0	1 (4%)
CHLORPHENOXAMINE HYDROCHLORIDE	0	0	0	0	0	0	1 (4%)
DEXAMETHASONE	0	0	0	1 (4%)	0	0	0
DIMETINDENE	0	0	0	0	0	1 (4%)	0
GENTAMICIN SULFATE	0	0	0	1 (4%)	0	0	0
LEVOMENTHOL	0	0	0	0	0	0	1 (4%)
MUSCULO-SKELETAL SYSTEM							
Any medication	1 (4%)	1 (4%)	1 (4%)	1 (4%)	3 (12%)	1 (4%)	2 (8%)
IBUPROFEN	0	0	1 (4%)	1 (4%)	1 (4%)	0	2 (8%)
ACETYLSALICYLIC ACID	0	1 (4%)	0	0	1 (4%)	0	0
LUMIRACOXIB	0	0	0	0	1 (4%)	1 (4%)	0
CELECOXIB	1 (4%)	0	0	0	0	0	0
DICLOFENAC SODIUM	0	0	0	1 (4%)	0	0	0
LEVOMENTHOL	0	0	0	0	0	0	1 (4%)
MELALEUCA CAJUPUTI OIL	0	0	0	0	0	0	1 (4%)
MELOXICAM	0	0	0	1 (4%)	0	0	0
MINT OIL	0	0	0	0	0	0	1 (4%)
SENSORY ORGANS							
Any medication	0	0	1 (4%)	3 (12%)	0	1 (4%)	1 (4%)
SODIUM CHLORIDE	0	0	1 (4%)	0	0	0	1 (4%)
ACYCLOVIR	0	0	0	1 (4%)	0	0	0
BETAMETHASONE ACETATE	0	0	0	1 (4%)	0	0	0
DEXAMETHASONE	0	0	0	1 (4%)	0	0	0
DICLOFENAC SODIUM	0	0	0	1 (4%)	0	0	0
GENTAMICIN SULFATE	0	0	0	1 (4%)	0	0	0

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Table 9.04
Summary of Concomitant Medications by Generic Term

ATC Level 1 Ingredient	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
PHENYLEPHRINE	0	0	0	0	0	1 (4%)	0
CARDIOVASCULAR SYSTEM							
Any medication	0	0	0	2 (8%)	0	1 (4%)	1 (4%)
BETAMETHASONE ACETATE	0	0	0	1 (4%)	0	0	0
BETAMETHASONE SODIUM PHOSPHATE	0	0	0	1 (4%)	0	0	0
CAMPHOR	0	0	0	0	0	0	1 (4%)
DEXAMETHASONE	0	0	0	1 (4%)	0	0	0
INDAPAMIDE	0	0	0	0	0	1 (4%)	0
PHENYLEPHRINE	0	0	0	0	0	1 (4%)	0
BLOOD AND BLOOD FORMING ORGANS							
Any medication	0	1 (4%)	1 (4%)	0	1 (4%)	0	1 (4%)
ACETYLSALICYLIC ACID	0	1 (4%)	0	0	1 (4%)	0	0
SODIUM CHLORIDE	0	0	1 (4%)	0	0	0	1 (4%)
GENITO URINARY SYSTEM AND SEX HORMONES							
Any medication	0	0	1 (4%)	1 (4%)	1 (4%)	0	2 (8%)
IBUPROFEN	0	0	1 (4%)	1 (4%)	1 (4%)	0	2 (8%)
ANTIINFECTIVES FOR SYSTEMIC USE							
Any medication	0	0	0	2 (8%)	0	0	0
ACYCLOVIR	0	0	0	1 (4%)	0	0	0
GENTAMICIN SULFATE	0	0	0	1 (4%)	0	0	0

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Table 9.04
Summary of Concomitant Medications by Generic Term

ATC Level 1 Ingredient	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES							
Any medication	0	0	0	2 (8%)	0	0	0
BETAMETHASONE SODIUM PHOSPHATE	0	0	0	1 (4%)	0	0	0
DEXAMETHASONE	0	0	0	1 (4%)	0	0	0

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Table 9.05
Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study

System Organ Class Preferred Term	4 mg PR/XL 24h (N=28)
ANY EVENT	1 (4%)
Vascular disorders	
Any Event	1 (4%)
Orthostatic hypotension	1 (4%)

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Table 9.06
Listing of Randomised Schedule

Subj.	Period	Randomised Treatment	Actual Treatment

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.

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Table 9.07
Listing of Concomitant Medications by Generic Term

Inv./ Subj./ Seq.	Treatment/ Period	ATC Level 1/ Ingredient/ Verbatim Text/ Indication	Dose/ Units/ Freq/ Route	Start Date/ Study Day/ Period Day	Stop Date/ Study Day/ Period Day	Started Pre-Trial?	Ongoing Medication?

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.

E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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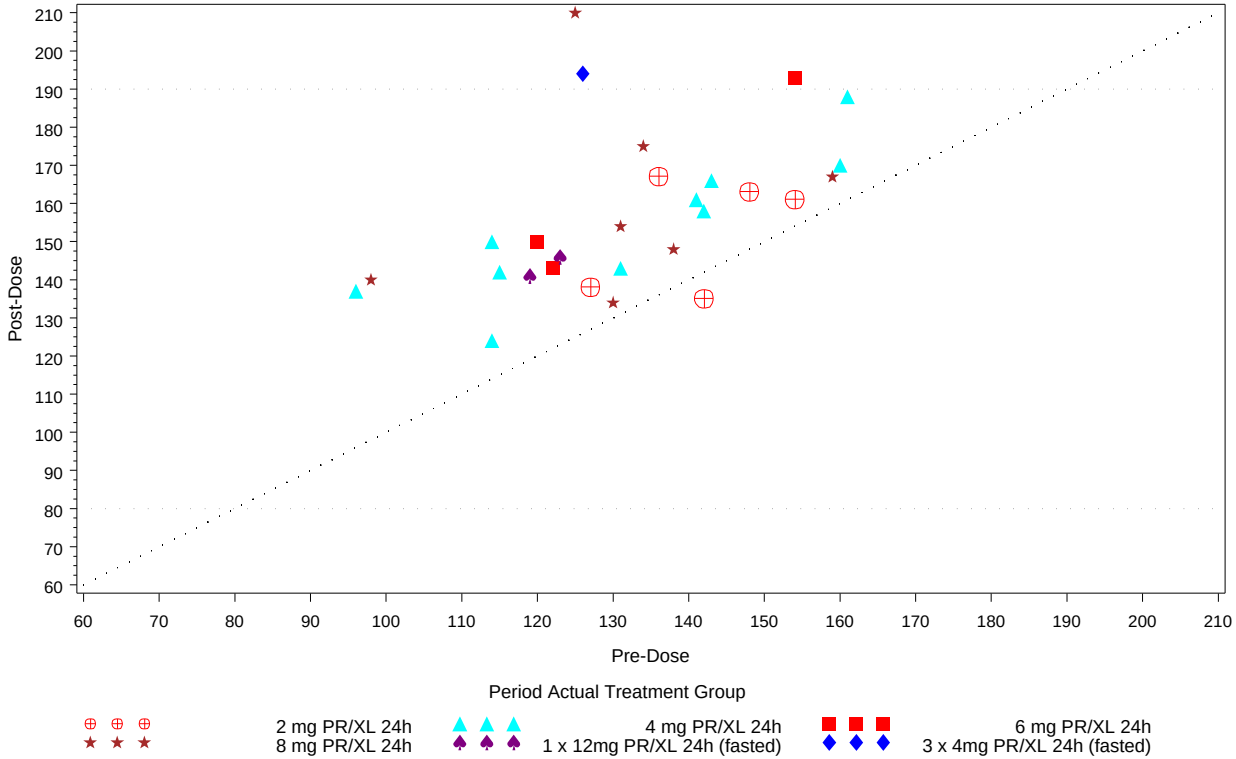
Figure 10.01
Maximum post dose ambulatory systolic blood pressure value vs pre-dose systolic blood pressure value on the day of the maximum post dose value



For subjects whose max. value occurred when pre-dose was missing, the next highest maximum with pre-dose value has been plotted.
For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to pre-dose.
Only valid ABPMs observed on a dose increase day and the last observation within a time interval are used within the displays.

[redacted]

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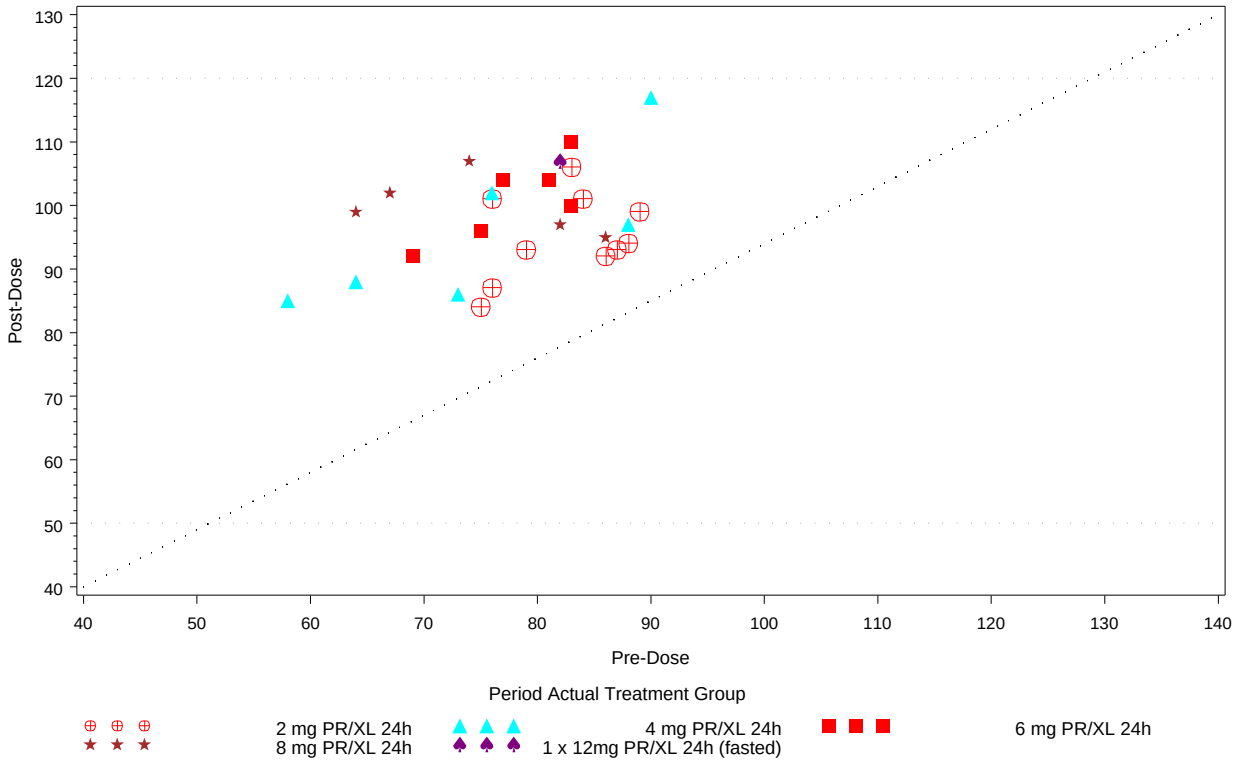
Figure 10.02
Maximum post dose ambulatory diastolic blood pressure value vs pre-dose diastolic blood pressure value on the day of the maximum post dose value



For subjects whose max. value occurred when pre-dose was missing, the next highest maximum with pre-dose value has been plotted.
For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to pre-dose
Only valid ABPMs observed on a dose increase day and the last observation within a time interval are used within the displays.

[redacted]

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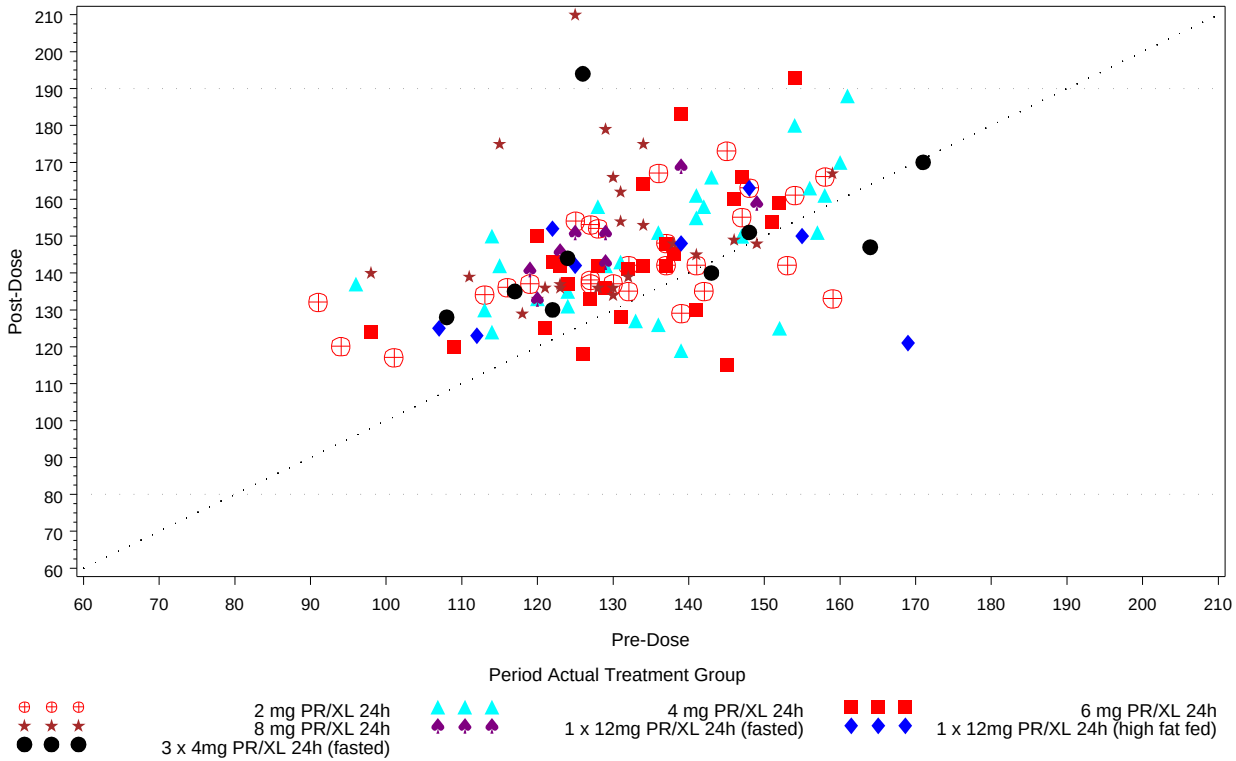
Figure 10.03
Maximum post dose ambulatory systolic blood pressure value vs pre-dose systolic blood pressure value by dose level



For subjects whose max. value occurred when pre-dose was missing, the next highest maximum with pre-dose value has been plotted.
For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to pre-dose.
Only valid ABPMs observed on a dose increase day and the last observation within a time interval are used within the displays.

[redacted]

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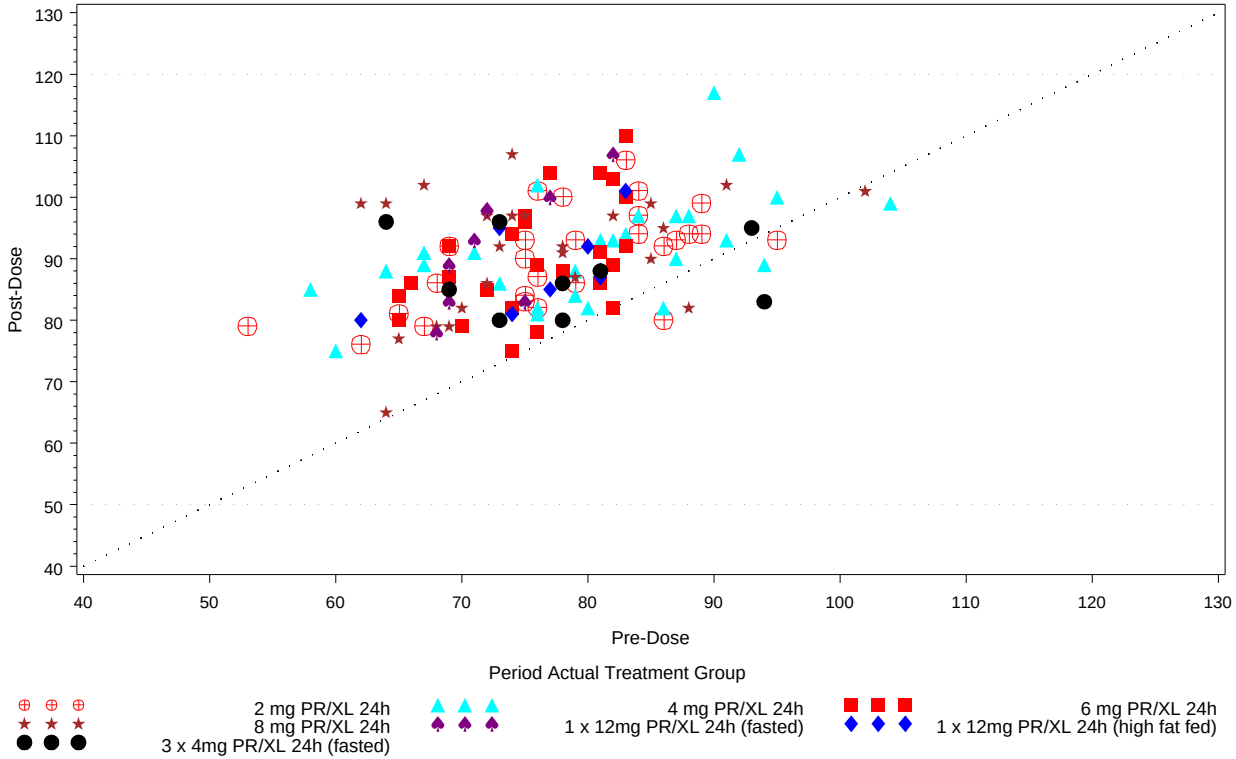
Figure 10.04
Maximum post dose ambulatory diastolic blood pressure value vs pre-dose diastolic blood pressure value by dose level



For subjects whose max. value occurred when pre-dose was missing, the next highest maximum with pre-dose value has been plotted.
For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to pre-dose.
Only valid ABPMs observed on a dose increase day and the last observation within a time interval are used within the displays.

[redacted]

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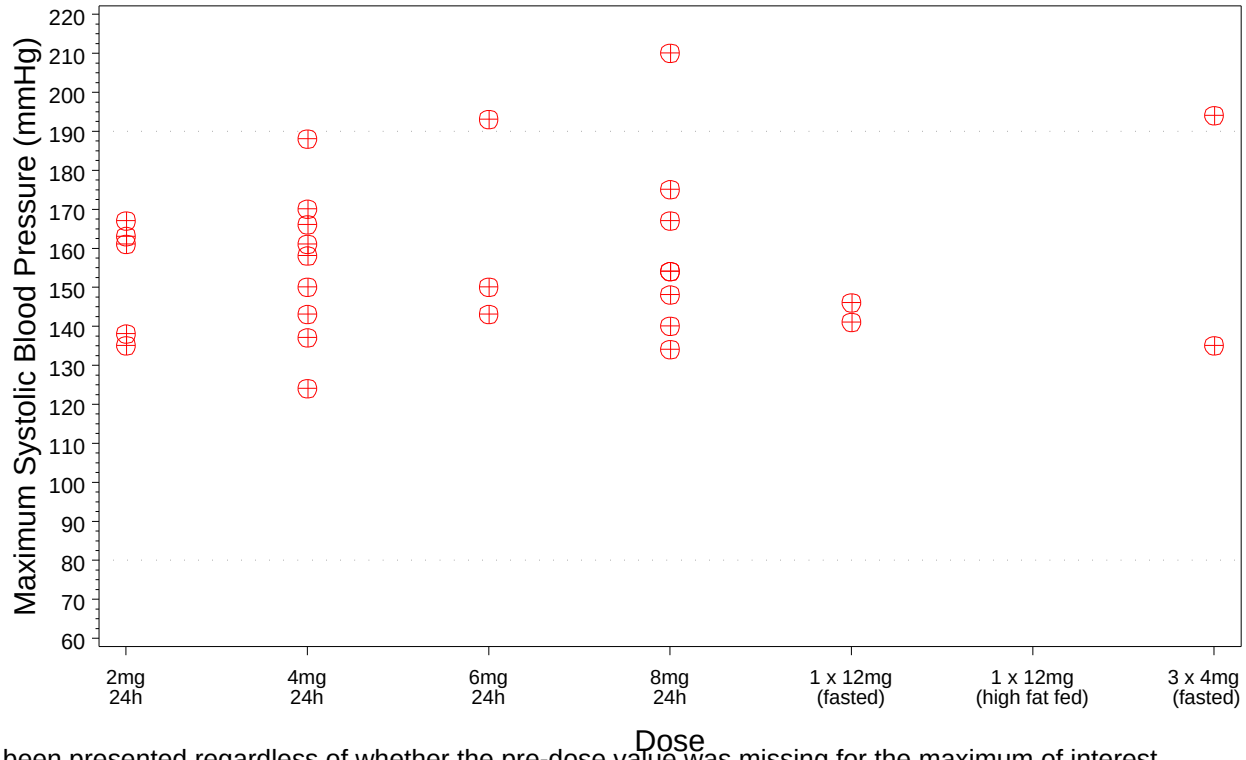
Figure 10.05
Maximum systolic blood pressure for each subject
by dose level when maximum occurred



Maximum values have been presented regardless of whether the pre-dose value was missing for the maximum of interest.
For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to pre-dose.
Only valid ABPMs observed on a dose increase day and the last observation within a time interval are used within the displays.
Some subjects may have the same maximum value during more than one dosing interval.

[redacted]

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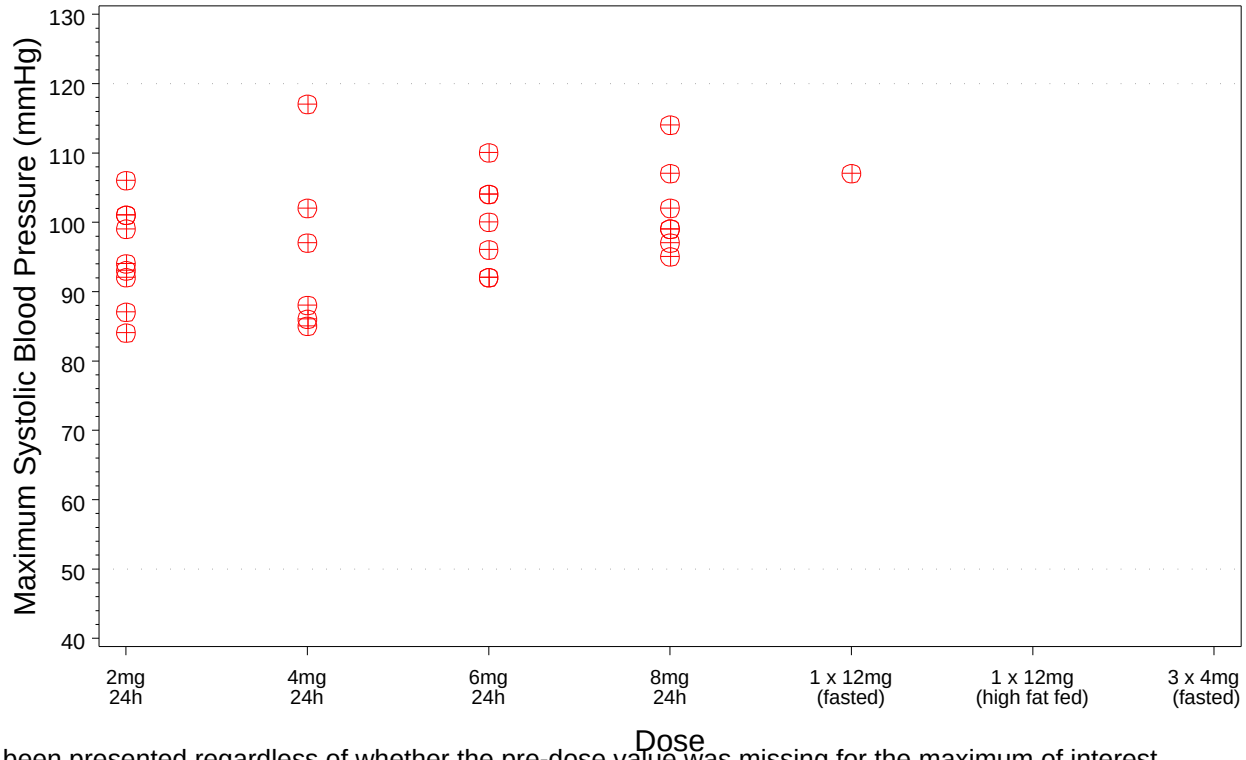
Figure 10.06
Maximum diastolic blood pressure for each subject
by dose level when maximum occurred



Maximum values have been presented regardless of whether the pre-dose value was missing for the maximum of interest.
For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to pre-dose.
Only valid ABPMs observed on a dose increase day and the last observation within a time interval are used within the displays.
Some subjects may have the same maximum value during more than one dosing interval.

[redacted]

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Table 10.01
Summary of Exposure to Study Drug

		2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Dose per administration	n	28	28	26	25	25	25	25
	Mean	2.0	4.0	6.0	8.0	12.0	12.0	12.0
	SD	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Median	2.0	4.0	6.0	8.0	12.0	12.0	12.0
	Min.	2	4	6	8	12	12	12
	Max.	2	4	6	8	12	12	12
Cumulative Dose (mg)	n	28	28	26	25	25	25	25
	Mean	14.0	27.6	41.5	56.0	36.0	36.0	36.0
	SD	0.00	2.27	2.35	0.00	0.00	0.00	0.00
	Median	14.0	28.0	42.0	56.0	36.0	36.0	36.0
	Min.	14	16	30	56	36	36	36
	Max.	14	28	42	56	36	36	36
Duration	n	28	28	26	25	25	25	25
	Mean	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	SD	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Min.	1	1	1	1	1	1	1
	Max.	1	1	1	1	1	1	1

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Table 10.02
Summary of All Adverse Events

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
ANY EVENT	7 (25%)	11 (39%)	2 (8%)	8 (32%)	11 (44%)	4 (16%)	9 (36%)
Nervous system disorders							
Any event	2 (7%)	6 (21%)	0	5 (20%)	7 (28%)	3 (12%)	5 (20%)
Headache	1 (4%)	5 (18%)	0	3 (12%)	2 (8%)	1 (4%)	3 (12%)
Dizziness	0	1 (4%)	0	2 (8%)	3 (12%)	2 (8%)	0
Somnolence	0	0	0	0	1 (4%)	0	2 (8%)
Convulsion	0	0	0	0	1 (4%)	0	0
Depressed level of consciousness	0	0	0	0	0	0	1 (4%)
Disturbance in attention	0	0	0	0	0	0	1 (4%)
Restless legs syndrome	0	1 (4%)	0	0	0	0	0
Syncope	1 (4%)	0	0	0	0	0	0
Tremor	0	0	0	0	1 (4%)	0	0
Gastrointestinal disorders							
Any event	4 (14%)	4 (14%)	1 (4%)	1 (4%)	5 (20%)	1 (4%)	3 (12%)
Nausea	2 (7%)	2 (7%)	0	1 (4%)	2 (8%)	0	2 (8%)
Constipation	1 (4%)	2 (7%)	0	0	1 (4%)	0	0
Abdominal pain upper	0	1 (4%)	0	0	1 (4%)	0	1 (4%)
Diarrhoea	0	0	1 (4%)	0	1 (4%)	0	1 (4%)
Gastric atony	0	0	1 (4%)	1 (4%)	0	0	0
Abdominal pain	0	0	0	0	0	1 (4%)	0
Dry mouth	1 (4%)	0	0	0	0	0	0
Dyspepsia	0	0	0	0	1 (4%)	0	0
Infections and infestations							
Any event	2 (7%)	0	0	2 (8%)	1 (4%)	0	1 (4%)
Influenza	0	0	0	0	1 (4%)	0	1 (4%)
Rhinitis	2 (7%)	0	0	0	0	0	0

[redacted]

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Table 10.02
Summary of All Adverse Events

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Nasopharyngitis	0	0	0	1 (4%)	0	0	0
Oral herpes	0	0	0	1 (4%)	0	0	0
General disorders and administration site conditions							
Any event	0	2 (7%)	0	0	0	0	1 (4%)
Fatigue	0	2 (7%)	0	0	0	0	0
Feeling abnormal	0	0	0	0	0	0	1 (4%)
Eye disorders							
Any event	0	0	0	1 (4%)	0	0	1 (4%)
Eye inflammation	0	0	0	1 (4%)	0	0	0
Vision blurred	0	0	0	0	0	0	1 (4%)
Injury, poisoning and procedural complications							
Any event	0	0	1 (4%)	1 (4%)	0	0	0
Joint sprain	0	0	1 (4%)	0	0	0	0
Ligament sprain	0	0	0	1 (4%)	0	0	0
Respiratory, thoracic and mediastinal disorders							
Any event	1 (4%)	1 (4%)	0	0	0	1 (4%)	0
Nasal congestion	1 (4%)	0	0	0	0	1 (4%)	0
Cough	0	1 (4%)	0	0	0	0	0
Skin and subcutaneous tissue disorders							
Any event	0	1 (4%)	0	0	1 (4%)	1 (4%)	0
Dermatitis contact	0	0	0	0	1 (4%)	1 (4%)	0

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Table 10.02
Summary of All Adverse Events

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Pruritus	0	1 (4%)	0	0	0	0	0
Cardiac disorders							
Any event	0	0	0	1 (4%)	0	0	0
Tachycardia	0	0	0	1 (4%)	0	0	0
Musculoskeletal and connective tissue disorders							
Any event	1 (4%)	0	0	0	0	0	0
Back pain	1 (4%)	0	0	0	0	0	0
Vascular disorders							
Any event	0	1 (4%)	0	0	0	0	0
Orthostatic hypotension	0	1 (4%)	0	0	0	0	0

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Table 10.03
Summary of Drug Related Adverse Events

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
ANY EVENT	6 (21%)	8 (29%)	1 (4%)	3 (12%)	4 (16%)	2 (8%)	4 (16%)
Nervous system disorders							
Any event	2 (7%)	5 (18%)	0	3 (12%)	2 (8%)	2 (8%)	2 (8%)
Headache	1 (4%)	3 (11%)	0	1 (4%)	0	1 (4%)	1 (4%)
Dizziness	0	1 (4%)	0	2 (8%)	1 (4%)	1 (4%)	0
Somnolence	0	0	0	0	1 (4%)	0	1 (4%)
Depressed level of consciousness	0	0	0	0	0	0	1 (4%)
Restless legs syndrome	0	1 (4%)	0	0	0	0	0
Syncope	1 (4%)	0	0	0	0	0	0
Gastrointestinal disorders							
Any event	4 (14%)	4 (14%)	1 (4%)	0	4 (16%)	1 (4%)	2 (8%)
Nausea	2 (7%)	2 (7%)	0	0	2 (8%)	0	2 (8%)
Constipation	1 (4%)	2 (7%)	0	0	1 (4%)	0	0
Diarrhoea	0	0	1 (4%)	0	1 (4%)	0	1 (4%)
Abdominal pain	0	0	0	0	0	1 (4%)	0
Abdominal pain upper	0	1 (4%)	0	0	0	0	0
Dry mouth	1 (4%)	0	0	0	0	0	0
Dyspepsia	0	0	0	0	1 (4%)	0	0
General disorders and administration site conditions							
Any event	0	1 (4%)	0	0	0	0	1 (4%)
Fatigue	0	1 (4%)	0	0	0	0	0
Feeling abnormal	0	0	0	0	0	0	1 (4%)
Eye disorders							
Any event	0	0	0	0	0	0	1 (4%)

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Table 10.03
Summary of Drug Related Adverse Events

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Vision blurred	0	0	0	0	0	0	1 (4%)
Respiratory, thoracic and mediastinal disorders							
Any event	1 (4%)	0	0	0	0	1 (4%)	0
Nasal congestion	1 (4%)	0	0	0	0	1 (4%)	0
Vascular disorders							
Any event	0	1 (4%)	0	0	0	0	0
Orthostatic hypotension	0	1 (4%)	0	0	0	0	0

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Table 10.04
Summary of Serious Adverse Events

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
ANY EVENT	0	0	1 (4%)	1 (4%)	0	0	0
Gastrointestinal disorders							
Any event	0	0	1 (4%)	1 (4%)	0	0	0
Gastric atony	0	0	1 (4%)	1 (4%)	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28) Mild	Moderate	Severe
ANY EVENT	3 (11%)	3 (11%)	1 (4%)
Nervous system disorders			
Any Event	1 (4%)	0	1 (4%)
Headache	1 (4%)	0	0
Dizziness	0	0	0
Somnolence	0	0	0
Convulsion	0	0	0
Depressed level of consciousness	0	0	0
Disturbance in attention	0	0	0
Restless legs syndrome	0	0	0
Syncope	0	0	1 (4%)
Tremor	0	0	0
Gastrointestinal disorders			
Any Event	2 (7%)	2 (7%)	0
Nausea	1 (4%)	1 (4%)	0
Constipation	0	1 (4%)	0
Abdominal pain upper	0	0	0
Diarrhoea	0	0	0
Gastric atony	0	0	0
Abdominal pain	0	0	0
Dry mouth	1 (4%)	0	0
Dyspepsia	0	0	0
Infections and infestations			
Any Event	2 (7%)	0	0
Influenza	0	0	0
Rhinitis	2 (7%)	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	4 mg PR/XL 24h (N=28) Mild	Moderate	Severe
ANY EVENT	6 (21%)	4 (14%)	1 (4%)
Nervous system disorders			
Any Event	3 (11%)	3 (11%)	0
Headache	2 (7%)	3 (11%)	0
Dizziness	1 (4%)	0	0
Somnolence	0	0	0
Convulsion	0	0	0
Depressed level of consciousness	0	0	0
Disturbance in attention	0	0	0
Restless legs syndrome	1 (4%)	0	0
Syncope	0	0	0
Tremor	0	0	0
Gastrointestinal disorders			
Any Event	1 (4%)	2 (7%)	1 (4%)
Nausea	0	1 (4%)	1 (4%)
Constipation	1 (4%)	1 (4%)	0
Abdominal pain upper	0	0	1 (4%)
Diarrhoea	0	0	0
Gastric atony	0	0	0
Abdominal pain	0	0	0
Dry mouth	0	0	0
Dyspepsia	0	0	0
Infections and infestations			
Any Event	0	0	0
Influenza	0	0	0
Rhinitis	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	6 mg PR/XL 24h (N=26) Mild	Moderate	Severe
ANY EVENT	0	2 (8%)	0
Nervous system disorders			
Any Event	0	0	0
Headache	0	0	0
Dizziness	0	0	0
Somnolence	0	0	0
Convulsion	0	0	0
Depressed level of consciousness	0	0	0
Disturbance in attention	0	0	0
Restless legs syndrome	0	0	0
Syncope	0	0	0
Tremor	0	0	0
Gastrointestinal disorders			
Any Event	0	1 (4%)	0
Nausea	0	0	0
Constipation	0	0	0
Abdominal pain upper	0	0	0
Diarrhoea	0	1 (4%)	0
Gastric atony	0	1 (4%)	0
Abdominal pain	0	0	0
Dry mouth	0	0	0
Dyspepsia	0	0	0
Infections and infestations			
Any Event	0	0	0
Influenza	0	0	0
Rhinitis	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	8 mg PR/XL 24h (N=25) Mild	Moderate	Severe
ANY EVENT	5 (20%)	3 (12%)	0
Nervous system disorders			
Any Event	5 (20%)	0	0
Headache	3 (12%)	0	0
Dizziness	2 (8%)	0	0
Somnolence	0	0	0
Convulsion	0	0	0
Depressed level of consciousness	0	0	0
Disturbance in attention	0	0	0
Restless legs syndrome	0	0	0
Syncope	0	0	0
Tremor	0	0	0
Gastrointestinal disorders			
Any Event	0	1 (4%)	0
Nausea	1 (4%)	0	0
Constipation	0	0	0
Abdominal pain upper	0	0	0
Diarrhoea	0	0	0
Gastric atony	0	1 (4%)	0
Abdominal pain	0	0	0
Dry mouth	0	0	0
Dyspepsia	0	0	0
Infections and infestations			
Any Event	2 (8%)	0	0
Influenza	0	0	0
Rhinitis	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	1 x 12mg PR/XL 24h (fasted) (N=25) Mild	Moderate	Severe
ANY EVENT	8 (32%)	3 (12%)	0
Nervous system disorders			
Any Event	6 (24%)	1 (4%)	0
Headache	2 (8%)	0	0
Dizziness	3 (12%)	0	0
Somnolence	0	1 (4%)	0
Convulsion	1 (4%)	0	0
Depressed level of consciousness	0	0	0
Disturbance in attention	0	0	0
Restless legs syndrome	0	0	0
Syncope	0	0	0
Tremor	1 (4%)	0	0
Gastrointestinal disorders			
Any Event	4 (16%)	1 (4%)	0
Nausea	2 (8%)	0	0
Constipation	1 (4%)	0	0
Abdominal pain upper	1 (4%)	0	0
Diarrhoea	0	1 (4%)	0
Gastric atony	0	0	0
Abdominal pain	0	0	0
Dry mouth	0	0	0
Dyspepsia	1 (4%)	0	0
Infections and infestations			
Any Event	0	1 (4%)	0
Influenza	0	1 (4%)	0
Rhinitis	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	1 x 12mg PR/XL 24h (high fat fed) (N=25) Mild	Moderate	Severe
ANY EVENT	3 (12%)	1 (4%)	0
Nervous system disorders			
Any Event	3 (12%)	0	0
Headache	1 (4%)	0	0
Dizziness	2 (8%)	0	0
Somnolence	0	0	0
Convulsion	0	0	0
Depressed level of consciousness	0	0	0
Disturbance in attention	0	0	0
Restless legs syndrome	0	0	0
Syncope	0	0	0
Tremor	0	0	0
Gastrointestinal disorders			
Any Event	1 (4%)	0	0
Nausea	0	0	0
Constipation	0	0	0
Abdominal pain upper	0	0	0
Diarrhoea	0	0	0
Gastric atony	0	0	0
Abdominal pain	1 (4%)	0	0
Dry mouth	0	0	0
Dyspepsia	0	0	0
Infections and infestations			
Any Event	0	0	0
Influenza	0	0	0
Rhinitis	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	3 x 4mg PR/XL 24h (fasted) (N=25) Mild	Moderate	Severe
ANY EVENT	6 (24%)	2 (8%)	1 (4%)
Nervous system disorders			
Any Event	5 (20%)	0	0
Headache	3 (12%)	0	0
Dizziness	0	0	0
Somnolence	2 (8%)	0	0
Convulsion	0	0	0
Depressed level of consciousness	1 (4%)	0	0
Disturbance in attention	1 (4%)	0	0
Restless legs syndrome	0	0	0
Syncope	0	0	0
Tremor	0	0	0
Gastrointestinal disorders			
Any Event	1 (4%)	1 (4%)	1 (4%)
Nausea	1 (4%)	0	1 (4%)
Constipation	0	0	0
Abdominal pain upper	0	1 (4%)	0
Diarrhoea	0	0	1 (4%)
Gastric atony	0	0	0
Abdominal pain	0	0	0
Dry mouth	0	0	0
Dyspepsia	0	0	0
Infections and infestations			
Any Event	0	1 (4%)	0
Influenza	0	1 (4%)	0
Rhinitis	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28) Mild	Moderate	Severe
Nasopharyngitis	0	0	0
Oral herpes	0	0	0
General disorders and administration site conditions			
Any Event	0	0	0
Fatigue	0	0	0
Feeling abnormal	0	0	0
Eye disorders			
Any Event	0	0	0
Eye inflammation	0	0	0
Vision blurred	0	0	0
Injury, poisoning and procedural complications			
Any Event	0	0	0
Joint sprain	0	0	0
Ligament sprain	0	0	0
Respiratory, thoracic and mediastinal disorders			
Any Event	1 (4%)	0	0
Nasal congestion	1 (4%)	0	0
Cough	0	0	0
Skin and subcutaneous tissue disorders			
Any Event	0	0	0
Dermatitis contact	0	0	0
Pruritus	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	4 mg PR/XL 24h (N=28) Mild	Moderate	Severe
Nasopharyngitis	0	0	0
Oral herpes	0	0	0
General disorders and administration site conditions			
Any Event	2 (7%)	0	0
Fatigue	2 (7%)	0	0
Feeling abnormal	0	0	0
Eye disorders			
Any Event	0	0	0
Eye inflammation	0	0	0
Vision blurred	0	0	0
Injury, poisoning and procedural complications			
Any Event	0	0	0
Joint sprain	0	0	0
Ligament sprain	0	0	0
Respiratory, thoracic and mediastinal disorders			
Any Event	1 (4%)	0	0
Nasal congestion	0	0	0
Cough	1 (4%)	0	0
Skin and subcutaneous tissue disorders			
Any Event	1 (4%)	0	0
Dermatitis contact	0	0	0
Pruritus	1 (4%)	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	6 mg PR/XL 24h (N=26) Mild	Moderate	Severe
Nasopharyngitis	0	0	0
Oral herpes	0	0	0
General disorders and administration site conditions			
Any Event	0	0	0
Fatigue	0	0	0
Feeling abnormal	0	0	0
Eye disorders			
Any Event	0	0	0
Eye inflammation	0	0	0
Vision blurred	0	0	0
Injury, poisoning and procedural complications			
Any Event	0	1 (4%)	0
Joint sprain	0	1 (4%)	0
Ligament sprain	0	0	0
Respiratory, thoracic and mediastinal disorders			
Any Event	0	0	0
Nasal congestion	0	0	0
Cough	0	0	0
Skin and subcutaneous tissue disorders			
Any Event	0	0	0
Dermatitis contact	0	0	0
Pruritus	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	8 mg PR/XL 24h (N=25) Mild	Moderate	Severe
Nasopharyngitis	1 (4%)	0	0
Oral herpes	1 (4%)	0	0
General disorders and administration site conditions			
Any Event	0	0	0
Fatigue	0	0	0
Feeling abnormal	0	0	0
Eye disorders			
Any Event	0	1 (4%)	0
Eye inflammation	0	1 (4%)	0
Vision blurred	0	0	0
Injury, poisoning and procedural complications			
Any Event	0	1 (4%)	0
Joint sprain	0	0	0
Ligament sprain	0	1 (4%)	0
Respiratory, thoracic and mediastinal disorders			
Any Event	0	0	0
Nasal congestion	0	0	0
Cough	0	0	0
Skin and subcutaneous tissue disorders			
Any Event	0	0	0
Dermatitis contact	0	0	0
Pruritus	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	1 x 12mg PR/XL 24h (fasted) (N=25) Mild	Moderate	Severe
Nasopharyngitis	0	0	0
Oral herpes	0	0	0
General disorders and administration site conditions			
Any Event	0	0	0
Fatigue	0	0	0
Feeling abnormal	0	0	0
Eye disorders			
Any Event	0	0	0
Eye inflammation	0	0	0
Vision blurred	0	0	0
Injury, poisoning and procedural complications			
Any Event	0	0	0
Joint sprain	0	0	0
Ligament sprain	0	0	0
Respiratory, thoracic and mediastinal disorders			
Any Event	0	0	0
Nasal congestion	0	0	0
Cough	0	0	0
Skin and subcutaneous tissue disorders			
Any Event	1 (4%)	0	0
Dermatitis contact	1 (4%)	0	0
Pruritus	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	1 x 12mg PR/XL 24h (high fat fed) (N=25) Mild	Moderate	Severe
Nasopharyngitis	0	0	0
Oral herpes	0	0	0
General disorders and administration site conditions			
Any Event	0	0	0
Fatigue	0	0	0
Feeling abnormal	0	0	0
Eye disorders			
Any Event	0	0	0
Eye inflammation	0	0	0
Vision blurred	0	0	0
Injury, poisoning and procedural complications			
Any Event	0	0	0
Joint sprain	0	0	0
Ligament sprain	0	0	0
Respiratory, thoracic and mediastinal disorders			
Any Event	1 (4%)	0	0
Nasal congestion	1 (4%)	0	0
Cough	0	0	0
Skin and subcutaneous tissue disorders			
Any Event	0	1 (4%)	0
Dermatitis contact	0	1 (4%)	0
Pruritus	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	3 x 4mg PR/XL 24h (fasted) (N=25) Mild	Moderate	Severe
Nasopharyngitis	0	0	0
Oral herpes	0	0	0
General disorders and administration site conditions			
Any Event	1 (4%)	0	0
Fatigue	0	0	0
Feeling abnormal	1 (4%)	0	0
Eye disorders			
Any Event	1 (4%)	0	0
Eye inflammation	0	0	0
Vision blurred	1 (4%)	0	0
Injury, poisoning and procedural complications			
Any Event	0	0	0
Joint sprain	0	0	0
Ligament sprain	0	0	0
Respiratory, thoracic and mediastinal disorders			
Any Event	0	0	0
Nasal congestion	0	0	0
Cough	0	0	0
Skin and subcutaneous tissue disorders			
Any Event	0	0	0
Dermatitis contact	0	0	0
Pruritus	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	2 mg PR/XL 24h (N=28) Mild	Moderate	Severe
Cardiac disorders			
Any Event	0	0	0
Tachycardia	0	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	1 (4%)	0
Back pain	0	1 (4%)	0
Vascular disorders			
Any Event	0	0	0
Orthostatic hypotension	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	4 mg PR/XL 24h (N=28) Mild	Moderate	Severe
Cardiac disorders			
Any Event	0	0	0
Tachycardia	0	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	0	0
Back pain	0	0	0
Vascular disorders			
Any Event	0	1 (4%)	0
Orthostatic hypotension	0	1 (4%)	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	6 mg PR/XL 24h (N=26) Mild	Moderate	Severe
Cardiac disorders			
Any Event	0	0	0
Tachycardia	0	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	0	0
Back pain	0	0	0
Vascular disorders			
Any Event	0	0	0
Orthostatic hypotension	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	8 mg PR/XL 24h (N=25) Mild	Moderate	Severe
Cardiac disorders			
Any Event	1 (4%)	0	0
Tachycardia	1 (4%)	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	0	0
Back pain	0	0	0
Vascular disorders			
Any Event	0	0	0
Orthostatic hypotension	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	1 x 12mg PR/XL 24h (fasted) (N=25) Mild	 Moderate	 Severe
Cardiac disorders			
Any Event	0	0	0
Tachycardia	0	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	0	0
Back pain	0	0	0
Vascular disorders			
Any Event	0	0	0
Orthostatic hypotension	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	1 x 12mg PR/XL 24h (high fat fed) (N=25) Mild	Moderate	Severe
Cardiac disorders			
Any Event	0	0	0
Tachycardia	0	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	0	0
Back pain	0	0	0
Vascular disorders			
Any Event	0	0	0
Orthostatic hypotension	0	0	0

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Table 10.05
Summary of Adverse Events by Maximum Intensity/Grade

System Organ Class Preferred Term	3 x 4mg PR/XL 24h (fasted) (N=25) Mild	Moderate	Severe
Cardiac disorders			
Any Event	0	0	0
Tachycardia	0	0	0
Musculoskeletal and connective tissue disorders			
Any Event	0	0	0
Back pain	0	0	0
Vascular disorders			
Any Event	0	0	0
Orthostatic hypotension	0	0	0

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Table 10.06
Summary of All Adverse Events of Special Interest

Topic Preferred Term	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)
ANY EVENT	1 (4%)	2 (7%)	1 (4%)	3 (12%)	3 (12%)	2 (8%)
Hypotension						
Any event	0	2 (7%)	0	2 (8%)	3 (12%)	2 (8%)
Dizziness	0	1 (4%)	0	2 (8%)	3 (12%)	2 (8%)
Orthostatic hypotension	0	1 (4%)	0	0	0	0
Fall/Injury						
Any event	0	0	1 (4%)	1 (4%)	0	0
Joint sprain	0	0	1 (4%)	0	0	0
Ligament sprain	0	0	0	1 (4%)	0	0
Syncope						
Any event	1 (4%)	0	0	0	0	0
Syncope	1 (4%)	0	0	0	0	0

Note: Topic refers to the categorisation of adverse events of special interest.

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Table 10.07
Summary of All Adverse Events (Total Counts)

		Total (N=28)
Number of Subjects with AEs Overall		22 (79%)
Number of AEs Overall		81
Number of Subjects with Drug Related AEs Overall		15 (54%)
Number of Drug Related AEs Overall		44
Number of Subjects with AEs Overall by Maximum Intensity	Mild	10 (36%)
	Moderate	9 (32%)
	Severe	3 (11%)

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 1							
PRE-DOSE 1							
n	28 (100%)	0	0	0	0	0	0
Normal	22 (79%)	0	0	0	0	0	0
Abnormal - not clinically significant	6 (21%)	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	28 (100%)	0	0	0	0	0	0
Normal	21 (75%)	0	0	0	0	0	0
Abnormal - not clinically significant	7 (25%)	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	28 (100%)	0	0	0	0	0	0
Normal	21 (75%)	0	0	0	0	0	0
Abnormal - not clinically significant	7 (25%)	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 8							
PRE-DOSE 1							

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
n	0	28 (100%)	0	0	0	0	0
Normal	0	22 (79%)	0	0	0	0	0
Abnormal - not clinically significant	0	6 (21%)	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 12-14							
PRE-DOSE 1							
n	0	27 (96%)	0	0	0	0	0
Normal	0	22 (79%)	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Abnormal - not clinically significant	0	5 (18%)	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 15							
PRE-DOSE 1							
n	0	0	26 (100%)	0	0	0	0
Normal	0	0	21 (81%)	0	0	0	0
Abnormal - not clinically significant	0	0	5 (19%)	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 22							
PRE-DOSE 1							
n	0	0	0	25 (100%)	0	0	0
Normal	0	0	0	22 (88%)	0	0	0
Abnormal - not clinically significant	0	0	0	3 (12%)	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 26-28							
PRE-DOSE 1							
n	0	0	0	25 (100%)	0	0	0
Normal	0	0	0	23 (92%)	0	0	0
Abnormal - not clinically significant	0	0	0	2 (8%)	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 29							
PRE-DOSE 1							
n	0	0	0	0	8 (32%)	8 (32%)	9 (36%)
Normal	0	0	0	0	6 (24%)	8 (32%)	9 (36%)
Abnormal - not clinically significant	0	0	0	0	2 (8%)	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 31							
PRE-DOSE 1							
n	0	0	0	0	8 (32%)	8 (32%)	9 (36%)
Normal	0	0	0	0	5 (20%)	7 (28%)	9 (36%)
Abnormal - not clinically significant	0	0	0	0	3 (12%)	1 (4%)	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 32							
PRE-DOSE 1							
n	0	0	0	0	9 (36%)	8 (32%)	8 (32%)
Normal	0	0	0	0	7 (28%)	6 (24%)	7 (28%)
Abnormal - not clinically significant	0	0	0	0	2 (8%)	2 (8%)	1 (4%)
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 34							
PRE-DOSE 1							
n	0	0	0	0	9 (36%)	8 (32%)	8 (32%)
Normal	0	0	0	0	9 (36%)	8 (32%)	6 (24%)
Abnormal - not clinically significant	0	0	0	0	0	0	2 (8%)
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 35							
PRE-DOSE 1							
n	0	0	0	0	8 (32%)	9 (36%)	8 (32%)
Normal	0	0	0	0	7 (28%)	7 (28%)	8 (32%)
Abnormal - not clinically significant	0	0	0	0	1 (4%)	2 (8%)	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
PRE-DOSE 3							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
DAY 37							
PRE-DOSE 1							
n	0	0	0	0	8 (32%)	9 (36%)	8 (32%)
Normal	0	0	0	0	8 (32%)	7 (28%)	8 (32%)
Abnormal - not clinically significant	0	0	0	0	0	2 (8%)	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 2							
n	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0
PRE-DOSE 3							
n	0	0	0	0	0	0	0

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Table 10.08
Summary of ECG Findings

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Normal	0	0	0	0	0	0	0
Abnormal - not clinically significant	0	0	0	0	0	0	0
Abnormal - clinically significant	0	0	0	0	0	0	0
Not available	0	0	0	0	0	0	0

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ROP109087

Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (BPM)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	66.29	8.021	66.50	51.	82
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	66.32	8.019	67.00	48.	78
			DAY 12-14	PRE-DOSE 1	27	65.85	7.634	65.00	52.	82
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	71.08	10.556	74.00	52.	88
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	64.08	7.141	64.00	52.	75
			DAY 26-28	PRE-DOSE 1	25	65.20	8.302	64.00	51.	83
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	64.00	13.266	64.00	49.	84
			DAY 31	PRE-DOSE 1	8	61.50	10.981	57.50	50.	83
			DAY 32	PRE-DOSE 1	9	68.89	11.450	71.00	48.	83
			DAY 34	PRE-DOSE 1	9	63.11	7.079	67.00	50.	70
			DAY 35	PRE-DOSE 1	8	73.50	6.887	73.50	64.	82
			DAY 37	PRE-DOSE 1	8	68.88	7.900	67.50	60.	80
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	68.25	8.067	68.50	55.	81
			DAY 31	PRE-DOSE 1	8	61.38	7.289	64.50	46.	67
			DAY 32	PRE-DOSE 1	8	73.00	12.939	78.50	51.	84
			DAY 34	PRE-DOSE 1	8	66.00	6.761	66.00	57.	74
			DAY 35	PRE-DOSE 1	9	66.78	11.809	67.00	45.	82
			DAY 37	PRE-DOSE 1	9	62.89	11.241	59.00	47.	84
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	73.00	6.910	76.00	58.	79
			DAY 31	PRE-DOSE 1	9	64.89	6.547	66.00	53.	75

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (BPM)	3 x 4mg PR/XL 24h (fasted)	25	DAY 32	PRE-DOSE 1	8	68.63	12.118	66.00	52.	93
			DAY 34	PRE-DOSE 1	8	61.88	9.172	62.50	49.	78
			DAY 35	PRE-DOSE 1	8	72.75	10.899	73.50	58.	87
			DAY 37	PRE-DOSE 1	8	66.25	8.956	69.00	52.	78
PR Interval (MSEC)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	170.98	27.635	170.67	120.	252
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	168.07	28.339	171.00	108.	250
			DAY 12-14	PRE-DOSE 1	27	166.96	28.357	168.00	108.	242
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	163.92	29.145	162.00	116.	254
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	172.32	29.859	172.00	120.	238
			DAY 26-28	PRE-DOSE 1	25	168.48	29.554	170.00	116.	240
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	171.25	42.721	170.00	116.	252
			DAY 31	PRE-DOSE 1	8	173.50	32.998	173.00	130.	226
			DAY 32	PRE-DOSE 1	9	174.22	17.985	176.00	144.	198
			DAY 34	PRE-DOSE 1	9	174.00	18.276	178.00	138.	198
			DAY 35	PRE-DOSE 1	8	175.50	32.597	174.00	124.	238
			DAY 37	PRE-DOSE 1	8	172.00	29.626	172.00	122.	216
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	168.00	15.194	165.00	140.	188
			DAY 31	PRE-DOSE 1	8	166.50	25.674	173.00	122.	204

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
PR Interval (MSEC)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 32	PRE-DOSE 1	8	155.25	38.007	155.00	110.	230
			DAY 34	PRE-DOSE 1	8	156.75	31.349	161.00	122.	216
			DAY 35	PRE-DOSE 1	9	186.00	35.539	180.00	158.	276
			DAY 37	PRE-DOSE 1	9	184.44	31.269	176.00	154.	254
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	171.11	29.105	174.00	124.	218
			DAY 31	PRE-DOSE 1	9	172.00	29.682	164.00	122.	210
			DAY 32	PRE-DOSE 1	8	189.25	27.876	182.00	164.	250
			DAY 34	PRE-DOSE 1	8	188.25	30.377	181.00	148.	248
			DAY 35	PRE-DOSE 1	8	155.00	26.208	164.00	118.	188
			DAY 37	PRE-DOSE 1	8	153.75	26.130	163.00	108.	178
QRS Duration (MSEC)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	93.12	14.591	90.67	78.	150
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	92.14	13.705	90.00	74.	140
			DAY 12-14	PRE-DOSE 1	27	95.04	14.103	94.00	76.	146
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	91.46	10.652	94.00	72.	118
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	93.12	9.833	92.00	78.	116
			DAY 26-28	PRE-DOSE 1	25	90.88	8.964	90.00	76.	110
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	95.75	13.328	98.00	78.	118
			DAY 31	PRE-DOSE 1	8	94.75	13.264	93.00	80.	114

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
QRS Duration (MSEC)	1 x 12mg PR/XL 24h (fasted)	25	DAY 32	PRE-DOSE 1	9	90.44	9.262	90.00	76.	106
			DAY 34	PRE-DOSE 1	9	92.89	7.688	94.00	80.	100
			DAY 35	PRE-DOSE 1	8	92.00	6.414	93.00	82.	100
			DAY 37	PRE-DOSE 1	8	90.25	5.497	90.00	82.	96
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	92.50	7.309	93.00	84.	106
			DAY 31	PRE-DOSE 1	8	92.75	7.005	91.00	86.	108
			DAY 32	PRE-DOSE 1	8	98.50	15.109	95.00	82.	130
			DAY 34	PRE-DOSE 1	8	91.25	6.923	89.00	82.	102
			DAY 35	PRE-DOSE 1	9	94.00	12.530	92.00	78.	116
			DAY 37	PRE-DOSE 1	9	94.89	12.374	96.00	78.	114
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	90.89	5.207	92.00	84.	98
			DAY 31	PRE-DOSE 1	9	90.67	6.856	92.00	78.	102
			DAY 32	PRE-DOSE 1	8	93.00	12.329	96.00	78.	114
			DAY 34	PRE-DOSE 1	8	91.75	11.081	93.00	74.	110
			DAY 35	PRE-DOSE 1	8	94.75	9.677	93.00	84.	110
			DAY 37	PRE-DOSE 1	8	94.25	7.815	91.00	86.	106
QT Interval (MSEC)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	417.57	20.796	415.00	372.	458
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	412.21	19.591	412.00	376.	454
			DAY 12-14	PRE-DOSE 1	27	420.22	20.831	416.00	386.	476
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	404.23	24.419	399.00	364.	448

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
QT Interval (MSEC)	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	417.76	21.318	416.00	380.	464
			DAY 26-28	PRE-DOSE 1	25	417.04	17.636	414.00	386.	450
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	419.50	29.871	427.00	372.	458
			DAY 31	PRE-DOSE 1	8	428.50	30.850	431.00	372.	476
			DAY 32	PRE-DOSE 1	9	402.67	20.591	392.00	386.	452
			DAY 34	PRE-DOSE 1	9	421.11	17.353	420.00	390.	450
			DAY 35	PRE-DOSE 1	8	398.25	16.884	396.00	380.	422
			DAY 37	PRE-DOSE 1	8	410.75	21.406	413.00	376.	442
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	409.50	16.690	408.00	390.	438
			DAY 31	PRE-DOSE 1	8	421.75	11.732	417.00	412.	448
			DAY 32	PRE-DOSE 1	8	396.75	25.855	387.00	366.	440
			DAY 34	PRE-DOSE 1	8	409.00	12.142	406.00	398.	436
			DAY 35	PRE-DOSE 1	9	414.00	27.313	410.00	368.	466
			DAY 37	PRE-DOSE 1	9	424.00	25.846	418.00	382.	468
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	400.67	17.944	400.00	380.	442
			DAY 31	PRE-DOSE 1	9	415.56	15.026	414.00	394.	448
			DAY 32	PRE-DOSE 1	8	407.75	28.454	415.00	346.	436
			DAY 34	PRE-DOSE 1	8	426.75	19.797	430.00	388.	448
			DAY 35	PRE-DOSE 1	8	399.00	23.299	392.00	376.	444
			DAY 37	PRE-DOSE 1	8	413.00	16.388	417.00	386.	438

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
QTcB (MSEC)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	436.27	20.761	436.50	389.	473
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	430.89	20.397	431.00	373.	457
			DAY 12-14	PRE-DOSE 1	27	437.63	19.234	437.00	386.	468
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	437.38	17.440	439.00	397.	471
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	430.96	19.608	430.00	395.	479
			DAY 26-28	PRE-DOSE 1	25	432.24	16.964	435.00	394.	460
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	433.88	19.387	435.00	405.	462
			DAY 31	PRE-DOSE 1	8	435.38	17.138	438.50	406.	463
			DAY 32	PRE-DOSE 1	9	430.89	23.735	433.00	379.	460
			DAY 34	PRE-DOSE 1	9	433.89	23.406	437.00	386.	463
			DAY 35	PRE-DOSE 1	8	437.50	10.889	437.50	415.	449
			DAY 37	PRE-DOSE 1	8	436.50	10.198	437.50	420.	453
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	437.00	20.626	442.50	398.	457
			DAY 31	PRE-DOSE 1	8	428.63	22.803	436.50	377.	444
			DAY 32	PRE-DOSE 1	8	435.00	16.151	437.00	405.	463
			DAY 34	PRE-DOSE 1	8	427.88	18.712	434.00	401.	452
			DAY 35	PRE-DOSE 1	9	435.11	15.775	430.00	419.	466
			DAY 37	PRE-DOSE 1	9	434.78	15.417	431.00	408.	458

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
QTcB (MSEC)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	438.56	10.760	437.00	423.	457
			DAY 31	PRE-DOSE 1	9	431.78	12.143	431.00	414.	449
			DAY 32	PRE-DOSE 1	8	433.25	13.467	432.00	416.	454
			DAY 34	PRE-DOSE 1	8	435.38	15.847	440.00	414.	453
			DAY 35	PRE-DOSE 1	8	437.75	19.189	442.00	396.	458
			DAY 37	PRE-DOSE 1	8	434.63	20.156	441.50	402.	454
QTcF (MSEC)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	430.40	18.369	432.55	389.	473
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	425.12	19.652	420.89	373.	456
			DAY 12-14	PRE-DOSE 1	27	432.36	16.958	435.26	386.	459
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	425.62	14.479	424.61	396.	449
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	426.00	18.039	421.63	395.	470
			DAY 26-28	PRE-DOSE 1	25	427.52	13.767	427.44	394.	444
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	425.25	15.942	422.45	405.	448
			DAY 31	PRE-DOSE 1	8	429.50	18.004	430.50	406.	465
			DAY 32	PRE-DOSE 1	9	419.61	18.118	423.29	378.	441
			DAY 34	PRE-DOSE 1	9	427.53	20.273	435.74	385.	452
			DAY 35	PRE-DOSE 1	8	425.42	13.164	426.44	404.	446
			DAY 37	PRE-DOSE 1	8	428.91	12.290	433.28	408.	442

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
QTcF (MSEC)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	426.56	16.399	431.87	398.	447
			DAY 31	PRE-DOSE 1	8	424.29	20.582	432.62	377.	437
			DAY 32	PRE-DOSE 1	8	420.71	12.179	417.59	405.	439
			DAY 34	PRE-DOSE 1	8	421.63	15.127	423.03	400.	439
			DAY 35	PRE-DOSE 1	9	426.17	10.618	425.06	408.	445
			DAY 37	PRE-DOSE 1	9	428.14	10.432	427.34	408.	442
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	426.86	10.209	423.30	412.	440
			DAY 31	PRE-DOSE 1	9	425.77	10.789	426.89	406.	441
			DAY 32	PRE-DOSE 1	8	423.83	13.576	426.23	400.	439
			DAY 34	PRE-DOSE 1	8	429.50	12.246	430.84	412.	443
			DAY 35	PRE-DOSE 1	8	423.60	13.298	426.16	395.	439
			DAY 37	PRE-DOSE 1	8	425.60	14.421	424.05	401.	442
RR Interval (MSEC)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	919.43	114.522	902.91	731.	1169
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	918.94	123.736	895.72	769.	1250
			DAY 12-14	PRE-DOSE 1	27	922.99	107.097	923.08	731.	1153
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	863.87	139.359	810.81	681.	1153
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	947.79	107.583	937.50	800.	1153
			DAY 26-28	PRE-DOSE 1	25	934.34	116.367	937.50	722.	1176

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.09
Summary of ECG Values

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
RR Interval (MSEC)	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	973.15	198.602	938.42	714.	1224
			DAY 31	PRE-DOSE 1	8	1000.35	160.188	1044.19	722.	1200
			DAY 32	PRE-DOSE 1	9	896.79	176.478	845.07	722.	1250
			DAY 34	PRE-DOSE 1	9	962.56	119.287	895.52	857.	1200
			DAY 35	PRE-DOSE 1	8	822.69	77.827	816.36	731.	937
			DAY 37	PRE-DOSE 1	8	880.90	97.535	888.94	750.	1000
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	890.27	108.713	875.96	740.	1090
			DAY 31	PRE-DOSE 1	8	992.06	139.972	930.29	895.	1304
			DAY 32	PRE-DOSE 1	8	850.31	183.578	764.36	714.	1176
			DAY 34	PRE-DOSE 1	8	917.58	94.861	910.97	810.	1052
			DAY 35	PRE-DOSE 1	9	927.62	188.527	895.52	731.	1333
			DAY 37	PRE-DOSE 1	9	980.30	168.036	1016.95	714.	1276
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	829.36	88.850	789.47	759.	1034
			DAY 31	PRE-DOSE 1	9	933.43	98.516	909.09	800.	1132
			DAY 32	PRE-DOSE 1	8	896.48	146.735	909.09	645.	1153
			DAY 34	PRE-DOSE 1	8	988.74	148.701	960.55	769.	1224
			DAY 35	PRE-DOSE 1	8	841.89	131.584	819.40	689.	1034
			DAY 37	PRE-DOSE 1	8	921.24	132.457	869.75	769.	1153

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
Heart rate (BPM)	4 mg PR/XL 24h	66.286	28	DAY 8	PRE-DOSE 1	28	0.036	6.4510	-1.333	-7.33
				DAY 12-14	PRE-DOSE 1	27	-0.309	5.2379	0.000	-12.00
	6 mg PR/XL 24h	66.286	26	DAY 15	PRE-DOSE 1	26	5.333	6.6252	4.833	-4.67
	8 mg PR/XL 24h	66.286	25	DAY 22	PRE-DOSE 1	25	-1.987	4.8252	-3.333	-8.67
				DAY 26-28	PRE-DOSE 1	25	-0.867	5.6051	-1.333	-12.00
	1 x 12mg PR/XL 24h (fasted)	66.286	25	DAY 29	PRE-DOSE 1	8	-0.000	7.2506	-0.500	-9.67
				DAY 31	PRE-DOSE 1	8	-2.500	5.2554	-2.000	-10.67
				DAY 32	PRE-DOSE 1	9	2.630	7.9503	3.667	-10.00
				DAY 34	PRE-DOSE 1	9	-3.148	4.7437	-5.000	-8.00
				DAY 35	PRE-DOSE 1	8	5.583	5.4968	6.167	-5.00
				DAY 37	PRE-DOSE 1	8	0.958	4.1954	1.000	-8.00
	1 x 12mg PR/XL 24h (high fat fed)	66.286	25	DAY 29	PRE-DOSE 1	8	4.000	6.4930	3.333	-7.00
				DAY 31	PRE-DOSE 1	8	-2.875	4.0471	-4.000	-8.67
				DAY 32	PRE-DOSE 1	8	3.833	10.7275	5.000	-13.67
				DAY 34	PRE-DOSE 1	8	-3.167	3.5901	-4.000	-7.67
				DAY 35	PRE-DOSE 1	9	1.852	7.2171	1.333	-6.33
				DAY 37	PRE-DOSE 1	9	-2.037	5.6259	-2.333	-11.00
	3 x 4mg PR/XL 24h (fasted)	66.286	25	DAY 29	PRE-DOSE 1	9	3.481	6.5216	1.667	-5.00
				DAY 31	PRE-DOSE 1	9	-4.630	6.0010	-3.667	-12.33
				DAY 32	PRE-DOSE 1	8	5.875	8.4627	10.667	-8.67

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
Heart rate (BPM)	4 mg PR/XL 24h	66.286	28	DAY 8	PRE-DOSE 1	24.67
				DAY 12-14	PRE-DOSE 1	10.67
	6 mg PR/XL 24h	66.286	26	DAY 15	PRE-DOSE 1	19.67
	8 mg PR/XL 24h	66.286	25	DAY 22	PRE-DOSE 1	8.67
				DAY 26-28	PRE-DOSE 1	9.67
	1 x 12mg PR/XL 24h (fasted)	66.286	25	DAY 29	PRE-DOSE 1	12.00
				DAY 31	PRE-DOSE 1	4.67
				DAY 32	PRE-DOSE 1	13.00
				DAY 34	PRE-DOSE 1	5.67
				DAY 35	PRE-DOSE 1	12.33
				DAY 37	PRE-DOSE 1	5.67
	1 x 12mg PR/XL 24h (high fat fed)	66.286	25	DAY 29	PRE-DOSE 1	12.33
				DAY 31	PRE-DOSE 1	3.33
				DAY 32	PRE-DOSE 1	17.33
				DAY 34	PRE-DOSE 1	1.67
				DAY 35	PRE-DOSE 1	13.67
				DAY 37	PRE-DOSE 1	7.67
	3 x 4mg PR/XL 24h (fasted)	66.286	25	DAY 29	PRE-DOSE 1	15.67
				DAY 31	PRE-DOSE 1	5.67
				DAY 32	PRE-DOSE 1	12.67

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
Heart rate (BPM)	3 x 4mg PR/XL 24h (fasted)	66.286	25	DAY 34	PRE-DOSE 1	8	-0.875	6.9212	-0.167	-11.67
				DAY 35	PRE-DOSE 1	8	7.250	9.4630	10.500	-9.67
				DAY 37	PRE-DOSE 1	8	0.750	6.1043	2.667	-9.67
PR Interval (MSEC)	4 mg PR/XL 24h	170.976	28	DAY 8	PRE-DOSE 1	28	-2.905	10.2483	-1.667	-26.00
				DAY 12-14	PRE-DOSE 1	27	-3.852	9.8767	-2.667	-34.67
	6 mg PR/XL 24h	170.976	26	DAY 15	PRE-DOSE 1	26	-7.154	10.9391	-4.667	-39.33
	8 mg PR/XL 24h	170.976	25	DAY 22	PRE-DOSE 1	25	0.400	11.7395	0.667	-22.00
				DAY 26-28	PRE-DOSE 1	25	-3.440	9.3624	-4.667	-27.33
	1 x 12mg PR/XL 24h (fasted)	170.976	25	DAY 29	PRE-DOSE 1	8	-0.583	8.1294	-3.000	-10.67
				DAY 31	PRE-DOSE 1	8	1.667	14.0294	7.000	-26.67
				DAY 32	PRE-DOSE 1	9	0.741	9.7322	-0.667	-12.67
				DAY 34	PRE-DOSE 1	9	0.519	10.3375	-2.667	-18.67
				DAY 35	PRE-DOSE 1	8	5.250	7.9557	4.000	-3.33
				DAY 37	PRE-DOSE 1	8	1.750	6.3139	1.000	-9.33
	1 x 12mg PR/XL 24h (high fat fed)	170.976	25	DAY 29	PRE-DOSE 1	8	-3.333	9.6478	-4.000	-14.00
				DAY 31	PRE-DOSE 1	8	-4.833	21.3772	-1.333	-56.00
				DAY 32	PRE-DOSE 1	8	-0.583	9.2954	-0.333	-16.67
				DAY 34	PRE-DOSE 1	8	0.917	4.7933	2.667	-8.00
				DAY 35	PRE-DOSE 1	9	-0.741	13.3102	0.667	-22.67

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
Heart rate (BPM)	3 x 4mg PR/XL 24h (fasted)	66.286	25	DAY 34	PRE-DOSE 1	11.00
				DAY 35	PRE-DOSE 1	17.00
				DAY 37	PRE-DOSE 1	6.67
PR Interval (MSEC)	4 mg PR/XL 24h	170.976	28	DAY 8	PRE-DOSE 1	15.33
				DAY 12-14	PRE-DOSE 1	10.00
	6 mg PR/XL 24h	170.976	26	DAY 15	PRE-DOSE 1	5.33
	8 mg PR/XL 24h	170.976	25	DAY 22	PRE-DOSE 1	36.00
				DAY 26-28	PRE-DOSE 1	13.33
	1 x 12mg PR/XL 24h (fasted)	170.976	25	DAY 29	PRE-DOSE 1	12.00
				DAY 31	PRE-DOSE 1	17.33
				DAY 32	PRE-DOSE 1	18.00
				DAY 34	PRE-DOSE 1	14.00
				DAY 35	PRE-DOSE 1	22.67
				DAY 37	PRE-DOSE 1	12.00
	1 x 12mg PR/XL 24h (high fat fed)	170.976	25	DAY 29	PRE-DOSE 1	12.67
				DAY 31	PRE-DOSE 1	12.00
				DAY 32	PRE-DOSE 1	14.67
				DAY 34	PRE-DOSE 1	5.33
				DAY 35	PRE-DOSE 1	23.33

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
PR Interval (MSEC)	1 x 12mg PR/XL 24h (high fat fed)	170.976	25	DAY 37	PRE-DOSE 1	9	-2.296	9.6443	1.333	-18.67
	3 x 4mg PR/XL 24h (fasted)	170.976	25	DAY 29	PRE-DOSE 1	9	-1.407	10.2385	2.000	-19.33
				DAY 31	PRE-DOSE 1	9	-0.519	16.6158	-5.333	-16.67
				DAY 32	PRE-DOSE 1	8	3.000	10.8672	1.000	-13.33
				DAY 34	PRE-DOSE 1	8	2.000	6.2029	1.333	-4.67
				DAY 35	PRE-DOSE 1	8	-1.917	7.5377	-2.333	-13.33
				DAY 37	PRE-DOSE 1	8	-3.167	7.1336	-0.667	-18.67
QRS Duration (MSEC)	4 mg PR/XL 24h	93.119	28	DAY 8	PRE-DOSE 1	28	-0.976	5.6466	-0.667	-15.33
				DAY 12-14	PRE-DOSE 1	27	1.383	3.4687	0.667	-4.67
	6 mg PR/XL 24h	93.119	26	DAY 15	PRE-DOSE 1	26	0.000	5.4845	1.333	-10.00
	8 mg PR/XL 24h	93.119	25	DAY 22	PRE-DOSE 1	25	1.227	3.4837	1.333	-5.33
				DAY 26-28	PRE-DOSE 1	25	-1.013	4.8615	-0.667	-16.00
	1 x 12mg PR/XL 24h (fasted)	93.119	25	DAY 29	PRE-DOSE 1	8	2.250	6.6946	0.333	-5.33
				DAY 31	PRE-DOSE 1	8	1.250	3.8121	0.667	-3.33
				DAY 32	PRE-DOSE 1	9	-2.148	5.2787	-0.667	-12.00
				DAY 34	PRE-DOSE 1	9	0.296	5.0784	-2.000	-6.67
				DAY 35	PRE-DOSE 1	8	2.500	3.5232	3.333	-2.67
				DAY 37	PRE-DOSE 1	8	0.750	2.6292	1.000	-2.67

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
PR Interval (MSEC)	1 x 12mg PR/XL 24h (high fat fed)	170.976	25	DAY 37	PRE-DOSE 1	10.67
	3 x 4mg PR/XL 24h (fasted)	170.976	25	DAY 29	PRE-DOSE 1	12.00
				DAY 31	PRE-DOSE 1	38.00
				DAY 32	PRE-DOSE 1	20.67
				DAY 34	PRE-DOSE 1	10.00
				DAY 35	PRE-DOSE 1	10.00
				DAY 37	PRE-DOSE 1	5.33
QRS Duration (MSEC)	4 mg PR/XL 24h	93.119	28	DAY 8	PRE-DOSE 1	10.67
				DAY 12-14	PRE-DOSE 1	10.00
	6 mg PR/XL 24h	93.119	26	DAY 15	PRE-DOSE 1	9.33
	8 mg PR/XL 24h	93.119	25	DAY 22	PRE-DOSE 1	7.33
				DAY 26-28	PRE-DOSE 1	6.67
	1 x 12mg PR/XL 24h (fasted)	93.119	25	DAY 29	PRE-DOSE 1	16.67
				DAY 31	PRE-DOSE 1	6.67
				DAY 32	PRE-DOSE 1	5.33
				DAY 34	PRE-DOSE 1	7.33
				DAY 35	PRE-DOSE 1	6.67
				DAY 37	PRE-DOSE 1	4.67

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
QRS Duration (MSEC)	1 x 12mg PR/XL 24h (high fat fed)	93.119	25	DAY 29	PRE-DOSE 1	8	1.167	4.0903	2.333	-5.33
				DAY 31	PRE-DOSE 1	8	1.417	2.8605	1.667	-2.67
				DAY 32	PRE-DOSE 1	8	7.500	17.6374	2.000	-3.33
				DAY 34	PRE-DOSE 1	8	0.250	4.2154	-1.000	-4.00
				DAY 35	PRE-DOSE 1	9	0.815	6.5386	0.667	-8.67
				DAY 37	PRE-DOSE 1	9	1.704	4.7855	1.333	-4.67
	3 x 4mg PR/XL 24h (fasted)	93.119	25	DAY 29	PRE-DOSE 1	9	-0.074	5.7585	1.333	-12.00
				DAY 31	PRE-DOSE 1	9	-0.296	3.4978	0.000	-6.00
				DAY 32	PRE-DOSE 1	8	1.000	3.1673	1.000	-5.33
				DAY 34	PRE-DOSE 1	8	-0.250	2.2800	-0.333	-4.00
				DAY 35	PRE-DOSE 1	8	1.917	3.8287	1.000	-2.00
				DAY 37	PRE-DOSE 1	8	1.417	4.0698	0.667	-4.00
QT Interval (MSEC)	4 mg PR/XL 24h	417.571	28	DAY 8	PRE-DOSE 1	28	-5.357	10.9492	-4.333	-24.67
				DAY 12-14	PRE-DOSE 1	27	1.457	14.8704	2.000	-27.33
	6 mg PR/XL 24h	417.571	26	DAY 15	PRE-DOSE 1	26	-13.897	19.5693	-11.000	-55.33
	8 mg PR/XL 24h	417.571	25	DAY 22	PRE-DOSE 1	25	0.613	14.3706	0.667	-22.67
				DAY 26-28	PRE-DOSE 1	25	-0.107	12.4524	1.333	-31.33
	1 x 12mg PR/XL 24h (fasted)	417.571	25	DAY 29	PRE-DOSE 1	8	0.417	21.7867	0.333	-32.00
				DAY 31	PRE-DOSE 1	8	9.417	14.7678	9.000	-14.00

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

[redacted]

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
QRS Duration (MSEC)	1 x 12mg PR/XL 24h (high fat fed)	93.119	25	DAY 29	PRE-DOSE 1	7.33
				DAY 31	PRE-DOSE 1	4.67
				DAY 32	PRE-DOSE 1	50.67
				DAY 34	PRE-DOSE 1	8.67
				DAY 35	PRE-DOSE 1	10.00
				DAY 37	PRE-DOSE 1	12.00
	3 x 4mg PR/XL 24h (fasted)	93.119	25	DAY 29	PRE-DOSE 1	6.00
				DAY 31	PRE-DOSE 1	4.00
				DAY 32	PRE-DOSE 1	4.67
				DAY 34	PRE-DOSE 1	2.67
				DAY 35	PRE-DOSE 1	7.33
				DAY 37	PRE-DOSE 1	8.67
QT Interval (MSEC)	4 mg PR/XL 24h	417.571	28	DAY 8	PRE-DOSE 1	14.00
				DAY 12-14	PRE-DOSE 1	29.33
	6 mg PR/XL 24h	417.571	26	DAY 15	PRE-DOSE 1	14.00
	8 mg PR/XL 24h	417.571	25	DAY 22	PRE-DOSE 1	30.00
				DAY 26-28	PRE-DOSE 1	19.33
	1 x 12mg PR/XL 24h (fasted)	417.571	25	DAY 29	PRE-DOSE 1	32.00
				DAY 31	PRE-DOSE 1	36.00

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

[redacted]

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
QT Interval (MSEC)	1 x 12mg PR/XL 24h (fasted)	417.571	25	DAY 32	PRE-DOSE 1	9	-15.259	24.7845	-25.333	-40.00
				DAY 34	PRE-DOSE 1	9	3.185	18.6809	6.000	-17.33
				DAY 35	PRE-DOSE 1	8	-16.083	17.0878	-18.667	-38.67
				DAY 37	PRE-DOSE 1	8	-3.583	20.7844	-8.333	-26.67
	1 x 12mg PR/XL 24h (high fat fed)	417.571	25	DAY 29	PRE-DOSE 1	8	-13.750	22.6385	-19.667	-37.33
				DAY 31	PRE-DOSE 1	8	-1.500	10.9065	-1.333	-15.33
				DAY 32	PRE-DOSE 1	8	-12.917	17.7672	-11.000	-40.00
				DAY 34	PRE-DOSE 1	8	-0.667	15.0217	0.000	-32.00
				DAY 35	PRE-DOSE 1	9	-4.370	22.9204	-4.000	-44.00
				DAY 37	PRE-DOSE 1	9	5.630	17.3977	10.000	-19.33
	3 x 4mg PR/XL 24h (fasted)	417.571	25	DAY 29	PRE-DOSE 1	9	-9.333	19.5164	-12.000	-39.33
				DAY 31	PRE-DOSE 1	9	5.556	16.4621	7.333	-23.33
				DAY 32	PRE-DOSE 1	8	-16.000	23.6187	-26.333	-37.33
				DAY 34	PRE-DOSE 1	8	3.000	20.3056	2.333	-26.00
				DAY 35	PRE-DOSE 1	8	-19.583	22.4215	-24.000	-51.33
				DAY 37	PRE-DOSE 1	8	-5.583	7.4997	-4.000	-17.33
QTcB (MSEC)	4 mg PR/XL 24h	436.274	28	DAY 8	PRE-DOSE 1	28	-5.381	14.7516	-6.000	-34.00
				DAY 12-14	PRE-DOSE 1	27	0.198	10.9213	-1.333	-21.33
	6 mg PR/XL 24h	436.274	26	DAY 15	PRE-DOSE 1	26	1.333	9.7671	1.667	-21.00
	8 mg PR/XL 24h	436.274	25	DAY 22	PRE-DOSE 1	25	-5.067	15.8011	-3.000	-45.00

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
QT Interval (MSEC)	1 x 12mg PR/XL 24h (fasted)	417.571	25	DAY 32	PRE-DOSE 1	38.00
				DAY 34	PRE-DOSE 1	36.00
				DAY 35	PRE-DOSE 1	11.33
				DAY 37	PRE-DOSE 1	29.33
	1 x 12mg PR/XL 24h (high fat fed)	417.571	25	DAY 29	PRE-DOSE 1	29.33
				DAY 31	PRE-DOSE 1	11.33
				DAY 32	PRE-DOSE 1	20.00
				DAY 34	PRE-DOSE 1	16.00
				DAY 35	PRE-DOSE 1	24.00
				DAY 37	PRE-DOSE 1	28.00
	3 x 4mg PR/XL 24h (fasted)	417.571	25	DAY 29	PRE-DOSE 1	28.00
				DAY 31	PRE-DOSE 1	34.00
				DAY 32	PRE-DOSE 1	28.00
				DAY 34	PRE-DOSE 1	36.00
				DAY 35	PRE-DOSE 1	24.00
				DAY 37	PRE-DOSE 1	2.67
QTcB (MSEC)	4 mg PR/XL 24h	436.274	28	DAY 8	PRE-DOSE 1	33.00
				DAY 12-14	PRE-DOSE 1	36.00
	6 mg PR/XL 24h	436.274	26	DAY 15	PRE-DOSE 1	21.67
	8 mg PR/XL 24h	436.274	25	DAY 22	PRE-DOSE 1	25.00

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
QTcB (MSEC)	8 mg PR/XL 24h	436.274	25	DAY 26-28	PRE-DOSE 1	25	-3.787	12.7631	-4.333	-33.67
	1 x 12mg PR/XL 24h (fasted)	436.274	25	DAY 29	PRE-DOSE 1	8	2.875	17.0545	7.000	-25.67
				DAY 31	PRE-DOSE 1	8	4.375	14.9872	5.667	-24.67
				DAY 32	PRE-DOSE 1	9	-8.148	19.5442	-10.333	-48.00
				DAY 34	PRE-DOSE 1	9	-5.148	17.5469	0.000	-34.67
				DAY 35	PRE-DOSE 1	8	-0.167	14.2127	-0.833	-21.00
				DAY 37	PRE-DOSE 1	8	-1.167	18.6981	-2.000	-31.00
	1 x 12mg PR/XL 24h (high fat fed)	436.274	25	DAY 29	PRE-DOSE 1	8	-1.250	14.0224	1.500	-24.00
				DAY 31	PRE-DOSE 1	8	-9.625	9.6122	-8.000	-29.00
				DAY 32	PRE-DOSE 1	8	-2.167	23.0052	-6.000	-32.00
				DAY 34	PRE-DOSE 1	8	-9.292	10.1222	-7.667	-29.67
				DAY 35	PRE-DOSE 1	9	2.074	10.0177	4.667	-18.33
				DAY 37	PRE-DOSE 1	9	1.741	11.2507	5.000	-16.33
	3 x 4mg PR/XL 24h (fasted)	436.274	25	DAY 29	PRE-DOSE 1	9	0.037	15.0485	0.000	-25.00
				DAY 31	PRE-DOSE 1	9	-6.741	11.4295	-7.000	-24.67
				DAY 32	PRE-DOSE 1	8	1.750	6.6685	-1.333	-5.67
				DAY 34	PRE-DOSE 1	8	3.875	7.2767	3.667	-6.67
				DAY 35	PRE-DOSE 1	8	0.000	10.7762	0.667	-23.00
				DAY 37	PRE-DOSE 1	8	-3.125	12.6854	3.333	-22.33
QTcF (MSEC)	4 mg PR/XL 24h	430.405	28	DAY 8	PRE-DOSE 1	28	-5.280	13.2700	-4.616	-30.35
				DAY 12-14	PRE-DOSE 1	27	1.005	10.2479	0.002	-21.00

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

[redacted]

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
QTcB (MSEC)	8 mg PR/XL 24h	436.274	25	DAY 26-28	PRE-DOSE 1	21.00
	1 x 12mg PR/XL 24h (fasted)	436.274	25	DAY 29	PRE-DOSE 1	25.67
				DAY 31	PRE-DOSE 1	27.67
				DAY 32	PRE-DOSE 1	13.00
				DAY 34	PRE-DOSE 1	17.00
				DAY 35	PRE-DOSE 1	28.00
				DAY 37	PRE-DOSE 1	33.00
	1 x 12mg PR/XL 24h (high fat fed)	436.274	25	DAY 29	PRE-DOSE 1	15.67
				DAY 31	PRE-DOSE 1	0.67
				DAY 32	PRE-DOSE 1	32.00
				DAY 34	PRE-DOSE 1	3.67
				DAY 35	PRE-DOSE 1	14.00
				DAY 37	PRE-DOSE 1	17.67
	3 x 4mg PR/XL 24h (fasted)	436.274	25	DAY 29	PRE-DOSE 1	25.00
				DAY 31	PRE-DOSE 1	9.00
				DAY 32	PRE-DOSE 1	13.67
				DAY 34	PRE-DOSE 1	17.67
				DAY 35	PRE-DOSE 1	12.00
				DAY 37	PRE-DOSE 1	12.67
QTcF (MSEC)	4 mg PR/XL 24h	430.405	28	DAY 8	PRE-DOSE 1	32.59
				DAY 12-14	PRE-DOSE 1	35.56

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
QTcF (MSEC)	6 mg PR/XL 24h	430.405	26	DAY 15	PRE-DOSE 1	26	-4.130	10.0882	-4.050	-23.02
	8 mg PR/XL 24h	430.405	25	DAY 22	PRE-DOSE 1	25	-3.472	13.1504	-3.390	-35.56
				DAY 26-28	PRE-DOSE 1	25	-1.953	9.8774	-4.102	-21.47
	1 x 12mg PR/XL 24h (fasted)	430.405	25	DAY 29	PRE-DOSE 1	8	-0.563	14.3614	3.714	-24.97
				DAY 31	PRE-DOSE 1	8	3.693	13.8508	5.256	-24.25
				DAY 32	PRE-DOSE 1	9	-11.841	17.6578	-10.732	-46.39
				DAY 34	PRE-DOSE 1	9	-3.918	15.5456	-3.661	-28.87
				DAY 35	PRE-DOSE 1	8	-5.481	12.7906	-5.564	-21.37
				DAY 37	PRE-DOSE 1	8	-1.987	18.4718	-3.401	-29.23
	1 x 12mg PR/XL 24h (high fat fed)	430.405	25	DAY 29	PRE-DOSE 1	8	-5.882	14.0487	-4.904	-27.63
				DAY 31	PRE-DOSE 1	8	-8.147	8.0266	-7.370	-23.29
				DAY 32	PRE-DOSE 1	8	-8.020	16.6009	-11.109	-28.34
				DAY 34	PRE-DOSE 1	8	-7.095	10.2032	-4.976	-29.32
				DAY 35	PRE-DOSE 1	9	-1.323	9.7139	-0.619	-17.54
				DAY 37	PRE-DOSE 1	9	0.646	9.5245	0.192	-13.83
	3 x 4mg PR/XL 24h (fasted)	430.405	25	DAY 29	PRE-DOSE 1	9	-3.223	13.0911	-6.644	-22.19
				DAY 31	PRE-DOSE 1	9	-4.314	8.4503	-8.892	-12.55
				DAY 32	PRE-DOSE 1	8	-4.156	6.8976	-2.738	-15.71
				DAY 34	PRE-DOSE 1	8	1.515	6.4223	2.430	-10.19
				DAY 35	PRE-DOSE 1	8	-6.660	9.6202	-4.596	-21.11
				DAY 37	PRE-DOSE 1	8	-4.661	11.1827	-2.142	-21.89

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

[redacted]

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
QTcF (MSEC)	6 mg PR/XL 24h	430.405	26	DAY 15	PRE-DOSE 1	10.16
	8 mg PR/XL 24h	430.405	25	DAY 22	PRE-DOSE 1	21.33
				DAY 26-28	PRE-DOSE 1	20.94
	1 x 12mg PR/XL 24h (fasted)	430.405	25	DAY 29	PRE-DOSE 1	15.37
				DAY 31	PRE-DOSE 1	23.00
				DAY 32	PRE-DOSE 1	12.90
				DAY 34	PRE-DOSE 1	19.55
				DAY 35	PRE-DOSE 1	20.50
				DAY 37	PRE-DOSE 1	31.77
	1 x 12mg PR/XL 24h (high fat fed)	430.405	25	DAY 29	PRE-DOSE 1	15.36
				DAY 31	PRE-DOSE 1	1.17
				DAY 32	PRE-DOSE 1	18.75
				DAY 34	PRE-DOSE 1	2.26
				DAY 35	PRE-DOSE 1	9.82
				DAY 37	PRE-DOSE 1	14.52
	3 x 4mg PR/XL 24h (fasted)	430.405	25	DAY 29	PRE-DOSE 1	16.25
				DAY 31	PRE-DOSE 1	9.06
				DAY 32	PRE-DOSE 1	6.27
				DAY 34	PRE-DOSE 1	10.64
				DAY 35	PRE-DOSE 1	6.29
				DAY 37	PRE-DOSE 1	12.26

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

[redacted]

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
RR Interval (MSEC)	4 mg PR/XL 24h	919.434	28	DAY 8	PRE-DOSE 1	28	-0.498	99.6155	14.969	-380.04
				DAY 12-14	PRE-DOSE 1	27	1.446	71.0011	-0.088	-136.77
	6 mg PR/XL 24h	919.434	26	DAY 15	PRE-DOSE 1	26	-63.148	83.4820	-48.226	-215.87
	8 mg PR/XL 24h	919.434	25	DAY 22	PRE-DOSE 1	25	25.375	73.9278	41.195	-169.52
				DAY 26-28	PRE-DOSE 1	25	11.929	82.7214	14.320	-135.03
	1 x 12mg PR/XL 24h (fasted)	919.434	25	DAY 29	PRE-DOSE 1	8	13.741	120.8679	19.084	-202.27
				DAY 31	PRE-DOSE 1	8	40.940	98.0752	25.563	-98.09
				DAY 32	PRE-DOSE 1	9	-17.709	117.5759	-58.484	-158.11
				DAY 34	PRE-DOSE 1	9	48.054	73.4608	62.082	-78.02
				DAY 35	PRE-DOSE 1	8	-71.632	75.3066	-72.804	-190.20
				DAY 37	PRE-DOSE 1	8	-13.424	57.0288	-13.969	-76.16
	1 x 12mg PR/XL 24h (high fat fed)	919.434	25	DAY 29	PRE-DOSE 1	8	-54.400	86.2460	-52.048	-190.20
				DAY 31	PRE-DOSE 1	8	47.394	80.6059	56.102	-59.76
				DAY 32	PRE-DOSE 1	8	-26.846	140.9012	-56.268	-186.96
				DAY 34	PRE-DOSE 1	8	40.427	50.2796	48.458	-19.24
				DAY 35	PRE-DOSE 1	9	-15.250	118.8592	-17.270	-215.84
				DAY 37	PRE-DOSE 1	9	37.433	87.0042	25.427	-102.51
	3 x 4mg PR/XL 24h (fasted)	919.434	25	DAY 29	PRE-DOSE 1	9	-40.393	82.1991	-18.322	-188.09
				DAY 31	PRE-DOSE 1	9	63.680	85.5172	54.200	-78.02

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

[redacted]

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
RR Interval (MSEC)	4 mg PR/XL 24h	919.434	28	DAY 8	PRE-DOSE 1	154.18
				DAY 12-14	PRE-DOSE 1	131.32
	6 mg PR/XL 24h	919.434	26	DAY 15	PRE-DOSE 1	64.98
	8 mg PR/XL 24h	919.434	25	DAY 22	PRE-DOSE 1	126.05
				DAY 26-28	PRE-DOSE 1	147.79
	1 x 12mg PR/XL 24h (fasted)	919.434	25	DAY 29	PRE-DOSE 1	186.69
				DAY 31	PRE-DOSE 1	210.22
				DAY 32	PRE-DOSE 1	179.69
				DAY 34	PRE-DOSE 1	138.53
				DAY 35	PRE-DOSE 1	63.69
				DAY 37	PRE-DOSE 1	106.98
	1 x 12mg PR/XL 24h (high fat fed)	919.434	25	DAY 29	PRE-DOSE 1	92.10
				DAY 31	PRE-DOSE 1	202.84
				DAY 32	PRE-DOSE 1	223.71
				DAY 34	PRE-DOSE 1	112.60
				DAY 35	PRE-DOSE 1	163.82
				DAY 37	PRE-DOSE 1	159.45
	3 x 4mg PR/XL 24h (fasted)	919.434	25	DAY 29	PRE-DOSE 1	82.10
				DAY 31	PRE-DOSE 1	179.69

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.
RR Interval (MSEC)	3 x 4mg PR/XL 24h (fasted)	919.434	25	DAY 32	PRE-DOSE 1	8	-80.100	136.0385	-111.114	-232.02
				DAY 34	PRE-DOSE 1	8	12.159	122.5792	3.385	-188.29
				DAY 35	PRE-DOSE 1	8	-85.605	120.5740	-111.493	-204.01
				DAY 37	PRE-DOSE 1	8	-6.261	89.8851	-38.131	-96.86

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.10
Summary of Change from Baseline in ECG Values

	Treatment	Mean Baseline [1]	N	Visit	Planned Relative Time	Max.
RR Interval (MSEC)	3 x 4mg PR/XL 24h (fasted)	919.434	25	DAY 32	PRE-DOSE 1	164.07
				DAY 34	PRE-DOSE 1	234.71
				DAY 35	PRE-DOSE 1	147.08
				DAY 37	PRE-DOSE 1	147.08

[1] Mean Baseline is the average of the 3 pre-dose values on Day 1

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	134.6	19.20	136.0	97	166
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	129.6	18.39	125.5	93	167
			DAY 12-14	PRE-DOSE 1	27	130.3	18.90	126.0	98	176
				4H	27	127.4	18.45	125.0	100	177
				6H	27	121.4	16.96	118.0	94	180
				12H	27	123.7	16.25	121.0	93	177
				24H	27	132.6	19.20	128.0	101	167
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	123.5	18.66	122.5	87	160
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	129.2	16.99	130.0	103	165
			DAY 26-28	PRE-DOSE 1	25	132.5	24.56	126.0	96	214
				4H	25	128.8	19.28	123.0	98	175
				6H	25	126.0	20.66	124.0	99	184
				12H	25	128.8	19.60	125.0	102	168
				24H	25	135.3	21.84	129.0	105	190
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	130.4	13.81	129.0	117	160
			DAY 31	PRE-DOSE 1	8	129.1	13.84	123.5	118	157
				4H	8	122.3	5.68	121.0	117	131
				6H	8	121.3	13.85	119.5	102	141
				12H	8	124.1	12.54	118.0	113	149
				24H	8	137.0	17.74	133.5	116	161
			DAY 32	PRE-DOSE 1	9	124.3	22.66	115.0	101	166
			DAY 34	PRE-DOSE 1	9	132.7	30.31	124.0	99	192
				4H	9	130.3	27.13	124.0	103	188
				6H	9	131.4	35.62	128.0	103	218

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	1 x 12mg PR/XL 24h (fasted)	25	DAY 34	12H	9	132.9	32.66	120.0	109	215
				24H	9	130.1	28.12	123.0	100	191
			DAY 35	PRE-DOSE 1	8	122.4	22.88	120.5	96	161
			DAY 37	PRE-DOSE 1	8	131.6	20.67	131.0	108	168
				4H	8	130.1	18.85	129.0	107	163
				6H	8	123.9	21.74	119.5	97	161
				12H	8	135.1	17.06	134.0	112	154
				24H	8	131.0	25.43	120.0	98	169
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	123.8	24.39	119.0	94	171
			DAY 31	PRE-DOSE 1	8	130.9	18.36	131.5	101	163
				4H	8	122.1	15.20	121.5	101	151
				6H	8	122.8	21.60	120.0	100	161
				12H	8	127.1	19.10	126.0	107	169
				24H	8	130.3	20.13	127.0	104	165
			DAY 32	PRE-DOSE 1	8	127.1	14.08	124.5	113	156
			DAY 34	PRE-DOSE 1	8	124.0	12.00	120.0	113	151
				4H	8	122.6	15.77	119.0	109	159
				6H	8	121.5	20.26	117.0	93	153
				12H	8	121.8	12.14	118.5	112	150
				24H	8	123.6	19.63	116.0	104	165
			DAY 35	PRE-DOSE 1	9	133.2	25.21	128.0	108	191
			DAY 37	PRE-DOSE 1	9	135.3	32.98	148.0	92	190
				4H	9	127.2	32.70	114.0	99	197
				6H	9	137.0	36.31	142.0	102	218
				12H	9	137.0	14.82	137.0	115	160
				24H	9	143.2	24.88	141.0	119	192

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	129.3	28.92	119.0	102	190
			DAY 31	PRE-DOSE 1	9	133.2	25.88	128.0	98	179
				4H	9	132.0	21.35	128.0	105	156
				6H	9	125.1	27.74	113.0	93	165
				12H	9	135.7	27.87	126.0	98	174
				24H	9	132.7	26.39	123.0	92	172
			DAY 32	PRE-DOSE 1	8	134.9	26.65	138.0	98	165
			DAY 34	PRE-DOSE 1	8	134.9	18.16	133.0	112	167
				4H	8	133.3	17.69	133.5	111	161
				6H	8	128.8	15.96	126.5	109	159
				12H	8	126.5	15.02	124.0	109	159
				24H	8	133.1	16.13	134.5	112	161
			DAY 35	PRE-DOSE 1	8	118.5	8.54	118.5	102	131
			DAY 37	PRE-DOSE 1	8	118.9	13.91	119.5	99	134
				4H	8	115.4	10.84	114.5	102	132
				6H	8	116.0	14.28	115.5	99	139
				12H	8	121.1	13.82	122.5	95	146
				24H	8	119.5	10.28	123.0	100	131
Diastolic BP (mmHg)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	76.2	8.18	75.5	59	89
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	76.0	8.90	75.0	59	90
			DAY 12-14	PRE-DOSE 1	27	75.6	7.51	75.0	57	86
				4H	27	74.7	7.23	73.0	63	92
				6H	27	69.7	8.35	70.0	56	85
				12H	27	69.9	7.93	72.0	54	81
				24H	27	74.8	7.94	76.0	56	91

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	69.7	8.81	68.0	52	90
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	75.2	10.80	75.0	53	97
			DAY 26-28	PRE-DOSE 1	25	76.4	9.39	78.0	59	95
				4H	25	76.8	7.47	77.0	63	92
				6H	25	71.7	9.08	74.0	51	86
				12H	25	75.4	10.29	74.0	60	105
				24H	25	76.5	9.07	74.0	59	99
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	71.6	6.30	69.5	66	83
			DAY 31	PRE-DOSE 1	8	71.4	4.17	71.5	66	79
				4H	8	71.5	6.02	71.5	63	80
				6H	8	68.0	4.47	67.5	61	76
				12H	8	71.1	7.47	71.0	61	80
				24H	8	76.1	8.90	75.5	58	90
			DAY 32	PRE-DOSE 1	9	69.8	9.38	71.0	59	86
			DAY 34	PRE-DOSE 1	9	75.9	6.86	77.0	64	87
				4H	9	74.2	10.97	74.0	58	88
				6H	9	73.2	10.16	70.0	64	93
				12H	9	74.9	10.23	74.0	64	98
				24H	9	74.2	7.90	72.0	64	88
			DAY 35	PRE-DOSE 1	8	71.4	6.78	71.5	62	83
			DAY 37	PRE-DOSE 1	8	79.8	8.08	82.0	68	89
				4H	8	80.1	4.85	81.0	70	86
				6H	8	76.0	7.91	77.5	66	86
				12H	8	79.0	5.71	79.5	72	86
				24H	8	78.8	7.19	80.0	68	89

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	71.5	11.46	71.0	58	91
			DAY 31	PRE-DOSE 1	8	78.5	6.99	79.0	64	87
				4H	8	75.6	7.85	77.0	62	85
				6H	8	73.1	10.84	73.5	58	87
				12H	8	76.3	4.56	76.0	70	82
				24H	8	76.8	7.78	78.0	65	86
			DAY 32	PRE-DOSE 1	8	71.1	8.89	71.0	58	88
			DAY 34	PRE-DOSE 1	8	74.4	6.44	73.5	66	88
				4H	8	73.0	8.59	71.0	61	91
				6H	8	72.6	7.07	74.0	62	83
				12H	8	73.0	8.07	74.5	61	84
				24H	8	73.6	7.95	73.0	65	90
			DAY 35	PRE-DOSE 1	9	69.1	7.91	67.0	60	88
			DAY 37	PRE-DOSE 1	9	71.0	8.28	69.0	60	86
				4H	9	67.6	10.27	66.0	55	87
				6H	9	71.6	11.18	70.0	62	100
				12H	9	74.0	6.04	74.0	66	85
				24H	9	76.7	6.93	73.0	69	89
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	72.3	7.79	72.0	59	84
			DAY 31	PRE-DOSE 1	9	75.3	7.40	73.0	66	91
				4H	9	75.0	6.40	76.0	67	88
				6H	9	72.6	10.37	69.0	61	96
				12H	9	74.6	5.29	76.0	63	82
				24H	9	74.8	9.40	73.0	59	95
			DAY 32	PRE-DOSE 1	8	77.6	7.23	75.5	67	87
			DAY 34	PRE-DOSE 1	8	77.9	7.20	74.5	71	88
				4H	8	80.0	7.25	83.5	68	87

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 34	6H	8	75.4	9.49	72.5	65	92
				12H	8	73.0	8.73	73.0	58	85
				24H	8	78.4	10.77	79.5	60	90
			DAY 35	PRE-DOSE 1	8	69.8	6.30	68.0	61	79
			DAY 37	PRE-DOSE 1	8	73.3	6.27	74.5	61	80
				4H	8	69.9	6.01	70.0	60	77
				6H	8	69.1	10.26	67.5	54	85
				12H	8	72.0	7.98	74.5	54	80
				24H	8	73.5	7.13	75.5	63	82
Heart rate (beats/min)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	65.2	7.67	65.0	51	80
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	65.8	7.31	66.0	49	78
			DAY 12-14	PRE-DOSE 1	27	67.2	8.72	65.0	49	84
				4H	27	65.5	8.65	64.0	51	81
				6H	27	67.7	8.71	67.0	47	88
				12H	27	69.9	8.67	71.0	49	86
				24H	27	65.5	8.64	67.0	48	77
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	70.7	10.83	74.0	51	87
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	64.8	7.53	67.0	52	80
			DAY 26-28	PRE-DOSE 1	25	65.4	9.18	62.0	51	87
				4H	25	65.6	9.02	64.0	50	86
				6H	25	66.7	7.44	66.0	51	81
				12H	25	68.5	9.11	67.0	53	87
				24H	25	64.5	7.38	65.0	51	78

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	64.8	13.29	62.5	51	86
			DAY 31	PRE-DOSE 1	8	61.4	10.14	58.0	49	80
				4H	8	62.5	7.58	61.5	53	76
				6H	8	64.8	8.48	62.0	52	76
				12H	8	68.6	9.12	69.0	52	82
				24H	8	64.0	7.48	65.0	53	76
			DAY 32	PRE-DOSE 1	9	69.8	9.60	71.0	54	80
			DAY 34	PRE-DOSE 1	9	66.3	6.40	67.0	56	76
				4H	9	63.0	3.64	62.0	58	68
				6H	9	65.1	5.53	63.0	57	75
				12H	9	70.3	7.50	68.0	62	84
				24H	9	65.7	4.03	66.0	58	71
			DAY 35	PRE-DOSE 1	8	74.1	7.49	74.0	62	86
			DAY 37	PRE-DOSE 1	8	69.4	8.83	68.5	59	85
				4H	8	68.8	8.91	66.0	57	83
				6H	8	71.0	6.32	70.5	63	80
				12H	8	75.6	10.42	74.0	61	91
				24H	8	71.4	10.73	69.0	54	90
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	69.0	6.46	68.5	60	81
			DAY 31	PRE-DOSE 1	8	62.3	5.80	64.0	53	68
				4H	8	64.6	7.25	65.5	51	75
				6H	8	67.3	8.03	66.0	57	84
				12H	8	65.8	4.74	66.5	57	74
				24H	8	61.0	6.57	61.5	50	70
			DAY 32	PRE-DOSE 1	8	75.1	13.43	81.0	53	86
			DAY 34	PRE-DOSE 1	8	67.8	7.54	71.0	55	75
				4H	8	72.1	6.81	71.0	63	81

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 34	6H	8	74.9	10.62	71.0	64	97
				12H	8	75.6	8.28	74.5	65	88
				24H	8	70.9	8.63	71.0	57	86
			DAY 35	PRE-DOSE 1	9	67.0	10.50	67.0	50	82
			DAY 37	PRE-DOSE 1	9	64.2	11.54	59.0	49	85
				4H	9	64.8	11.02	62.0	47	85
				6H	9	63.3	10.72	66.0	43	80
				12H	9	69.8	7.51	73.0	57	82
				24H	9	64.6	6.00	62.0	55	73
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	72.6	6.54	76.0	58	78
			DAY 31	PRE-DOSE 1	9	66.8	7.10	65.0	55	77
				4H	9	68.8	10.69	66.0	54	86
				6H	9	72.8	9.88	72.0	60	88
				12H	9	72.7	9.54	71.0	60	92
				24H	9	69.1	7.25	68.0	58	81
			DAY 32	PRE-DOSE 1	8	69.3	8.40	67.0	62	87
			DAY 34	PRE-DOSE 1	8	62.5	8.73	63.0	50	76
				4H	8	61.3	9.32	63.0	45	76
				6H	8	61.9	7.14	62.0	53	72
				12H	8	64.8	9.71	66.5	51	80
				24H	8	60.9	7.38	59.5	50	72
			DAY 35	PRE-DOSE 1	8	72.3	9.72	72.0	57	86
			DAY 37	PRE-DOSE 1	8	66.1	7.32	68.0	54	77
				4H	8	65.6	6.80	64.5	56	79
				6H	8	68.5	5.88	67.0	60	78
				12H	8	71.0	6.97	72.5	57	79
				24H	8	69.1	6.53	67.5	61	79

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	131.7	21.97	128.5	81	174
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	128.6	21.68	126.0	76	161
			DAY 12-14	PRE-DOSE 1	27	129.1	21.36	128.0	85	172
				4H	27	122.5	23.12	122.0	58	168
				6H	27	119.9	21.40	118.0	72	172
				12H	27	120.0	19.11	116.0	59	148
				24H	27	129.4	23.49	125.0	74	170
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	121.7	19.75	121.0	95	166
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	127.2	18.87	124.0	96	159
			DAY 26-28	PRE-DOSE 1	25	134.4	22.80	131.0	92	181
				4H	25	126.7	18.48	128.0	95	159
				6H	25	125.1	20.62	118.0	87	187
				12H	25	126.0	22.71	122.0	74	167
				24H	25	130.7	20.64	131.0	95	175
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	139.9	20.16	133.5	117	175
			DAY 31	PRE-DOSE 1	8	133.3	22.02	129.0	105	173
				4H	8	122.8	12.20	119.5	113	151
				6H	8	128.1	20.41	119.0	109	160
				12H	8	128.6	20.96	119.5	114	166
				24H	8	137.8	21.03	132.5	118	180
			DAY 32	PRE-DOSE 1	9	117.4	21.01	118.0	84	144
			DAY 34	PRE-DOSE 1	9	130.6	27.39	132.0	96	178
				4H	9	122.0	23.93	123.0	85	158
				6H	9	123.7	21.77	127.0	87	162

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	1 x 12mg PR/XL 24h (fasted)	25	DAY 34	12H	9	120.3	29.20	119.0	79	178
				24H	9	117.2	16.18	123.0	93	135
			DAY 35	PRE-DOSE 1	8	119.5	20.47	115.0	95	155
			DAY 37	PRE-DOSE 1	8	127.1	24.03	128.0	99	168
				4H	8	125.1	17.20	130.0	100	150
				6H	8	123.8	27.67	124.5	81	169
				12H	8	123.3	16.30	123.5	94	148
				24H	8	133.6	23.43	137.5	102	180
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	127.6	22.83	122.0	102	159
			DAY 31	PRE-DOSE 1	8	128.5	22.90	133.5	93	164
				4H	8	125.5	14.78	120.0	103	144
				6H	8	124.9	24.37	131.5	84	156
				12H	8	131.1	15.39	132.5	105	152
				24H	8	127.1	21.83	125.5	98	160
			DAY 32	PRE-DOSE 1	8	122.0	18.91	119.0	101	160
			DAY 34	PRE-DOSE 1	8	121.9	11.12	123.5	101	133
				4H	8	119.8	17.49	117.5	95	146
				6H	8	115.1	13.13	117.5	87	131
				12H	8	116.9	7.32	117.5	106	128
				24H	8	116.8	16.66	112.5	97	150
			DAY 35	PRE-DOSE 1	9	124.6	25.87	126.0	77	160
			DAY 37	PRE-DOSE 1	9	131.4	34.42	146.0	73	175
				4H	9	125.4	20.83	135.0	92	148
				6H	9	123.4	25.56	128.0	92	171
				12H	9	127.9	15.22	130.0	102	147
				24H	9	141.3	23.58	146.0	114	190

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	113.8	15.40	108.0	97	138
			DAY 31	PRE-DOSE 1	9	117.0	25.24	114.0	83	166
				4H	9	119.7	21.40	116.0	81	155
				6H	9	108.7	23.90	104.0	78	158
				12H	9	124.4	23.08	119.0	97	171
				24H	9	121.6	16.76	119.0	100	149
			DAY 32	PRE-DOSE 1	8	138.6	27.27	144.5	98	180
			DAY 34	PRE-DOSE 1	8	135.6	21.58	134.5	99	167
				4H	8	135.5	17.48	134.0	111	163
				6H	8	131.8	20.72	137.5	104	167
				12H	8	126.6	13.95	125.5	110	151
				24H	8	135.3	24.91	148.5	93	156
			DAY 35	PRE-DOSE 1	8	112.1	20.43	112.5	78	135
			DAY 37	PRE-DOSE 1	8	118.8	16.97	117.5	92	141
				4H	8	117.1	8.61	117.5	105	130
				6H	8	121.1	11.32	123.5	102	136
				12H	8	121.4	8.77	121.5	106	132
				24H	8	118.9	8.95	117.0	105	133
Diastolic BP (mmHg)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	79.1	10.04	81.5	51	95
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	81.4	12.39	81.5	52	104
			DAY 12-14	PRE-DOSE 1	27	78.8	9.23	79.0	56	97
				4H	27	78.6	11.00	77.0	39	97
				6H	27	72.5	9.61	72.0	54	89
				12H	27	74.7	13.85	76.0	36	102
				24H	27	78.9	11.45	78.0	50	106

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	73.2	8.06	73.0	55	91
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	79.5	10.74	80.0	54	98
			DAY 26-28	PRE-DOSE 1	25	81.9	11.40	83.0	64	105
				4H	25	79.8	8.94	78.0	67	99
				6H	25	77.7	10.93	78.0	50	95
				12H	25	77.8	14.42	78.0	39	110
				24H	25	81.2	9.57	77.0	69	102
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	80.0	6.97	76.5	74	93
			DAY 31	PRE-DOSE 1	8	77.1	5.87	74.5	72	89
				4H	8	76.8	9.08	76.0	66	88
				6H	8	76.8	7.36	79.0	64	84
				12H	8	80.4	9.30	78.0	70	96
				24H	8	82.0	8.28	84.0	68	93
			DAY 32	PRE-DOSE 1	9	72.4	11.42	69.0	60	90
			DAY 34	PRE-DOSE 1	9	82.4	7.97	81.0	73	97
				4H	9	76.1	14.21	75.0	51	96
				6H	9	76.9	9.78	82.0	65	89
				12H	9	76.7	11.31	76.0	61	93
				24H	9	81.1	12.88	76.0	65	102
			DAY 35	PRE-DOSE 1	8	76.0	12.04	76.0	55	92
			DAY 37	PRE-DOSE 1	8	84.4	12.12	88.5	66	97
				4H	8	86.0	8.43	86.5	72	96
				6H	8	81.5	14.50	84.0	61	100
				12H	8	81.9	9.66	83.5	67	94
				24H	8	89.1	16.05	88.5	70	120

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	81.5	11.82	83.5	66	97
			DAY 31	PRE-DOSE 1	8	87.3	10.12	90.5	67	101
				4H	8	79.4	8.73	79.5	66	91
				6H	8	82.1	9.66	84.5	69	95
				12H	8	82.1	6.69	82.5	73	94
				24H	8	86.9	16.81	86.0	68	114
			DAY 32	PRE-DOSE 1	8	76.0	6.21	74.0	68	86
			DAY 34	PRE-DOSE 1	8	78.5	5.63	81.5	69	84
				4H	8	74.5	7.39	74.5	65	88
				6H	8	73.5	9.09	76.5	56	84
				12H	8	80.3	4.98	78.5	75	89
				24H	8	75.9	11.24	76.5	55	93
			DAY 35	PRE-DOSE 1	9	72.1	9.29	72.0	57	85
			DAY 37	PRE-DOSE 1	9	73.4	8.80	74.0	57	89
				4H	9	69.9	7.36	68.0	61	84
				6H	9	73.1	11.49	73.0	58	98
				12H	9	72.9	9.20	73.0	62	90
				24H	9	78.9	7.90	77.0	67	94
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	74.4	7.60	74.0	66	92
			DAY 31	PRE-DOSE 1	9	74.4	9.13	70.0	65	94
				4H	9	71.8	11.14	68.0	57	89
				6H	9	68.0	10.63	68.0	48	85
				12H	9	76.9	9.73	80.0	63	94
				24H	9	77.8	11.33	79.0	60	92
			DAY 32	PRE-DOSE 1	8	82.8	9.78	83.5	68	97
			DAY 34	PRE-DOSE 1	8	83.0	7.35	83.0	73	93
				4H	8	85.1	9.00	86.5	71	101

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

CONFIDENTIAL

Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 34	6H	8	81.3	11.74	81.0	63	99
				12H	8	76.1	10.41	81.0	58	84
				24H	8	81.8	15.61	82.0	57	107
			DAY 35	PRE-DOSE 1	8	75.8	10.44	75.5	60	90
			DAY 37	PRE-DOSE 1	8	80.5	11.26	82.0	61	98
				4H	8	78.6	10.18	79.5	61	95
				6H	8	75.9	8.06	77.5	63	86
				12H	8	80.3	9.44	81.5	66	95
				24H	8	84.9	9.75	84.5	72	103
Heart rate (beats/min)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	28	73.9	9.08	75.0	55	90
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	75.1	10.17	77.5	51	92
			DAY 12-14	PRE-DOSE 1	27	74.1	10.54	76.0	54	94
				4H	27	76.3	12.47	77.0	44	94
				6H	27	77.4	10.80	78.0	55	100
				12H	27	80.6	10.20	82.0	58	96
				24H	27	77.0	11.03	81.0	55	95
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	83.5	14.50	86.0	63	112
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	72.4	9.70	73.0	55	93
			DAY 26-28	PRE-DOSE 1	25	75.0	11.81	74.0	54	110
				4H	25	75.7	9.69	75.0	57	98
				6H	25	76.9	8.10	77.0	58	94
				12H	25	78.1	10.10	80.0	62	99
				24H	25	75.6	10.65	77.0	53	89

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	72.0	13.35	71.0	53	90
			DAY 31	PRE-DOSE 1	8	70.4	13.55	68.0	51	97
				4H	8	74.4	10.72	75.0	57	94
				6H	8	77.5	10.57	81.5	58	87
				12H	8	81.6	12.64	85.5	58	95
				24H	8	73.0	10.46	74.0	57	83
			DAY 32	PRE-DOSE 1	9	82.2	13.30	88.0	59	95
			DAY 34	PRE-DOSE 1	9	72.8	9.71	77.0	56	84
				4H	9	75.7	3.91	76.0	68	81
				6H	9	77.6	5.00	77.0	68	84
				12H	9	83.3	9.34	86.0	66	98
				24H	9	83.0	10.97	85.0	62	96
			DAY 35	PRE-DOSE 1	8	86.8	12.95	86.5	69	105
			DAY 37	PRE-DOSE 1	8	74.8	16.93	77.5	45	99
				4H	8	83.6	10.93	84.5	70	100
				6H	8	83.5	9.71	83.0	69	96
				12H	8	85.8	11.62	88.5	67	99
				24H	8	84.1	14.97	83.0	61	105
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	82.0	10.97	81.5	69	97
			DAY 31	PRE-DOSE 1	8	71.3	7.65	73.0	59	82
				4H	8	73.3	6.50	71.5	65	85
				6H	8	74.9	5.57	73.5	70	86
				12H	8	78.8	10.85	75.5	67	101
				24H	8	73.4	11.35	74.5	55	91
			DAY 32	PRE-DOSE 1	8	84.4	12.89	86.0	63	101
			DAY 34	PRE-DOSE 1	8	79.1	8.39	80.0	66	93
				4H	8	86.6	5.21	86.0	77	95

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.11
Summary of Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 34	6H	8	88.1	9.25	86.0	73	104
				12H	8	88.0	9.04	88.5	74	104
				24H	8	83.0	10.31	83.0	73	105
			DAY 35	PRE-DOSE 1	9	77.3	14.70	85.0	57	95
			DAY 37	PRE-DOSE 1	9	70.1	13.11	62.0	58	87
				4H	9	73.6	11.63	70.0	58	96
				6H	9	72.4	11.76	74.0	53	87
				12H	9	76.7	10.06	79.0	64	93
				24H	9	73.4	10.27	68.0	62	88
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	84.1	8.61	86.0	62	91
			DAY 31	PRE-DOSE 1	9	74.3	9.60	75.0	58	89
				4H	9	79.0	13.56	78.0	58	107
				6H	9	83.3	12.90	86.0	64	105
				12H	9	83.8	11.91	83.0	65	108
				24H	9	82.1	11.77	85.0	59	101
			DAY 32	PRE-DOSE 1	8	79.0	14.57	78.0	57	103
			DAY 34	PRE-DOSE 1	8	68.6	10.21	69.0	54	83
				4H	8	72.6	10.25	70.0	61	88
				6H	8	73.0	11.77	74.0	57	88
				12H	8	72.6	15.42	69.5	57	101
				24H	8	68.4	9.02	68.0	57	85
			DAY 35	PRE-DOSE 1	8	84.8	10.63	83.0	70	105
			DAY 37	PRE-DOSE 1	8	75.4	8.75	77.0	61	85
				4H	8	76.4	8.30	78.0	66	87
				6H	8	82.3	7.05	83.0	72	92
				12H	8	85.6	5.58	87.0	73	91
				24H	8	83.8	10.96	84.0	67	100

NOTE: PRE-DOSE readings are the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	-5.08	11.020	-5.33	-32.0	17.3
			DAY 12-14	PRE-DOSE 1	27	-4.89	10.070	-6.33	-24.7	11.0
				4H	27	-7.74	13.795	-9.00	-32.0	17.0
				6H	27	-13.78	15.620	-16.00	-42.0	15.0
				12H	27	-11.41	14.782	-12.00	-38.0	20.0
				24H	27	-2.56	13.642	-1.33	-34.0	21.7
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	-12.09	17.305	-12.67	-64.0	16.0
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	-7.04	12.269	-4.67	-41.0	12.7
			DAY 26-28	PRE-DOSE 1	25	-3.72	15.571	-2.00	-37.0	49.0
				4H	25	-7.40	10.741	-4.67	-35.0	10.0
				6H	25	-10.16	15.311	-10.67	-43.0	25.0
				12H	25	-7.44	11.962	-5.00	-34.0	8.0
				24H	25	-0.92	11.289	1.00	-23.3	25.0
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	-5.92	16.961	-2.00	-42.0	10.3
			DAY 31	PRE-DOSE 1	8	-7.17	19.982	-3.33	-40.0	15.0
				4H	8	-14.04	17.058	-11.33	-42.0	6.0
				6H	8	-15.04	20.721	-10.67	-57.0	6.7
				12H	8	-12.17	23.142	-7.50	-46.0	13.3
				24H	8	0.71	19.763	4.00	-43.0	22.3
			DAY 32	PRE-DOSE 1	9	-11.52	17.301	-5.33	-36.0	8.7
			DAY 34	PRE-DOSE 1	9	-3.19	16.650	-8.33	-23.0	27.0
				4H	9	-5.52	21.850	-4.33	-33.7	24.7
				6H	9	-4.41	28.264	-10.33	-41.7	53.0
				12H	9	-2.96	24.476	-9.33	-26.0	50.0
				24H	9	-5.74	17.316	-4.33	-31.0	26.0

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	1 x 12mg PR/XL 24h (fasted)	25	DAY 35	PRE-DOSE 1	8	-14.13	7.599	-16.17	-25.3	-3.7
			DAY 37	PRE-DOSE 1	8	-4.88	10.101	-5.33	-20.3	6.7
				4H	8	-6.38	10.844	-3.83	-21.3	6.7
				6H	8	-12.63	13.085	-12.00	-31.3	7.7
				12H	8	-1.38	15.766	-0.50	-26.7	24.7
				24H	8	-5.50	10.954	-1.50	-27.7	4.3
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	-9.08	15.235	-5.00	-32.0	7.7
			DAY 31	PRE-DOSE 1	8	-1.96	9.164	-3.17	-13.7	14.7
				4H	8	-10.71	21.531	-16.17	-43.7	14.7
				6H	8	-10.08	17.884	-5.50	-41.7	13.7
				12H	8	-5.71	11.203	-9.00	-17.7	10.0
				24H	8	-2.58	10.120	-1.00	-21.7	8.7
			DAY 32	PRE-DOSE 1	8	-2.54	15.986	1.17	-33.0	17.0
			DAY 34	PRE-DOSE 1	8	-5.67	18.483	-2.67	-42.0	13.7
				4H	8	-7.04	14.931	-1.33	-39.0	4.7
				6H	8	-8.17	22.322	-10.67	-38.0	40.7
				12H	8	-7.92	17.233	-2.33	-45.0	7.0
				24H	8	-6.04	19.076	-4.00	-46.0	16.3
			DAY 35	PRE-DOSE 1	9	-11.78	15.788	-17.00	-25.7	26.0
			DAY 37	PRE-DOSE 1	9	-9.67	27.060	-5.33	-53.7	25.0
				4H	9	-17.78	29.961	-24.00	-54.0	32.0
				6H	9	-8.00	27.775	-12.33	-36.7	53.0
				12H	9	-8.00	9.100	-5.00	-26.0	1.3
				24H	9	-1.78	16.711	-3.00	-22.0	27.0
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	-9.78	19.023	-7.00	-32.3	25.0

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 31	PRE-DOSE 1	9	-5.89	9.677	-9.00	-17.0	14.0
				4H	9	-7.11	11.250	-5.00	-31.0	5.3
				6H	9	-14.00	13.473	-10.33	-39.0	7.0
				12H	9	-3.44	14.360	-5.33	-29.0	21.0
				24H	9	-6.44	11.364	0.33	-26.3	5.7
			DAY 32	PRE-DOSE 1	8	-8.25	20.710	-5.00	-47.7	22.3
			DAY 34	PRE-DOSE 1	8	-8.25	10.093	-8.50	-28.0	2.3
				4H	8	-9.87	14.164	-6.83	-34.7	8.7
				6H	8	-14.37	8.224	-15.83	-25.7	-2.3
				12H	8	-16.62	13.083	-14.33	-42.0	-2.3
				24H	8	-10.00	8.300	-11.17	-21.7	0.7
			DAY 35	PRE-DOSE 1	8	-7.50	20.018	4.33	-43.0	9.0
			DAY 37	PRE-DOSE 1	8	-7.12	25.648	-1.00	-60.0	19.0
				4H	8	-10.63	21.575	-8.50	-50.0	17.0
				6H	8	-10.00	28.132	-2.33	-60.0	21.7
				12H	8	-4.87	16.920	1.67	-36.0	9.7
				24H	8	-6.50	15.552	-4.50	-38.0	10.0
Diastolic BP (mmHg)	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	-0.11	8.448	1.33	-25.3	10.3
			DAY 12-14	PRE-DOSE 1	27	-0.78	6.770	-1.00	-12.7	13.3
				4H	27	-1.70	8.260	-2.33	-16.3	11.3
				6H	27	-6.70	8.351	-6.67	-27.7	4.3
				12H	27	-6.44	7.247	-6.67	-18.7	6.3
				24H	27	-1.59	7.579	-1.67	-22.3	12.0
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	-6.86	9.566	-4.83	-26.3	12.0

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	-1.21	7.533	-1.67	-16.7	16.3
			DAY 26-28	PRE-DOSE 1	25	0.07	7.518	2.00	-17.3	21.3
				4H	25	0.39	6.533	0.33	-11.7	10.7
				6H	25	-4.69	8.658	-2.67	-29.7	6.0
				12H	25	-0.93	8.340	-1.33	-19.7	17.0
				24H	25	0.15	7.140	1.33	-19.3	11.0
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	-1.58	5.227	-1.67	-9.0	8.3
			DAY 31	PRE-DOSE 1	8	-1.83	5.828	-3.00	-9.0	9.3
				4H	8	-1.71	6.883	-1.67	-10.0	7.3
				6H	8	-5.21	6.705	-6.50	-12.0	6.3
				12H	8	-2.08	4.556	-2.67	-8.0	5.7
				24H	8	2.92	3.753	2.67	-1.7	8.7
			DAY 32	PRE-DOSE 1	9	-6.78	9.094	-2.67	-21.7	2.0
			DAY 34	PRE-DOSE 1	9	-0.67	9.037	0.33	-14.0	13.3
				4H	9	-2.33	11.158	-1.00	-19.7	13.3
				6H	9	-3.33	12.826	-7.67	-20.7	19.3
				12H	9	-1.67	12.131	-3.00	-15.7	24.3
				24H	9	-2.33	10.165	-4.67	-19.7	14.3
			DAY 35	PRE-DOSE 1	8	-7.96	8.977	-6.50	-23.3	2.7
			DAY 37	PRE-DOSE 1	8	0.42	8.759	1.17	-18.3	9.7
				4H	8	0.79	10.046	1.33	-17.3	12.7
				6H	8	-3.33	9.342	-2.50	-21.3	12.7
				12H	8	-0.33	8.599	-1.33	-12.3	12.7
				24H	8	-0.58	6.630	-0.33	-10.3	12.7
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	-6.08	8.368	-4.17	-20.7	2.3

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 31	PRE-DOSE 1	8	0.92	6.281	3.00	-12.7	6.7
				4H	8	-1.96	12.872	2.00	-26.7	11.3
				6H	8	-4.46	10.439	-1.50	-29.7	3.0
				12H	8	-1.33	7.010	-1.67	-8.7	11.3
				24H	8	-0.83	8.591	0.83	-19.7	6.3
			DAY 32	PRE-DOSE 1	8	-3.54	9.137	-1.00	-22.3	7.3
			DAY 34	PRE-DOSE 1	8	-0.29	8.418	1.67	-15.3	9.7
				4H	8	-1.67	7.492	1.83	-18.3	3.7
				6H	8	-2.04	8.201	-3.67	-12.3	16.3
				12H	8	-1.67	9.583	-3.00	-15.3	12.7
				24H	8	-1.04	5.138	0.00	-9.3	5.3
			DAY 35	PRE-DOSE 1	9	-7.70	9.498	-11.67	-17.0	14.3
			DAY 37	PRE-DOSE 1	9	-5.81	12.274	-5.00	-25.0	12.3
				4H	9	-9.26	12.869	-9.67	-31.0	13.3
				6H	9	-5.26	14.069	-6.00	-23.0	26.3
				12H	9	-2.81	8.300	-4.67	-14.0	13.7
				24H	9	-0.15	8.349	0.33	-12.7	15.3
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	-5.78	10.991	-3.33	-22.3	9.3
			DAY 31	PRE-DOSE 1	9	-2.78	5.528	-5.00	-10.3	5.3
				4H	9	-3.11	6.896	-2.00	-17.7	4.7
				6H	9	-5.56	9.272	-3.33	-21.7	8.7
				12H	9	-3.56	6.700	-4.33	-12.7	4.3
				24H	9	-3.33	5.790	-2.67	-11.3	7.7
			DAY 32	PRE-DOSE 1	8	-0.25	7.146	3.00	-16.0	5.0
			DAY 34	PRE-DOSE 1	8	0.00	3.324	0.00	-5.0	4.7
				4H	8	2.13	5.339	2.00	-3.7	12.7
				6H	8	-2.50	4.231	-3.17	-6.7	3.3

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 34	12H	8	-4.88	6.854	-4.33	-15.0	2.7
				24H	8	0.50	6.928	2.33	-11.7	9.0
			DAY 35	PRE-DOSE 1	8	-3.17	6.626	-1.67	-14.7	5.3
			DAY 37	PRE-DOSE 1	8	0.33	8.552	0.50	-11.7	12.3
				4H	8	-3.04	11.509	-1.00	-23.7	11.3
				6H	8	-3.79	12.616	0.33	-24.7	8.3
				12H	8	-0.92	8.681	-1.50	-14.7	15.3
				24H	8	0.58	9.036	3.17	-13.0	11.3
Heart rate (beats/min)	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	0.52	5.686	0.33	-6.7	21.7
			DAY 12-14	PRE-DOSE 1	27	2.01	6.996	2.33	-9.3	19.3
				4H	27	0.35	5.867	-1.67	-8.7	15.3
				6H	27	2.53	6.665	1.67	-8.7	17.3
				12H	27	4.68	6.349	4.00	-4.3	24.7
				24H	27	0.35	5.118	-1.00	-6.3	11.7
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	5.94	7.159	6.17	-6.0	21.3
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	-0.21	5.318	0.00	-12.3	7.7
			DAY 26-28	PRE-DOSE 1	25	0.35	5.898	-0.33	-8.3	12.7
				4H	25	0.55	8.345	0.00	-11.7	32.7
				6H	25	1.63	6.273	1.67	-12.7	12.7
				12H	25	3.43	7.681	4.33	-7.7	23.3
				24H	25	-0.53	4.955	0.00	-9.3	10.3
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	1.79	8.177	3.17	-9.3	15.3

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (fasted)	25	DAY 31	PRE-DOSE 1	8	-1.58	5.485	-1.33	-11.3	6.3
				4H	8	-0.46	5.871	-2.17	-7.3	11.3
				6H	8	1.79	6.894	3.83	-8.3	11.3
				12H	8	5.67	9.338	6.33	-8.3	16.7
				24H	8	1.04	9.353	2.33	-12.3	14.7
			DAY 32	PRE-DOSE 1	9	4.19	7.683	2.00	-5.7	15.7
			DAY 34	PRE-DOSE 1	9	0.74	5.656	1.67	-7.7	8.7
				4H	9	-2.59	6.542	-1.33	-14.7	5.0
				6H	9	-0.48	8.209	-0.67	-11.7	13.0
				12H	9	4.74	9.087	4.67	-8.7	19.7
				24H	9	0.07	5.395	2.00	-6.7	6.7
			DAY 35	PRE-DOSE 1	8	7.58	5.166	7.83	-2.0	15.3
			DAY 37	PRE-DOSE 1	8	2.83	4.209	2.83	-5.0	8.3
				4H	8	2.21	4.280	2.33	-4.0	7.7
				6H	8	4.46	3.509	3.83	0.3	11.3
				12H	8	9.08	6.104	9.83	2.0	16.7
				24H	8	4.83	7.037	3.50	-4.0	16.0
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	5.25	5.288	5.50	-2.7	11.3
			DAY 31	PRE-DOSE 1	8	-1.50	3.271	-2.50	-4.7	5.0
				4H	8	0.87	8.500	-1.33	-10.7	16.3
				6H	8	3.50	8.576	3.67	-8.7	19.3
				12H	8	2.00	6.350	0.67	-4.7	12.0
				24H	8	-2.75	5.695	-1.17	-9.7	5.3
			DAY 32	PRE-DOSE 1	8	7.50	10.209	9.33	-10.0	21.0
			DAY 34	PRE-DOSE 1	8	0.13	4.205	-1.00	-6.0	6.0
				4H	8	4.50	2.296	4.67	1.0	7.3
				6H	8	7.25	6.637	6.67	-1.0	19.7

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Supine

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 34	12H	8	8.00	5.834	9.17	0.0	15.3
				24H	8	3.25	7.750	1.33	-8.0	14.3
			DAY 35	PRE-DOSE 1	9	3.07	6.683	1.67	-5.7	13.3
			DAY 37	PRE-DOSE 1	9	0.30	6.879	-1.33	-8.7	12.7
				4H	9	0.85	7.221	0.33	-8.7	12.7
				6H	9	-0.59	7.316	-1.67	-10.3	15.3
				12H	9	5.85	9.902	6.33	-8.7	23.3
				24H	9	0.63	6.628	0.67	-8.3	11.3
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	4.48	5.886	2.67	-5.7	13.7
			DAY 31	PRE-DOSE 1	9	-1.30	5.628	-1.00	-9.7	7.7
				4H	9	0.70	9.328	2.33	-15.7	12.7
				6H	9	4.70	9.234	5.33	-14.7	16.7
				12H	9	4.59	7.027	5.67	-7.7	14.7
				24H	9	1.04	6.040	2.67	-5.7	12.3
			DAY 32	PRE-DOSE 1	8	7.38	5.894	6.33	-1.0	15.3
			DAY 34	PRE-DOSE 1	8	0.63	8.949	-0.17	-10.3	20.3
				4H	8	-0.63	7.282	-3.50	-8.3	15.3
				6H	8	0.00	7.976	-0.17	-8.3	17.3
				12H	8	2.88	8.225	-1.17	-4.3	20.3
				24H	8	-1.00	5.486	-2.17	-8.3	10.3
			DAY 35	PRE-DOSE 1	8	7.42	7.778	9.83	-8.0	15.3
			DAY 37	PRE-DOSE 1	8	1.29	4.057	2.00	-4.0	6.0
				4H	8	0.79	6.066	1.67	-9.7	7.7
				6H	8	3.67	6.824	4.33	-6.7	13.0
				12H	8	6.17	5.237	6.33	-3.7	11.3
				24H	8	4.29	5.975	3.33	-2.7	14.0

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	-3.20	13.068	-4.33	-26.3	31.7
			DAY 12-14	PRE-DOSE 1	27	-2.94	12.383	-2.33	-28.0	22.7
				4H	27	-9.53	14.741	-10.67	-46.7	22.3
				6H	27	-12.20	18.963	-11.67	-72.7	21.7
				12H	27	-12.01	19.927	-11.00	-58.0	19.0
				24H	27	-2.64	15.002	-5.00	-42.7	26.3
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	-12.31	19.176	-8.00	-53.0	29.0
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	-7.51	17.728	-2.67	-49.7	18.7
			DAY 26-28	PRE-DOSE 1	25	-0.31	14.087	-2.00	-28.0	35.3
				4H	25	-8.03	14.439	-5.33	-49.7	16.7
				6H	25	-9.63	18.730	-6.00	-57.7	13.0
				12H	25	-8.67	17.281	-7.33	-49.7	21.7
				24H	25	-3.99	16.200	-0.33	-49.7	25.7
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	0.54	14.657	4.00	-31.0	12.0
			DAY 31	PRE-DOSE 1	8	-6.08	19.747	-2.50	-32.0	20.7
				4H	8	-16.58	16.831	-11.00	-49.0	1.0
				6H	8	-11.21	13.240	-10.00	-36.0	6.7
				12H	8	-10.71	12.060	-6.67	-33.0	4.3
				24H	8	-1.58	11.818	-1.33	-24.0	18.0
			DAY 32	PRE-DOSE 1	9	-18.04	28.267	-13.67	-60.7	15.3
			DAY 34	PRE-DOSE 1	9	-4.93	24.615	0.67	-44.0	32.3
				4H	9	-13.48	23.557	-14.00	-59.7	17.3
				6H	9	-11.81	23.643	-7.33	-57.7	16.3
				12H	9	-15.15	33.794	-7.33	-61.7	32.3
				24H	9	-18.26	19.268	-10.67	-49.7	6.3

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	1 x 12mg PR/XL 24h (fasted)	25	DAY 35	PRE-DOSE 1	8	-9.71	7.011	-10.33	-18.0	4.7
			DAY 37	PRE-DOSE 1	8	-2.08	6.849	-2.83	-11.0	7.7
				4H	8	-4.08	10.518	-5.83	-17.0	9.7
				6H	8	-5.46	19.507	-2.67	-39.0	21.0
				12H	8	-5.96	18.914	-8.00	-39.0	20.7
				24H	8	4.42	16.399	4.83	-18.0	32.0
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	-3.33	19.293	2.00	-37.3	20.7
			DAY 31	PRE-DOSE 1	8	-2.46	11.048	-2.67	-18.3	14.3
				4H	8	-5.46	18.196	-10.17	-28.3	19.0
				6H	8	-6.08	18.482	-2.00	-47.3	11.3
				12H	8	0.17	12.151	-2.00	-17.0	17.0
				24H	8	-3.83	21.131	-5.17	-39.0	32.7
			DAY 32	PRE-DOSE 1	8	-2.33	21.669	-5.33	-31.0	36.0
			DAY 34	PRE-DOSE 1	8	-2.46	11.521	-3.17	-18.7	13.0
				4H	8	-4.58	12.312	-5.67	-18.0	22.0
				6H	8	-9.21	14.748	-7.00	-34.0	8.7
				12H	8	-7.46	11.987	-2.50	-31.0	3.7
				24H	8	-7.58	11.425	-8.17	-27.0	10.3
			DAY 35	PRE-DOSE 1	9	-22.70	23.827	-18.00	-67.7	4.7
			DAY 37	PRE-DOSE 1	9	-15.81	31.205	-9.33	-62.3	29.3
				4H	9	-21.81	20.526	-22.00	-51.7	4.7
				6H	9	-23.81	25.439	-27.33	-59.7	25.3
				12H	9	-19.37	21.295	-21.33	-43.7	15.7
				24H	9	-5.93	18.124	-10.33	-32.0	16.0
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	-20.15	21.335	-17.67	-64.0	1.7

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 31	PRE-DOSE 1	9	-16.93	25.028	-9.33	-61.7	7.7
				4H	9	-14.26	20.624	-6.00	-63.7	1.7
				6H	9	-25.26	23.696	-22.00	-67.7	-0.3
				12H	9	-9.48	17.112	-5.33	-43.7	12.7
				24H	9	-12.37	15.716	-9.33	-41.0	9.3
			DAY 32	PRE-DOSE 1	8	-5.58	14.933	-3.00	-37.3	11.7
			DAY 34	PRE-DOSE 1	8	-8.58	7.657	-6.33	-21.7	3.0
				4H	8	-8.71	7.258	-11.50	-16.0	6.0
				6H	8	-12.46	12.953	-13.67	-32.0	3.0
				12H	8	-17.58	22.574	-15.50	-57.0	8.0
				24H	8	-8.96	14.240	-13.33	-23.3	22.7
			DAY 35	PRE-DOSE 1	8	-13.96	29.384	-3.83	-61.3	11.0
			DAY 37	PRE-DOSE 1	8	-7.33	21.899	-8.17	-46.0	22.0
				4H	8	-8.96	19.042	-10.83	-43.0	17.0
				6H	8	-4.96	18.630	-3.17	-46.0	12.3
				12H	8	-4.71	12.525	0.33	-24.3	5.3
				24H	8	-7.21	16.002	-4.17	-33.0	11.0
Diastolic BP (mmHg)	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	2.19	7.261	0.50	-11.3	20.0
			DAY 12-14	PRE-DOSE 1	27	-0.67	7.222	0.67	-17.3	11.7
				4H	27	-0.93	9.134	1.67	-20.3	14.3
				6H	27	-6.96	10.049	-5.67	-39.3	11.7
				12H	27	-4.74	9.436	-3.33	-22.0	17.7
				24H	27	-0.56	6.886	-1.33	-14.3	12.0
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	-7.33	9.701	-4.33	-27.3	8.7

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	-0.97	8.115	-1.33	-19.3	13.7
			DAY 26-28	PRE-DOSE 1	25	1.47	9.996	1.67	-24.3	20.3
				4H	25	-0.65	8.854	-1.33	-15.3	18.0
				6H	25	-2.77	11.212	-1.00	-41.3	11.7
				12H	25	-2.69	13.237	-0.67	-43.0	17.7
				24H	25	0.71	9.125	1.00	-21.3	19.7
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	1.42	5.471	1.33	-5.3	10.7
			DAY 31	PRE-DOSE 1	8	-1.46	7.402	-1.67	-9.3	12.0
				4H	8	-1.83	7.165	0.33	-12.3	6.7
				6H	8	-1.83	5.300	-0.83	-9.3	4.0
				12H	8	1.79	7.699	0.33	-6.3	19.0
				24H	8	3.42	4.793	3.83	-5.0	10.7
			DAY 32	PRE-DOSE 1	9	-8.59	12.817	-3.67	-29.3	4.0
			DAY 34	PRE-DOSE 1	9	1.41	11.248	2.67	-16.3	17.3
				4H	9	-4.93	14.145	-5.33	-29.3	12.0
				6H	9	-4.15	14.668	-1.33	-28.3	18.3
				12H	9	-4.37	15.420	-5.33	-27.3	22.3
				24H	9	0.07	11.944	-1.33	-17.3	16.0
			DAY 35	PRE-DOSE 1	8	-5.67	7.400	-6.17	-15.3	8.7
			DAY 37	PRE-DOSE 1	8	2.71	9.221	0.50	-13.0	16.0
				4H	8	4.33	8.524	2.33	-10.3	15.0
				6H	8	-0.17	12.891	-0.33	-23.0	19.0
				12H	8	0.21	10.820	-2.33	-11.3	19.7
				24H	8	7.46	15.053	4.17	-5.0	42.3
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	-2.04	8.245	-1.33	-17.0	11.0

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 31	PRE-DOSE 1	8	3.71	5.664	4.83	-4.3	12.0
				4H	8	-4.17	6.547	-4.50	-15.3	6.0
				6H	8	-1.42	6.104	-1.67	-8.7	7.0
				12H	8	-1.42	7.510	0.83	-19.3	4.3
				24H	8	3.33	14.203	0.17	-8.7	33.0
			DAY 32	PRE-DOSE 1	8	-1.21	8.850	0.17	-13.3	10.7
			DAY 34	PRE-DOSE 1	8	1.29	5.144	2.17	-5.3	8.7
				4H	8	-2.71	8.901	-1.17	-19.0	7.7
				6H	8	-3.71	9.169	-5.33	-12.0	16.7
				12H	8	3.04	5.788	2.83	-5.3	11.7
				24H	8	-1.33	7.807	-0.17	-15.3	8.7
			DAY 35	PRE-DOSE 1	9	-8.48	12.119	-7.33	-26.3	10.3
			DAY 37	PRE-DOSE 1	9	-7.15	14.366	-0.33	-25.3	14.3
				4H	9	-10.70	10.715	-9.00	-30.3	1.3
				6H	9	-7.48	15.426	-9.00	-27.3	17.3
				12H	9	-7.70	7.273	-7.33	-18.3	4.0
				24H	9	-1.70	9.091	0.67	-16.3	9.0
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	-4.93	12.881	-3.33	-25.3	11.3
			DAY 31	PRE-DOSE 1	9	-4.93	11.536	-0.33	-23.3	8.0
				4H	9	-7.59	11.652	-6.67	-34.3	3.0
				6H	9	-11.37	13.264	-14.00	-33.3	7.7
				12H	9	-2.48	8.007	-2.33	-17.3	8.0
				24H	9	-1.59	8.348	1.67	-14.3	8.7
			DAY 32	PRE-DOSE 1	8	-0.29	6.668	0.83	-9.3	8.0
			DAY 34	PRE-DOSE 1	8	-0.04	6.552	-0.83	-9.3	10.7
				4H	8	2.08	4.911	1.67	-6.3	9.0
				6H	8	-1.79	8.643	-2.33	-12.7	9.7

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 34	12H	8	-6.92	8.288	-7.50	-16.0	3.0
				24H	8	-1.29	10.018	-4.67	-16.0	12.3
			DAY 35	PRE-DOSE 1	8	-3.33	10.511	-0.17	-23.0	8.7
			DAY 37	PRE-DOSE 1	8	1.42	10.732	4.50	-20.3	13.7
				4H	8	-0.46	10.073	-2.67	-12.3	13.0
				6H	8	-3.21	8.599	-3.67	-15.3	12.7
				12H	8	1.17	6.852	1.83	-8.3	10.7
				24H	8	5.79	10.016	6.83	-9.3	18.7
Heart rate (beats/min)	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE 1	28	1.25	8.688	0.17	-15.7	30.7
			DAY 12-14	PRE-DOSE 1	27	0.27	6.863	1.33	-18.3	11.7
				4H	27	2.53	10.482	1.67	-29.3	26.0
				6H	27	3.60	8.693	5.67	-23.3	21.0
				12H	27	6.75	8.364	7.33	-7.7	30.0
				24H	27	3.23	8.362	2.67	-16.7	25.3
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE 1	26	10.08	10.272	9.33	-6.7	33.7
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE 1	25	-1.32	7.642	-1.67	-14.7	13.7
			DAY 26-28	PRE-DOSE 1	25	1.24	7.905	-1.33	-8.3	20.0
				4H	25	1.96	8.601	0.00	-14.7	20.7
				6H	25	3.16	8.233	1.33	-14.7	22.7
				12H	25	4.36	8.717	6.33	-8.7	27.7
				24H	25	1.84	7.632	0.67	-12.7	19.3
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	8	2.42	8.896	2.33	-10.3	16.0

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (fasted)	25	DAY 31	PRE-DOSE 1	8	0.79	8.624	3.00	-12.3	10.7
				4H	8	4.79	7.030	4.33	-6.3	14.7
				6H	8	7.92	8.695	10.00	-5.3	21.7
				12H	8	12.04	10.599	10.67	-5.3	28.7
				24H	8	3.42	12.000	6.00	-15.7	21.7
			DAY 32	PRE-DOSE 1	9	7.67	9.144	6.33	-4.3	18.3
			DAY 34	PRE-DOSE 1	9	-1.78	5.121	-1.33	-9.7	6.3
				4H	9	1.11	6.543	2.33	-10.7	12.7
				6H	9	3.00	7.596	4.67	-10.7	13.7
				12H	9	8.78	8.542	6.67	0.3	25.7
				24H	9	8.44	5.786	8.00	-1.3	16.7
			DAY 35	PRE-DOSE 1	8	9.71	9.014	12.67	-3.7	22.7
			DAY 37	PRE-DOSE 1	8	-2.29	14.919	1.67	-33.3	11.3
				4H	8	6.58	7.474	7.17	-4.7	17.7
				6H	8	6.46	6.773	6.67	-5.7	17.7
				12H	8	8.71	8.072	8.67	-4.7	18.7
				24H	8	7.08	11.672	8.00	-10.7	26.7
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE 1	8	6.42	9.312	4.50	-3.7	19.0
			DAY 31	PRE-DOSE 1	8	-4.33	4.754	-5.00	-10.7	2.7
				4H	8	-2.33	8.190	-2.67	-16.7	8.7
				6H	8	-0.71	8.464	-0.67	-16.7	11.7
				12H	8	3.17	13.813	-2.50	-11.7	26.7
				24H	8	-2.21	9.210	-1.00	-16.7	12.7
			DAY 32	PRE-DOSE 1	8	8.75	10.410	11.83	-15.7	17.3
			DAY 34	PRE-DOSE 1	8	3.50	6.299	3.83	-9.7	9.7
				4H	8	11.00	7.216	9.50	4.7	26.7
				6H	8	12.50	8.416	10.17	0.7	25.7

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

[redacted]

CONFIDENTIAL

Table 10.12
Summary of Change from Baseline for Vital Signs

Position: Standing

	Treatment	N	Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 34	12H	8	12.38	8.824	12.83	1.7	27.7
				24H	8	7.38	9.658	7.17	-3.7	23.7
			DAY 35	PRE-DOSE 1	9	6.85	8.398	10.33	-4.3	15.3
			DAY 37	PRE-DOSE 1	9	-0.37	5.879	-2.00	-7.7	9.3
				4H	9	3.07	5.899	3.33	-3.3	15.0
				6H	9	1.96	7.649	0.67	-8.3	19.0
				12H	9	6.19	7.426	4.00	0.7	25.0
				24H	9	2.96	6.253	2.33	-5.3	13.0
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE 1	9	8.26	6.825	10.33	-3.0	19.3
			DAY 31	PRE-DOSE 1	9	-1.52	3.934	-1.67	-5.3	6.3
				4H	9	3.15	7.522	3.33	-6.3	17.0
				6H	9	7.48	9.472	9.67	-7.7	21.3
				12H	9	7.93	6.405	8.33	-1.7	18.0
				24H	9	6.26	6.551	5.67	-4.3	18.3
			DAY 32	PRE-DOSE 1	8	8.00	11.006	10.67	-6.3	21.7
			DAY 34	PRE-DOSE 1	8	-2.38	8.216	-5.00	-10.7	14.0
				4H	8	1.62	6.802	-0.67	-5.7	15.0
				6H	8	2.00	10.156	-1.67	-6.3	24.0
				12H	8	1.62	9.797	-1.33	-7.7	22.7
				24H	8	-2.63	5.927	-3.83	-9.7	10.0
			DAY 35	PRE-DOSE 1	8	10.58	11.048	10.17	-3.7	27.0
			DAY 37	PRE-DOSE 1	8	1.21	4.055	0.50	-4.7	7.7
				4H	8	2.21	9.440	3.00	-17.7	12.7
				6H	8	8.08	10.874	9.17	-10.7	24.7
				12H	8	11.46	8.958	11.50	-3.7	28.7
				24H	8	9.58	7.300	9.00	1.3	20.7

NOTE: Baseline is defined as the average of the 3 Pre-Dose values on Day 1

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		> PCI ranges	0	4 (14%)	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	4 (15%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	8 (30%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	7 (26%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	11 (42%)	0	0	0	0
DAY 22	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	2 (8%)	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	5 (20%)	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	4H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	3 (12%)	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	12H	n	0	0	0	25	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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HM2007/00444/00
ROP109087

Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 26-28	12H	> PCI ranges	0	0	0	4 (16%)	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	3 (12%)	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	1 (13%)	1 (11%)
		< PCI ranges	0	0	0	0	0	1 (13%)	3 (33%)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	1 (13%)	0
		< PCI ranges	0	0	0	0	0	0	2 (22%)
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	1 (13%)	2 (22%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	5 (56%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 31	12H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	0	1 (13%)	2 (22%)
	24H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	2 (25%)	0
		< PCI ranges	0	0	0	0	0	0	3 (33%)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	3 (33%)	2 (25%)	0
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	2 (22%)	0	1 (13%)
		< PCI ranges	0	0	0	0	2 (22%)	0	0
	4H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	2 (22%)	0	0
		< PCI ranges	0	0	0	0	2 (22%)	1 (13%)	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
		< PCI ranges	0	0	0	0	2 (22%)	2 (25%)	1 (13%)
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
		< PCI ranges	0	0	0	0	3 (33%)	0	4 (50%)
	24H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	3 (33%)	0	2 (25%)
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	1 (13%)
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
		< PCI ranges	0	0	0	0	2 (25%)	3 (33%)	2 (25%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	2 (25%)	1 (11%)	1 (13%)
		< PCI ranges	0	0	0	0	1 (13%)	4 (44%)	1 (13%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	4H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	3 (38%)	0	2 (25%)
		< PCI ranges	0	0	0	0	1 (13%)	4 (44%)	2 (25%)
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	2 (25%)	2 (22%)	1 (13%)
		< PCI ranges	0	0	0	0	1 (13%)	3 (33%)	1 (13%)
	12H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	2 (25%)	0	1 (13%)
		< PCI ranges	0	0	0	0	2 (25%)	4 (44%)	0
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	2 (25%)
		< PCI ranges	0	0	0	0	0	2 (22%)	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	5 (19%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	6 (22%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	7 (26%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	8 (30%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		> PCI ranges	0	0	1 (4%)	0	0	0	0
		< PCI ranges	0	0	11 (42%)	0	0	0	0
DAY 22	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	2 (8%)	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
	4H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
	12H	n	0	0	0	25	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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HM2007/00444/00
ROP109087

Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 26-28	12H	> PCI ranges	0	0	0	2 (8%)	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	2 (25%)	3 (33%)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	1 (13%)	1 (11%)
	4H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	0	2 (25%)	1 (11%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	3 (38%)	1 (13%)	2 (22%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 31	12H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	0	0	2 (22%)
	24H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	1 (13%)	1 (11%)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	1 (13%)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	2 (22%)	1 (13%)	0
	4H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	1 (13%)
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	0
	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	6H	< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	0
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
		< PCI ranges	0	0	0	0	2 (22%)	2 (25%)	2 (25%)
	24H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	2 (22%)	0	1 (13%)
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
		< PCI ranges	0	0	0	0	2 (25%)	5 (56%)	1 (13%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	2 (25%)
		< PCI ranges	0	0	0	0	1 (13%)	4 (44%)	1 (13%)
	4H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	2 (25%)	1 (11%)	1 (13%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	4H	< PCI ranges	0	0	0	0	1 (13%)	4 (44%)	2 (25%)
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	1 (11%)	0
		< PCI ranges	0	0	0	0	1 (13%)	3 (33%)	2 (25%)
	12H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	1 (11%)	1 (13%)
		< PCI ranges	0	0	0	0	1 (13%)	1 (11%)	1 (13%)
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	1 (11%)	1 (13%)
		< PCI ranges	0	0	0	0	1 (13%)	1 (11%)	2 (25%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		> PCI ranges	0	3 (11%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		> PCI ranges	0	3 (11%)	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		> PCI ranges	0	0	8 (31%)	0	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	2 (8%)	0	0	0
	4H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	3 (12%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	3 (12%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	3 (12%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	2 (25%)	1 (11%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 31	4H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	0	1 (11%)
		< PCI ranges	0	0	0	0	0	1 (13%)	0
	6H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	0	1 (11%)
		< PCI ranges	0	0	0	0	0	1 (13%)	0
	12H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	3 (38%)	2 (25%)	2 (22%)
	24H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	0	1 (11%)
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	0
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	4 (44%)	2 (25%)	2 (25%)
		< PCI ranges	0	0	0	0	0	1 (13%)	0
DAY 34	4H	n	0	0	0	0	9	8	8

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	4H	> PCI ranges	0	0	0	0	0	1 (13%)	0
	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	2 (25%)	1 (13%)
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	2 (22%)	3 (38%)	1 (13%)
	24H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	2 (22%)	1 (13%)	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	1 (11%)	2 (25%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	0	0
	4H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	0	0	1 (13%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	1 (11%)	2 (25%)
	12H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	3 (38%)	1 (11%)	1 (13%)
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	2 (25%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		> PCI ranges	0	0	2 (8%)	0	0	0	0
DAY 26-28	4H	n	0	0	0	25	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 26-28	4H	> PCI ranges	0	0	0	1 (4%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	0	0
DAY 31	4H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	0	0	1 (11%)
	6H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	1 (11%)
	12H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	2 (25%)	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	2 (25%)	1 (13%)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	0	1 (13%)
	4H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	0	1 (13%)
	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	1 (13%)	1 (13%)
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	1 (13%)
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	1 (13%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside Range of Potential Clinical Importance - FDA

Parameter: Heart rate (beats/min) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
	12H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	2 (25%)	1 (11%)	0
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	5 (19%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	6 (22%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	10 (37%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		> PCI ranges	0	0	1 (4%)	0	0	0	0
		< PCI ranges	0	0	6 (23%)	0	0	0	0
DAY 22	PRE-DOSE 1	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
	4H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	5 (20%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	7 (28%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	6 (24%)	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 26-28	24H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	1 (13%)	2 (25%)	3 (33%)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	2 (25%)	0	3 (33%)
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	2 (25%)	2 (22%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	1 (13%)	5 (56%)
	12H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	0	2 (22%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

[redacted]

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 31	24H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	2 (22%)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	1 (13%)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	2 (22%)	0	1 (13%)
	4H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	2 (22%)	0	0
	6H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	3 (33%)	2 (25%)	3 (38%)
	12H	n	0	0	0	0	9	8	8

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	12H	> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	4 (44%)	1 (13%)	4 (50%)
	24H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	0	1 (13%)
		< PCI ranges	0	0	0	0	4 (44%)	1 (13%)	1 (13%)
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	4 (44%)	2 (25%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	1 (13%)
		< PCI ranges	0	0	0	0	0	3 (33%)	2 (25%)
	4H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	6 (67%)	1 (13%)
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	1 (11%)	0
		< PCI ranges	0	0	0	0	2 (25%)	6 (67%)	1 (13%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	12H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	1 (13%)	6 (67%)	2 (25%)
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	0	2 (22%)	2 (25%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	6 (22%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	11 (41%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	6 (22%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		> PCI ranges	0	2 (7%)	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	8 (31%)	0	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 22	PRE-DOSE 1	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	4H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	6 (24%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	0	1 (11%)
		< PCI ranges	0	0	0	0	1 (13%)	2 (25%)	4 (44%)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	3 (38%)	0	0
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	3 (38%)	3 (38%)	1 (11%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	3 (38%)	3 (33%)
	12H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	0	1 (11%)
		< PCI ranges	0	0	0	0	2 (25%)	0	1 (11%)
	24H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	1 (11%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	0	1 (13%)
		< PCI ranges	0	0	0	0	4 (44%)	1 (13%)	2 (25%)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	1 (13%)
	4H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	2 (22%)	0	0
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	2 (25%)
	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	2 (25%)
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	3 (38%)
	24H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	24H	< PCI ranges	0	0	0	0	2 (22%)	1 (13%)	1 (13%)
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
		< PCI ranges	0	0	0	0	2 (25%)	3 (33%)	3 (38%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	2 (22%)	0
		< PCI ranges	0	0	0	0	1 (13%)	3 (33%)	2 (25%)
	4H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	2 (22%)	0
		< PCI ranges	0	0	0	0	1 (13%)	5 (56%)	2 (25%)
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	1 (13%)
		< PCI ranges	0	0	0	0	3 (38%)	3 (33%)	2 (25%)
	12H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.13
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - FDA

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	12H	< PCI ranges	0	0	0	0	1 (13%)	1 (11%)	2 (25%)
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
		< PCI ranges	0	0	0	0	1 (13%)	1 (11%)	1 (13%)

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 12-14	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	2 (8%)	0	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	1 (11%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

[redacted]

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	2 (22%)
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	1 (11%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	2 (22%)
	24H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	0	0
DAY 34	4H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	0	0
	6H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	0	0
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	2 (22%)	0	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	2 (22%)	1 (13%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

[redacted]

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	2 (22%)	1 (13%)
	4H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	2 (22%)	0
	6H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	2 (22%)	0
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

[redacted]

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
DAY 12-14	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	3 (12%)	0	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	1 (13%)	2 (22%)
DAY 31	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	1 (13%)	0

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Diastolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 31	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	1 (13%)	1 (11%)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	1 (13%)	0
DAY 34	6H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	0	0
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	0	0
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	0
	4H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	1 (13%)
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
		< PCI ranges	0	0	0	0	1 (13%)	1 (11%)	2 (25%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		> PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	5 (19%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		< PCI ranges	0	2 (7%)	0	0	0	0	0
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	5 (19%)	0	0	0	0
DAY 22	PRE-DOSE 1	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	4 (16%)	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
	4H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

[redacted]

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 26-28	6H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	2 (22%)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	0	2 (22%)
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	0	1 (11%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	3 (33%)
	12H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	0	1 (11%)
	24H	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	0	1 (13%)	2 (22%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	0	1 (13%)	0
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	1 (13%)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	2 (22%)	0	0
	4H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	0	0
	6H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	1 (13%)	1 (13%)
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	3 (33%)	1 (13%)	3 (38%)
	24H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	3 (33%)	0	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	2 (22%)	2 (25%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	3 (33%)	1 (13%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	4H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	3 (33%)	1 (13%)
	6H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	3 (33%)	1 (13%)
	12H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	4 (44%)	0
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0
		< PCI ranges	0	0	0	0	0	2 (22%)	1 (13%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	5 (19%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	4 (15%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	2 (8%)	0	0	0	0
DAY 22	PRE-DOSE 1	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	2 (8%)	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
	4H	n	0	0	0	25	0	0	0

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 26-28	4H	< PCI ranges	0	0	0	1 (4%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	3 (12%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	2 (25%)	1 (11%)
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	0	0
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	1 (11%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	1 (13%)	1 (11%)
	12H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	2 (25%)	0	0
	24H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	0	0
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	1 (13%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	0	1 (13%)	0
	4H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	1 (13%)
	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
		< PCI ranges	0	0	0	0	0	1 (13%)	1 (13%)
	24H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	0	1 (13%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	2 (22%)	1 (13%)
	4H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
		< PCI ranges	0	0	0	0	0	4 (44%)	2 (25%)
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.14
Summary of Number of Change from Baseline Vital Signs Outside
Range of Potential Clinical Importance - Europe

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	6H	< PCI ranges	0	0	0	0	1 (13%)	2 (22%)	2 (25%)
	12H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	0	1 (13%)
	24H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	0	1 (13%)

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.15
Summary of Urinalysis Dipstick Results

No data to report

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Table 10.16
Summary of Investigational Product Status

	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
Completion Status							
Completed	28 (100%)	26 (93%)	25 (96%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)
Prematurely discontinued	0	2 (7%)	1 (4%)	0	0	0	0
Reason for Discontinuation							
Adverse event	0	1 (4%)	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Subject decided to withdraw	0	1 (4%)	1 (4%)	0	0	0	0
Lack of efficacy	0	0	0	0	0	0	0
Sponsor terminated study	0	0	0	0	0	0	0
Disease progression	0	0	0	0	0	0	0
Other, specify	0	0	0	0	0	0	0

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	27	131.8	17.86	132.0	91	159
				<0.5	2	136.0	16.97	136.0	124	148
				1	28	123.3	16.60	120.5	95	166
				2	26	128.2	16.48	125.5	103	160
				3	24	131.1	19.60	132.0	81	164
				4	26	127.3	16.33	127.0	94	155
				5	28	126.6	19.20	124.5	75	162
				6	26	121.7	12.92	121.5	99	144
				7	26	127.0	16.32	123.5	101	164
				8	27	127.9	20.34	124.0	69	167
				9	25	129.9	14.23	127.0	101	153
				10	26	126.8	15.67	128.5	85	163
				11	28	129.0	15.32	130.0	94	158
				12	27	128.1	18.26	130.0	88	173
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE	28	136.1	16.91	137.5	96	161
				<0.5	4	127.0	5.94	128.5	119	132
				1	27	128.6	18.77	130.0	95	161
				2	28	129.6	17.91	127.0	102	166
				3	26	128.8	18.47	122.5	112	188
				4	24	126.7	16.20	123.5	103	157
				5	23	126.5	20.15	126.0	91	171
				6	23	128.2	15.24	128.0	94	157
				7	26	128.6	17.60	127.5	90	162
				8	26	129.5	20.12	130.0	86	170

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	4 mg PR/XL 24h	28	DAY 8	9	27	132.7	15.42	134.0	106	166
				10	27	132.9	13.99	135.0	108	161
				11	28	130.9	18.63	130.5	100	180
				12	27	129.1	16.64	128.0	102	163
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE	26	132.5	13.17	133.0	98	154
				<0.5	4	121.3	13.55	122.0	106	135
				1	25	125.1	15.11	124.0	93	154
				2	22	129.4	14.77	124.5	104	157
				3	18	127.9	20.63	125.0	91	165
				4	22	128.4	17.51	131.0	96	173
				5	24	122.6	17.73	124.5	72	169
				6	22	125.1	18.50	125.5	75	175
				7	24	125.0	21.15	124.5	73	183
				8	23	128.0	17.32	127.0	97	166
				9	25	129.9	15.36	131.0	104	160
				10	24	131.2	18.82	129.0	107	193
				11	25	125.0	19.07	126.0	89	162
				12	23	128.0	15.90	130.0	103	164
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE	24	129.0	12.72	130.0	98	159
				<0.5	5	128.6	9.18	132.0	113	137
				1	25	129.2	13.82	129.0	102	156

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	8 mg PR/XL 24h	25	DAY 22	2	24	128.0	13.03	128.0	108	153
				3	24	128.7	17.06	128.5	96	172
				4	23	129.9	15.31	129.0	101	161
				5	22	126.8	18.24	128.5	91	165
				6	23	129.4	16.86	132.0	85	154
				7	23	131.8	20.01	130.0	90	179
				8	22	127.5	14.86	129.5	95	148
				9	24	136.3	16.85	136.5	94	167
				10	24	134.7	18.30	135.0	89	175
				11	25	137.4	24.90	132.0	87	210
				12	24	131.7	18.66	131.5	96	166
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE	8	129.1	10.23	127.0	119	149
				1	7	123.7	10.89	123.0	110	141
				2	8	132.8	16.26	133.0	111	159
				3	8	135.6	19.99	132.5	110	169
				4	8	129.4	14.26	133.0	107	147
				5	8	120.8	14.58	118.0	104	151
				6	8	124.0	14.98	118.0	101	143
				7	8	121.3	10.19	116.5	112	140
				8	8	124.1	11.69	120.5	113	146
				9	8	128.6	8.93	127.5	118	141
				10	7	129.1	7.47	130.0	115	137
				11	8	129.9	14.24	131.0	104	150

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	12	7	129.9	11.38	129.0	115	143
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE	8	134.6	21.78	132.0	107	169
				<0.5	3	128.7	10.60	127.0	119	140
				1	8	126.4	14.20	125.0	110	148
				2	7	129.1	10.22	130.0	112	141
				3	8	121.5	13.52	121.5	95	138
				4	8	129.0	13.50	127.0	107	150
				5	6	123.0	11.76	121.5	108	136
				6	8	128.4	17.61	125.0	109	153
				7	7	124.3	7.87	128.0	113	131
				8	8	128.0	11.48	125.5	113	145
				9	8	125.5	13.55	123.5	108	147
				10	8	131.3	14.42	131.0	117	163
				11	8	127.5	14.51	131.5	106	146
				12	6	121.5	19.48	122.5	98	147
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE	9	135.9	21.76	126.0	108	171
				<0.5	2	130.5	27.58	130.5	111	150
				1	9	131.4	18.18	131.0	107	167

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	2	8	124.6	15.83	123.5	104	157
				3	8	125.3	21.83	121.0	101	170
				4	9	127.2	18.22	129.0	105	161
				5	9	127.0	21.24	127.0	97	167
				6	9	128.4	16.72	124.0	108	163
				7	9	129.4	25.91	128.0	100	187
				8	9	130.3	28.35	123.0	101	194
				9	9	127.3	16.48	134.0	101	147
				10	9	133.1	18.56	131.0	109	164
				11	9	128.0	17.09	125.0	100	151
				12	7	129.3	10.70	130.0	108	140

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	27	77.9	9.56	78.0	53	95
				<0.5	2	70.0	4.24	70.0	67	73
				1	28	70.8	10.68	71.0	47	92
				2	26	75.2	7.42	75.0	63	91
				3	24	79.9	10.69	82.0	44	96
				4	26	77.5	9.78	76.0	58	97
				5	28	77.1	11.11	78.5	48	99
				6	26	78.0	7.60	79.0	65	94
				7	26	79.0	10.62	77.0	57	101
				8	27	79.9	12.44	79.0	41	106
				9	25	78.0	10.38	78.0	55	96
				10	26	77.8	11.62	80.0	47	101
				11	28	76.5	10.76	73.5	59	94
				12	27	77.5	10.11	77.0	57	100
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE	28	80.4	10.96	81.0	58	104
				<0.5	4	73.3	12.31	72.5	60	88
				1	27	73.1	11.09	74.0	46	90
				2	28	75.9	9.12	76.0	60	93
				3	26	78.0	11.39	80.0	60	100
				4	24	78.0	10.08	81.0	58	97
				5	23	75.8	12.57	78.0	54	97
				6	23	79.1	8.56	79.0	62	93
				7	26	78.4	11.21	77.0	62	117
				8	26	76.9	11.40	79.0	55	100

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	4 mg PR/XL 24h	28	DAY 8	9	27	82.7	8.79	82.0	64	99
				10	27	80.8	9.30	80.0	64	99
				11	28	79.2	12.36	79.0	52	107
				12	27	79.6	11.11	76.0	62	102
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE	26	76.0	5.92	76.0	65	83
				<0.5	4	69.3	5.12	70.5	62	74
				1	25	73.0	11.44	75.0	37	87
				2	22	78.5	7.99	80.0	63	95
				3	18	76.1	12.19	77.5	56	102
				4	22	80.1	12.23	80.0	56	100
				5	24	77.9	11.25	78.0	54	102
				6	22	77.0	12.13	78.5	48	101
				7	24	80.5	12.61	81.0	49	104
				8	23	81.0	8.67	81.0	67	104
				9	25	80.8	10.16	80.0	64	97
				10	24	80.1	10.70	80.0	61	110
				11	25	76.9	12.21	78.0	57	104
				12	23	76.9	9.74	74.0	64	103
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE	24	76.0	9.88	74.0	62	102
				<0.5	5	75.8	6.10	78.0	66	81
				1	25	74.5	9.93	75.0	52	97

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	8 mg PR/XL 24h	25	DAY 22	2	24	77.7	9.71	76.5	63	94
				3	24	80.0	9.55	81.0	58	97
				4	23	80.5	10.41	78.0	61	98
				5	22	79.0	13.30	78.5	46	107
				6	23	78.0	10.18	79.0	48	92
				7	23	81.1	11.12	82.0	51	102
				8	22	80.0	16.19	85.0	52	114
				9	24	82.8	11.61	85.0	49	101
				10	24	82.3	12.80	85.0	45	101
				11	25	80.4	12.70	80.0	48	102
				12	24	79.7	10.60	79.5	61	99
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE	8	72.9	4.82	71.5	68	82
				1	7	70.7	9.67	66.0	59	87
				2	8	76.6	13.65	75.5	50	94
				3	8	81.8	12.65	78.5	68	100
				4	8	78.4	10.45	79.0	63	94
				5	8	76.5	14.83	74.5	56	107
				6	8	79.8	10.00	81.0	64	93
				7	8	74.6	11.64	73.0	61	98
				8	8	74.6	9.21	73.5	59	87
				9	8	78.9	3.76	79.5	71	83
				10	7	79.3	6.05	80.0	68	85
				11	8	77.5	17.24	80.0	52	97

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	12	7	74.0	10.50	73.0	59	90
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE	8	76.4	6.80	78.5	62	83
				<0.5	3	76.3	2.52	76.0	74	79
				1	8	76.8	7.76	74.5	66	90
				2	7	79.6	6.32	81.0	71	87
				3	8	80.0	7.96	80.5	66	91
				4	8	80.6	4.93	80.5	73	88
				5	6	79.5	5.96	78.0	73	89
				6	8	81.4	8.81	79.5	71	94
				7	7	79.0	6.81	81.0	67	87
				8	8	79.4	6.65	78.5	72	92
				9	8	78.4	5.24	78.0	72	86
				10	8	82.5	8.30	80.5	73	101
				11	8	81.5	10.24	85.0	64	95
				12	6	76.7	6.86	77.0	66	86
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE	9	78.1	10.11	78.0	64	94
				<0.5	2	78.0	12.73	78.0	69	87
				1	9	76.0	8.23	74.0	67	96

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	2	8	73.8	6.58	72.5	67	85
				3	8	78.0	7.84	78.0	66	87
				4	9	75.3	5.59	76.0	69	84
				5	9	74.8	8.15	72.0	67	91
				6	9	80.9	6.60	80.0	73	95
				7	9	78.2	8.04	78.0	69	92
				8	9	75.3	11.98	77.0	62	96
				9	9	76.7	8.97	75.0	62	90
				10	9	78.0	5.07	76.0	71	85
				11	9	76.7	10.34	74.0	62	95
				12	7	74.7	4.72	75.0	67	82

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	2 mg PR/XL 24h	28	DAY 1	PRE-DOSE	27	80.6	12.02	82.0	55	101
				<0.5	2	77.0	7.07	77.0	72	82
				1	28	72.3	10.48	71.0	53	92
				2	26	71.5	12.07	71.0	50	101
				3	24	77.4	12.37	76.5	59	111
				4	26	82.9	19.82	81.0	60	160
				5	28	79.9	13.09	81.0	55	116
				6	26	79.0	14.78	79.0	54	113
				7	26	76.4	12.62	74.0	50	103
				8	27	74.6	14.19	72.0	52	106
				9	25	72.9	10.75	70.0	54	102
				10	26	74.4	12.20	70.5	56	96
				11	28	74.4	13.04	72.0	50	115
				12	27	73.7	12.11	74.0	48	101
	4 mg PR/XL 24h	28	DAY 8	PRE-DOSE	28	79.2	10.95	78.0	61	111
				<0.5	4	82.0	14.58	77.5	70	103
				1	27	73.0	9.40	71.0	57	97
				2	28	73.1	9.95	71.0	57	94
				3	26	79.0	15.14	78.0	58	131
				4	24	74.7	10.91	75.0	55	107
				5	23	74.7	11.04	76.0	54	92
				6	23	76.5	10.11	76.0	60	94
				7	26	75.4	10.86	71.5	62	96
				8	26	77.1	11.77	77.5	54	104
				9	27	75.7	12.85	74.0	57	110

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	4 mg PR/XL 24h	28	DAY 8	10	27	73.4	10.17	71.0	55	100
				11	28	74.7	9.80	75.0	51	97
				12	27	75.7	11.60	76.0	56	95
	6 mg PR/XL 24h	26	DAY 15	PRE-DOSE	26	79.4	9.54	81.5	61	95
				<0.5	4	84.3	18.64	82.0	68	105
				1	25	77.5	11.91	76.0	57	108
				2	22	81.7	15.11	79.0	63	127
				3	18	82.1	12.45	81.0	65	111
				4	22	82.8	11.96	86.5	56	104
				5	24	79.5	13.48	76.5	50	111
				6	22	80.4	10.54	79.0	66	110
				7	24	83.3	13.04	79.5	62	112
				8	23	80.0	12.74	78.0	54	106
				9	25	79.5	11.23	80.0	55	103
				10	24	77.7	16.68	77.0	50	139
				11	25	77.2	12.75	76.0	49	101
				12	23	76.2	10.24	76.0	53	96
	8 mg PR/XL 24h	25	DAY 22	PRE-DOSE	24	77.5	9.28	77.5	60	95
				<0.5	5	79.4	7.70	79.0	68	87
				1	25	73.0	9.94	74.0	57	93
				2	24	73.0	12.04	72.0	52	103
				3	24	80.8	19.78	75.0	58	137

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	8 mg PR/XL 24h	25	DAY 22	4	23	73.5	13.98	73.0	39	97
				5	22	73.9	12.66	72.5	55	94
				6	23	76.1	13.05	76.0	54	104
				7	23	76.6	12.04	73.0	57	105
				8	22	78.6	13.31	77.5	58	114
				9	24	79.3	14.48	77.5	53	107
				10	24	77.8	16.67	74.5	59	128
				11	25	74.9	11.85	72.0	55	105
				12	24	75.7	12.98	73.0	59	113
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE	8	72.4	9.47	72.5	57	86
				1	7	67.6	11.84	64.0	53	81
				2	8	70.5	10.70	73.5	54	83
				3	8	76.4	17.37	81.5	54	98
				4	8	73.0	14.89	71.0	57	95
				5	8	78.4	18.42	80.5	48	108
				6	8	78.6	15.16	83.5	55	95
				7	8	77.8	21.88	79.0	52	108
				8	8	75.1	14.92	80.5	48	92
				9	8	71.9	15.16	74.5	51	93
				10	7	70.6	14.23	72.0	54	92
				11	8	72.1	18.15	69.5	47	100
				12	7	74.1	16.26	69.0	58	98

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	PRE-DOSE	8	76.0	8.55	75.5	64	87
				<0.5	3	72.3	11.15	68.0	64	85
				1	8	71.1	8.31	74.0	58	80
				2	7	72.7	11.66	74.0	56	93
				3	8	75.3	15.50	69.0	59	104
				4	8	76.3	12.22	75.0	60	92
				5	6	77.5	16.13	75.5	61	107
				6	8	75.3	8.51	73.5	65	90
				7	7	77.1	19.20	71.0	58	111
				8	8	73.8	16.12	69.0	62	113
				9	8	71.5	7.05	71.5	61	83
				10	8	71.5	9.80	66.0	63	86
				11	8	74.0	16.91	68.5	61	113
				12	6	73.8	16.69	73.0	55	96
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	PRE-DOSE	9	80.3	5.72	78.0	74	90
				<0.5	2	79.0	1.41	79.0	78	80
				1	9	78.9	9.03	80.0	66	95
				2	8	74.6	15.46	72.5	58	97
				3	8	81.5	10.93	80.5	62	96
				4	9	78.9	9.70	75.0	65	97
				5	9	77.0	10.11	70.0	68	95
				6	9	82.8	13.42	82.0	66	102

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.17
Summary of ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	7	9	79.0	13.28	80.0	56	103
				8	9	75.6	10.41	77.0	62	90
				9	9	76.9	10.34	80.0	58	87
				10	9	76.8	12.12	81.0	58	90
				11	9	75.1	8.39	75.0	62	87
				12	7	74.0	13.19	74.0	55	93

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	2 mg PR/XL 24h	28	DAY 1	<0.5	1	-13.0		-13.0	-13	-13
				1	27	-9.2	15.35	-6.0	-47	21
				2	25	-3.6	13.32	-4.0	-30	29
				3	23	-0.5	11.40	-3.0	-18	22
				4	25	-5.5	18.14	-2.0	-65	19
				5	27	-4.7	15.03	-7.0	-35	26
				6	25	-9.7	18.92	-10.0	-56	41
				7	25	-6.4	15.86	-7.0	-42	28
				8	26	-4.0	18.30	-2.0	-44	31
				9	24	-3.6	16.49	-2.5	-38	24
				10	25	-5.6	17.69	-3.0	-41	26
				11	27	-3.3	17.77	0.0	-45	34
				12	27	-3.7	17.18	-4.0	-27	28
	4 mg PR/XL 24h	28	DAY 8	<0.5	4	-11.5	12.58	-16.0	-21	7
				1	27	-7.1	14.16	-9.0	-29	20
				2	28	-6.5	15.93	-9.0	-37	32
				3	26	-6.7	17.04	-6.5	-47	27
				4	24	-8.4	16.09	-9.0	-34	36
				5	23	-10.6	21.53	-10.0	-48	38
				6	23	-9.7	19.25	-12.0	-41	31
				7	26	-8.2	18.30	-11.5	-31	30
				8	26	-7.0	20.08	-9.5	-47	29
				9	27	-3.4	15.59	-6.0	-32	27
				10	27	-3.6	18.20	-6.0	-35	41

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	4 mg PR/XL 24h	28	DAY 8	11	28	-5.2	19.93	-6.5	-40	30
				12	27	-7.0	16.59	-8.0	-40	23
	6 mg PR/XL 24h	26	DAY 15	<0.5	4	-14.3	17.35	-9.5	-39	1
				1	25	-6.9	16.45	-4.0	-54	30
				2	22	-3.6	12.86	-4.0	-27	17
				3	18	-6.7	17.11	-6.0	-33	26
				4	22	-5.1	15.40	-8.0	-31	19
				5	24	-9.8	17.53	-8.0	-54	15
				6	22	-5.7	17.08	-4.0	-56	21
				7	24	-7.2	19.10	-11.0	-48	44
				8	23	-5.2	14.51	-5.0	-39	20
				9	25	-1.8	12.66	-3.0	-33	26
				10	24	-0.6	16.44	2.0	-36	39
				11	25	-7.3	16.29	-5.0	-39	21
				12	23	-3.3	12.51	-4.0	-28	30
	8 mg PR/XL 24h	25	DAY 22	<0.5	4	-5.8	6.13	-5.5	-12	0
				1	24	-0.0	12.17	1.5	-29	26
				2	23	-2.0	10.62	-4.0	-18	19
				3	23	-1.5	17.91	-2.0	-33	43
				4	23	1.7	15.36	-1.0	-28	32
				5	21	-2.0	20.73	2.0	-50	50

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	8 mg PR/XL 24h	25	DAY 22	6	22	-0.5	18.53	2.5	-45	23
				7	22	2.3	21.33	0.5	-33	50
				8	21	-1.3	16.27	-2.0	-36	33
				9	23	7.0	17.83	6.0	-47	41
				10	23	5.3	20.89	6.0	-52	60
				11	24	7.9	26.50	4.0	-43	85
				12	23	1.6	19.33	0.0	-34	36
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	1	7	-4.0	15.33	-2.0	-35	12
				2	8	3.6	10.16	2.5	-12	18
				3	8	6.5	17.71	3.0	-14	30
				4	8	0.3	10.74	3.5	-19	12
				5	8	-8.4	15.64	-9.0	-35	12
				6	8	-5.1	11.91	-4.0	-28	12
				7	8	-7.9	18.18	-7.5	-37	15
				8	8	-5.0	16.51	-7.5	-32	23
				9	8	-0.5	13.30	0.5	-27	16
				10	7	1.4	11.60	6.0	-22	11
				11	8	0.8	17.91	7.5	-31	21
				12	7	0.1	18.60	0.0	-25	22

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	<0.5	3	-21.0	26.51	-15.0	-50	2
				1	8	-8.3	21.51	-0.5	-53	9
				2	7	-0.6	17.05	2.0	-33	18
				3	8	-13.1	19.66	-9.0	-56	11
				4	8	-5.6	20.57	-1.5	-49	17
				5	6	-15.5	25.49	-12.5	-61	11
				6	8	-6.3	27.08	1.5	-60	30
				7	7	-14.3	21.78	-9.0	-56	11
				8	8	-6.6	19.77	1.0	-48	12
				9	8	-9.1	24.84	-2.5	-58	18
				10	8	-3.4	23.01	8.0	-52	15
				11	8	-7.1	21.28	-4.0	-54	18
				12	6	-6.7	12.24	-11.0	-20	12
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	<0.5	2	2.5	0.71	2.5	2	3
				1	9	-4.4	17.01	-4.0	-28	20
				2	8	-9.8	13.10	-10.0	-32	11
				3	8	-11.9	13.84	-7.5	-37	1
				4	9	-8.7	9.81	-11.0	-18	11
				5	9	-8.9	22.74	-4.0	-51	19
				6	9	-7.4	14.80	-8.0	-32	18
				7	9	-6.4	29.19	-17.0	-29	61
				8	9	-5.6	29.70	-15.0	-30	68

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Systolic blood pressure (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	9	9	-8.6	16.74	-3.0	-30	17
				10	9	-2.8	13.68	-8.0	-20	26
				11	9	-7.9	12.66	-10.0	-23	8
				12	7	-8.9	17.53	-16.0	-31	10

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	2 mg PR/XL 24h	28	DAY 1	<0.5	1	-11.0		-11.0	-11	-11
				1	27	-7.0	9.44	-7.0	-33	4
				2	25	-2.1	9.93	-4.0	-19	21
				3	23	2.3	7.46	1.0	-9	16
				4	25	-0.3	9.70	0.0	-16	19
				5	27	0.3	7.73	2.0	-18	10
				6	25	0.7	10.04	1.0	-21	26
				7	25	0.6	11.19	1.0	-26	18
				8	26	2.7	11.53	3.0	-19	25
				9	24	1.0	9.66	2.0	-21	18
				10	25	0.6	12.39	6.0	-26	17
				11	27	-1.2	10.57	-1.0	-25	20
				12	27	-0.4	10.04	1.0	-22	23
	4 mg PR/XL 24h	28	DAY 8	<0.5	4	-10.0	16.12	-11.0	-27	9
				1	27	-7.2	8.29	-6.0	-21	5
				2	28	-4.5	9.58	-4.0	-22	21
				3	26	-2.0	11.66	-0.5	-31	18
				4	24	-1.3	9.48	-0.5	-29	14
				5	23	-5.8	15.14	-4.0	-37	27
				6	23	-2.4	12.77	-2.0	-27	22
				7	26	-2.7	13.07	-5.5	-24	27
				8	26	-4.0	11.50	-2.5	-29	18
				9	27	1.9	10.80	4.0	-17	22
				10	27	0.3	11.82	-2.0	-20	24

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	4 mg PR/XL 24h	28	DAY 8	11	28	-1.2	15.31	1.0	-34	24
				12	27	-0.6	11.88	-1.0	-20	26
	6 mg PR/XL 24h	26	DAY 15	<0.5	4	-11.0	7.44	-9.5	-21	-4
				1	25	-3.1	10.00	-3.0	-28	19
				2	22	2.6	7.11	2.0	-13	13
				3	18	0.0	9.38	-0.5	-16	19
				4	22	3.6	10.24	3.0	-12	20
				5	24	1.0	10.18	0.5	-20	21
				6	22	0.8	12.20	1.5	-34	20
				7	24	4.0	11.20	2.5	-21	23
				8	23	4.8	7.98	5.0	-13	21
				9	25	4.9	8.73	5.0	-15	22
				10	24	4.3	10.57	4.5	-14	27
				11	25	0.8	11.31	0.0	-20	27
				12	23	1.3	8.98	2.0	-18	21
	8 mg PR/XL 24h	25	DAY 22	<0.5	4	-2.5	9.40	-3.5	-12	9
				1	24	-1.6	8.44	-1.0	-17	13
				2	23	1.1	9.57	2.0	-14	20
				3	23	4.1	9.13	5.0	-13	23
				4	23	5.2	10.49	4.0	-21	25
				5	21	3.0	14.62	4.0	-20	37

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	8 mg PR/XL 24h	25	DAY 22	6	22	1.1	11.09	5.5	-20	14
				7	22	4.7	12.67	2.5	-16	35
				8	21	2.4	12.06	7.0	-17	21
				9	23	7.1	9.95	8.0	-15	22
				10	23	5.6	10.99	4.0	-19	25
				11	24	4.0	13.65	2.0	-31	35
				12	23	2.6	10.16	1.0	-17	21
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	1	7	-0.9	7.80	-3.0	-10	10
				2	8	3.8	12.31	4.0	-18	22
				3	8	8.9	9.80	8.0	-2	23
				4	8	5.5	9.13	6.0	-12	17
				5	8	3.6	11.64	2.0	-13	25
				6	8	6.9	8.22	5.5	-4	21
				7	8	1.8	12.95	0.5	-18	26
				8	8	1.8	10.11	3.0	-15	12
				9	8	6.0	6.19	7.0	-5	14
				10	7	7.7	4.82	8.0	-1	14
				11	8	4.6	17.62	10.0	-17	22
				12	7	1.0	12.86	2.0	-23	19

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	<0.5	3	-3.3	3.21	-2.0	-7	-1
				1	8	0.4	4.90	-0.5	-5	10
				2	7	3.3	7.74	5.0	-10	14
				3	8	3.6	4.69	5.0	-5	8
				4	8	4.3	8.41	4.0	-10	18
				5	6	1.3	5.01	2.0	-8	6
				6	8	5.0	9.12	4.5	-7	19
				7	7	0.6	6.13	1.0	-10	7
				8	8	3.0	6.26	1.5	-6	12
				9	8	2.0	6.97	0.5	-9	14
				10	8	6.1	6.03	5.0	0	18
				11	8	5.1	7.64	3.5	-5	22
				12	6	1.0	10.12	-2.5	-8	14
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	<0.5	2	1.0	7.07	1.0	-4	6
				1	9	-2.1	13.68	-1.0	-22	23
				2	8	-4.0	13.45	1.5	-27	9
				3	8	-1.9	11.74	-4.0	-23	16
				4	9	-2.8	9.20	1.0	-21	6
				5	9	-3.3	12.69	-2.0	-25	18
				6	9	2.8	6.55	4.0	-13	11
				7	9	0.1	15.23	0.0	-21	25
				8	9	-2.8	15.91	-8.0	-16	32

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Diastolic blood pressure (mmHg)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	9	9	-1.4	13.88	2.0	-24	17
				10	9	-0.1	8.30	-2.0	-12	15
				11	9	-1.4	12.69	1.0	-23	22
				12	7	-3.7	14.37	3.0	-26	13

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	2 mg PR/XL 24h	28	DAY 1	<0.5	1	-4.0		-4.0	-4	-4
				1	27	-8.1	8.37	-7.0	-33	3
				2	25	-9.5	12.00	-10.0	-38	13
				3	23	-3.5	10.17	-3.0	-22	25
				4	25	1.8	19.75	-1.0	-21	79
				5	27	-0.5	11.50	-1.0	-19	22
				6	25	-2.2	15.43	1.0	-21	54
				7	25	-4.2	10.50	-5.0	-19	18
				8	26	-6.0	12.59	-3.5	-36	17
				9	24	-7.0	10.50	-5.5	-23	13
				10	25	-5.6	10.82	-5.0	-26	18
				11	27	-6.0	13.23	-6.0	-26	27
				12	27	-6.9	11.70	-5.0	-40	13
	4 mg PR/XL 24h	28	DAY 8	<0.5	4	2.0	10.61	-1.5	-6	17
				1	27	-6.0	10.17	-5.0	-43	11
				2	28	-6.1	11.69	-4.0	-53	18
				3	26	0.0	16.28	1.0	-44	55
				4	24	-4.2	14.81	-3.5	-56	20
				5	23	-6.1	11.60	-6.0	-48	8
				6	23	-3.7	13.30	-2.0	-48	17
				7	26	-4.3	13.04	-4.0	-44	17
				8	26	-2.3	15.24	-2.0	-57	27
				9	27	-3.6	15.59	-3.0	-54	25
				10	27	-5.5	15.17	-2.0	-56	21
				11	28	-4.5	16.63	-2.5	-60	31

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	4 mg PR/XL 24h	28	DAY 8	12	27	-3.6	15.02	-2.0	-55	16
	6 mg PR/XL 24h	26	DAY 15	<0.5	4	-1.3	9.71	-4.0	-9	12
				1	25	-2.4	9.29	-2.0	-18	22
				2	22	1.9	10.20	0.0	-16	32
				3	18	1.9	9.51	0.5	-18	28
				4	22	3.0	10.73	1.5	-16	21
				5	24	1.0	11.14	2.5	-17	31
				6	22	0.8	10.28	2.5	-15	20
				7	24	4.8	15.81	1.5	-19	50
				8	23	0.2	11.87	-2.0	-18	29
				9	25	0.2	10.48	1.0	-16	17
				10	24	-2.3	19.12	-1.5	-28	73
				11	25	-2.0	11.52	1.0	-27	24
				12	23	-3.4	9.68	-3.0	-19	16
	8 mg PR/XL 24h	25	DAY 22	<0.5	4	0.5	4.20	0.5	-4	5
				1	24	-5.1	7.09	-4.0	-23	8
				2	23	-6.1	6.26	-8.0	-20	5
				3	23	1.2	17.52	-2.0	-29	50
				4	23	-3.6	12.10	-2.0	-35	17
				5	21	-4.2	9.65	-5.0	-21	16
				6	22	-3.0	13.31	1.5	-30	13
				7	22	-1.7	11.16	3.0	-23	15

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	8 mg PR/XL 24h	25	DAY 22	8	21	-1.0	11.53	-2.0	-26	23
				9	23	1.7	14.83	4.0	-30	29
				10	23	-0.2	16.63	0.0	-28	58
				11	24	-3.1	11.55	-1.5	-29	22
				12	23	-2.5	11.52	0.0	-24	22
	1 x 12mg PR/XL 24h (fasted)	25	DAY 29	1	7	-4.7	9.76	-3.0	-22	8
				2	8	-1.9	9.55	0.0	-15	10
				3	8	4.0	11.66	2.0	-11	21
				4	8	0.6	13.02	3.0	-22	18
				5	8	6.0	10.97	5.5	-9	27
				6	8	6.3	8.33	8.5	-7	15
				7	8	5.4	16.60	1.5	-12	31
				8	8	2.8	10.22	-1.0	-9	21
				9	8	-0.5	9.89	-4.0	-11	16
				10	7	-1.7	8.64	-3.0	-12	15
				11	8	-0.3	12.90	-6.5	-13	23
				12	7	1.6	9.80	1.0	-10	21
	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	<0.5	3	-2.3	2.52	-2.0	-5	0
				1	8	-4.9	6.31	-5.0	-13	5

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	1 x 12mg PR/XL 24h (high fat fed)	25	DAY 29	2	7	-3.7	13.47	-10.0	-18	18
				3	8	-0.8	15.52	0.0	-20	29
				4	8	0.3	9.72	-2.0	-16	17
				5	6	2.0	14.68	2.5	-15	20
				6	8	-0.8	12.24	-0.5	-19	15
				7	7	1.0	22.22	1.0	-22	45
				8	8	-2.3	13.20	-6.5	-17	26
				9	8	-4.5	8.33	-4.5	-16	12
				10	8	-4.5	8.50	-1.0	-20	4
				11	8	-2.0	14.01	-2.0	-22	26
				12	6	-2.0	16.95	-3.5	-21	21
	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	<0.5	2	-7.5	6.36	-7.5	-12	-3
				1	9	-1.4	7.18	-1.0	-13	6
				2	8	-5.4	10.34	-4.5	-20	8
				3	8	0.6	11.19	1.0	-16	18
				4	9	-1.4	6.37	-1.0	-13	7
				5	9	-3.3	7.21	-6.0	-14	7
				6	9	2.4	11.30	4.0	-15	15
				7	9	-1.3	11.51	2.0	-22	13
				8	9	-4.8	8.97	-1.0	-20	6
				9	9	-3.4	9.46	-3.0	-20	7
				10	9	-3.6	11.41	-4.0	-20	12

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.18
Summary of Change from Baseline ABPM Measurements

	Treatment	N	Visit	Time Elapsed since dose interval (HRS)	n	Mean	SD	Median	Min.	Max.
Heart rate (beats/min)	3 x 4mg PR/XL 24h (fasted)	25	DAY 29	11	9	-5.2	7.07	-3.0	-16	5
				12	7	-4.6	10.58	-4.0	-19	12

Note: For subjects whose first ABPM reading was recorded at the same time as dose, this has been assigned to the pre-dose interval. Only valid measurements observed on a dose increase day (or scheduled visit), and the last observation within a time interval are used in the calculation of summary statistics.

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Table 10.19
Listing of ABPM Measurements Outside Clinical Concern range

Inv./ Subj.	Age(y)/ Sex/ Race	Treatment/ Period	Visit	Date of ambulatory BP reading	Time Elapsed since dose interval (HRS)	Study Day	Ambulatory Systolic Blood Pressure (mmHg)	Ambulatory Diastolic Blood Pressure (mmHg)
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.								

L = Lower than clinical concern range, H = Higher than clinical concern range
Upper Limit: Systolic BP >190mmHg, Diastolic BP >120mmHg
Lower Limit: Systolic BP <80mmHg, Diastolic BP <50mmHg
All ABPM measurements have been evaluated for Potential Clinical Concern.

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Diastolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 1	PRE-DOSE 1	n	28	0	0	0	0	0	0
		< PCI ranges	1 (4%)	0	0	0	0	0	0
DAY 12-14	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 26-28	12H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 31	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	1 (11%)
DAY 37	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	1 (13%)	0	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Heart rate (beats/min) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 12-14	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	0	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Heart rate (beats/min) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	24H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	1 (13%)	0	0
DAY 34	4H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	0	0	1 (13%)

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Heart rate (beats/min) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	0
	4H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	0
	6H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 1	PRE-DOSE 1	n	28	0	0	0	0	0	0
		> PCI ranges	1 (4%)	0	0	0	0	0	0
		< PCI ranges	1 (4%)	0	0	0	0	0	0
	PRE-DOSE 2	n	28	0	0	0	0	0	0
		< PCI ranges	1 (4%)	0	0	0	0	0	0
	PRE-DOSE 3	n	28	0	0	0	0	0	0
		< PCI ranges	1 (4%)	0	0	0	0	0	0
DAY 8	PRE-DOSE 1	n	0	28	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 12-14	PRE-DOSE 1	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	4H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
	6H	n	0	27	0	0	0	0	0
		< PCI ranges	0	3 (11%)	0	0	0	0	0
	12H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 12-14	24H	n	0	27	0	0	0	0	0
		< PCI ranges	0	1 (4%)	0	0	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
	12H	n	0	0	0	25	0	0	0
		< PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 31	PRE-DOSE 1	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	1 (11%)
	4H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	0	1 (11%)
	6H	n	0	0	0	0	8	8	9
		< PCI ranges	0	0	0	0	0	1 (13%)	2 (22%)

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 32	PRE-DOSE 1	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	0	0
DAY 34	4H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	0	0
	6H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	1 (11%)	1 (13%)	0
	12H	n	0	0	0	0	9	8	8
		< PCI ranges	0	0	0	0	2 (22%)	0	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	2 (25%)
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	0	1 (11%)	0
	6H	n	0	0	0	0	8	9	8
		< PCI ranges	0	0	0	0	1 (13%)	0	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Systolic blood pressure (mmHg) Standing

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 37	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 15	PRE-DOSE 1	n	0	0	26	0	0	0	0
		< PCI ranges	0	0	1 (4%)	0	0	0	0
DAY 26-28	PRE-DOSE 1	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
	6H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
	24H	n	0	0	0	25	0	0	0
		> PCI ranges	0	0	0	1 (4%)	0	0	0
DAY 29	PRE-DOSE 1	n	0	0	0	0	8	8	9
		> PCI ranges	0	0	0	0	0	0	1 (11%)
DAY 34	PRE-DOSE 1	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
	4H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.20
Summary of Number of Vital Signs Outside Range of Potential Clinical Importance- Europe

Parameter: Systolic blood pressure (mmHg) Supine

Visit	Planned Relative Time	Category	2 mg PR/XL 24h (N=28)	4 mg PR/XL 24h (N=28)	6 mg PR/XL 24h (N=26)	8 mg PR/XL 24h (N=25)	1 x 12mg PR/XL 24h (fasted) (N=25)	1 x 12mg PR/XL 24h (high fat fed) (N=25)	3 x 4mg PR/XL 24h (fasted) (N=25)
DAY 34	6H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
	12H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
	24H	n	0	0	0	0	9	8	8
		> PCI ranges	0	0	0	0	1 (11%)	0	0
DAY 35	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
DAY 37	PRE-DOSE 1	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
	4H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
	6H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0
	24H	n	0	0	0	0	8	9	8
		> PCI ranges	0	0	0	0	0	1 (11%)	0

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

[redacted]

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Table 10.21
Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance - FDA

Inv./ Subj./ Seq.	Age(y)/ Sex/ Race	Lab Test (Units)	Treatment/ Period	Planned Relative Time	Date/ Time	Converted Data Value	Normal Range	Flag[1] NR	CC

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.

E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[1] NR for Normal Range flag, CC for Clinical Concern flag; H=Above range, L=Below range.
N=No Clinical Concern range, U=Missing lab value, M=Missing reference range

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Table 10.22
Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance - Europe

Inv./ Subj./ Seq.	Age(y)/ Sex/ Race	Lab Test (Units)	Treatment/ Period	Planned Relative Time	Date/ Time	Converted Data Value	Normal Range	Flag[1] NR	CC

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.

E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[1] NR for Normal Range flag, CC for Clinical Concern flag; H=Above range, L=Below range.
N=No Clinical Concern range, U=Missing lab value, M=Missing reference range

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Table 10.23
Listing of Haematology Abnormalities of Potential Clinical Importance - FDA

Inv./ Subj./ Seq.	Age(y)/ Sex/ Race	Lab Test (Units)	Treatment/ Period	Planned Relative Time	Date/ Time	Converted Data Value	Normal Range	Flag[1] NR	CC

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.

E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[1] NR for Normal Range flag, CC for Clinical Concern flag; H=Above range, L=Below range.
N=No Clinical Concern range, U=Missing lab value, M=Missing reference range

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Table 10.24
Listing of Haematology Abnormalities of Potential Clinical Importance - Europe

No data to report

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E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[1] NR for Normal Range flag, CC for Clinical Concern flag; H=Above range, L=Below range.
N=No Clinical Concern range, U=Missing lab value, M=Missing reference range

[redacted]

Table 10.25
Listing of All Vital Signs for Subjects with Values of Potential Clinical Importance- Europe

Inv./ Subj.	Age(y)/ Sex/ Race	Treatment/ Period	Visit	Date/ Time	Planned Relative Time	Study Day/ Period Day	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)

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.

Systolic Range 90 - 180, Diastolic Range 50 - 115, Heart Rate Range 50 - 120

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Table 10.26
Listing of All Vital Signs for Subjects with Change from Baseline
Values of Potential Clinical Importance - FDA

Position: Supine

Inv./ Subj.	Age(y)/ Sex/ Race	Treatment/ Period	Visit	Date/ Time	Planned Relative Time	Study Day/ Period Day	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)

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.

Systolic Range >= +/-20 Change from Original Baseline Value
Diastolic Range >= +/-10 Change from Original Baseline Value
Heart Rate Range >= +/-15 Change from Original Baseline Value

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Table 10.27
Listing of All Vital Signs for Subjects with Change from Baseline
Values of Potential Clinical Importance - Europe

Position: Supine

Inv./ Subj.	Age(y)/ Sex/ Race	Treatment/ Period	Visit	Date/ Time	Planned Relative Time	Study Day/ Period Day	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)

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.

Systolic Range > +/-30 Change from Original Baseline Value
Diastolic Range > +/-20 Change from Original Baseline Value

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Table 10.28
Listing of All Adverse Events

Invid/ Subj./ Seq.	Treatment/ Period	Age(y)/ Sex/ Race/ Weight (kg)	Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Time/ Resolve Date/ Time/ Duration	Time Since Study 1st Dose/ Period 1st Dose/ Last Dose	Outcome/ Maximum Intensity/ Serious/ Withdrawal	Action Taken/ Relation to Study Drug

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]

E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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Table 10.29
Listing of All Vital Signs for Subjects with Adverse Events of Special interest

Position: Supine

Inv./ Subj.	Age(y)/ Sex/ Race	Treat ment/ Period	Visit	Date/ Time	Planned Relative Time	Study Day/ Period Day	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)

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.

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Pharmacokinetic Data Source Figures and Tables

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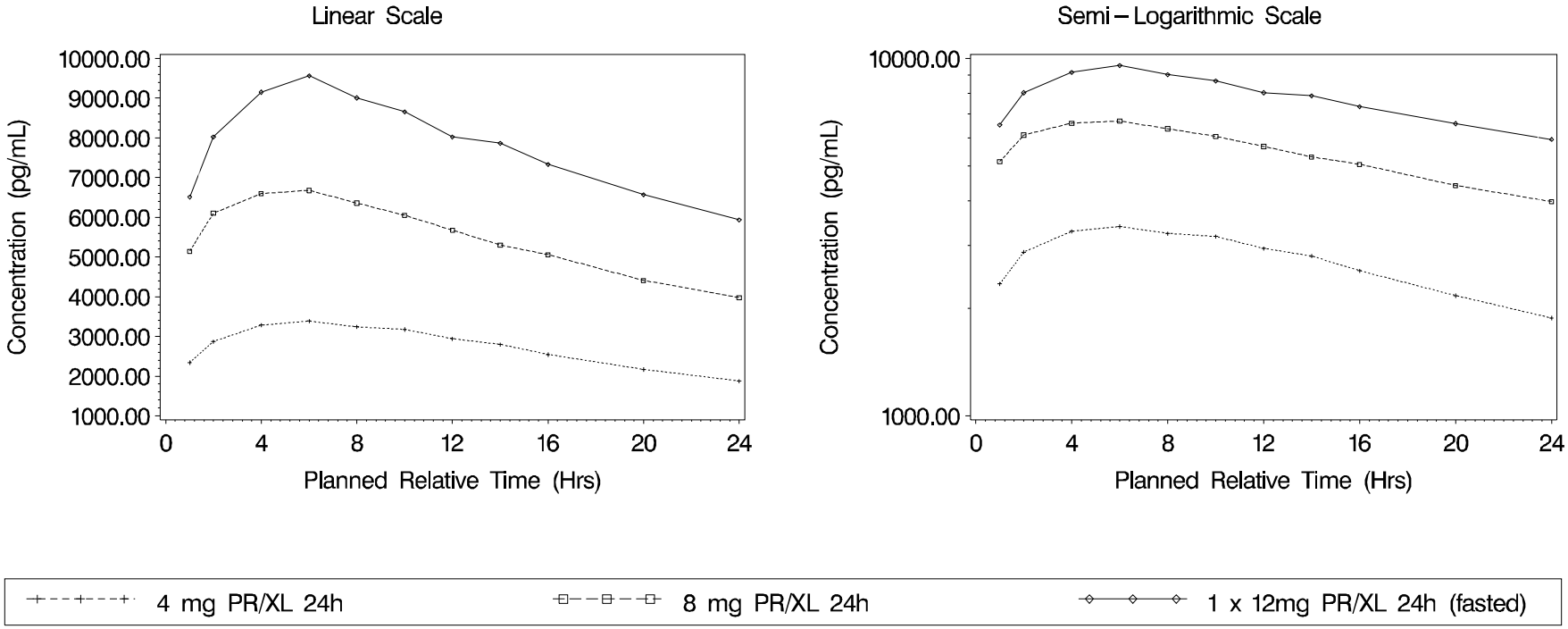
Mean Plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log) − B,D,E



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted)

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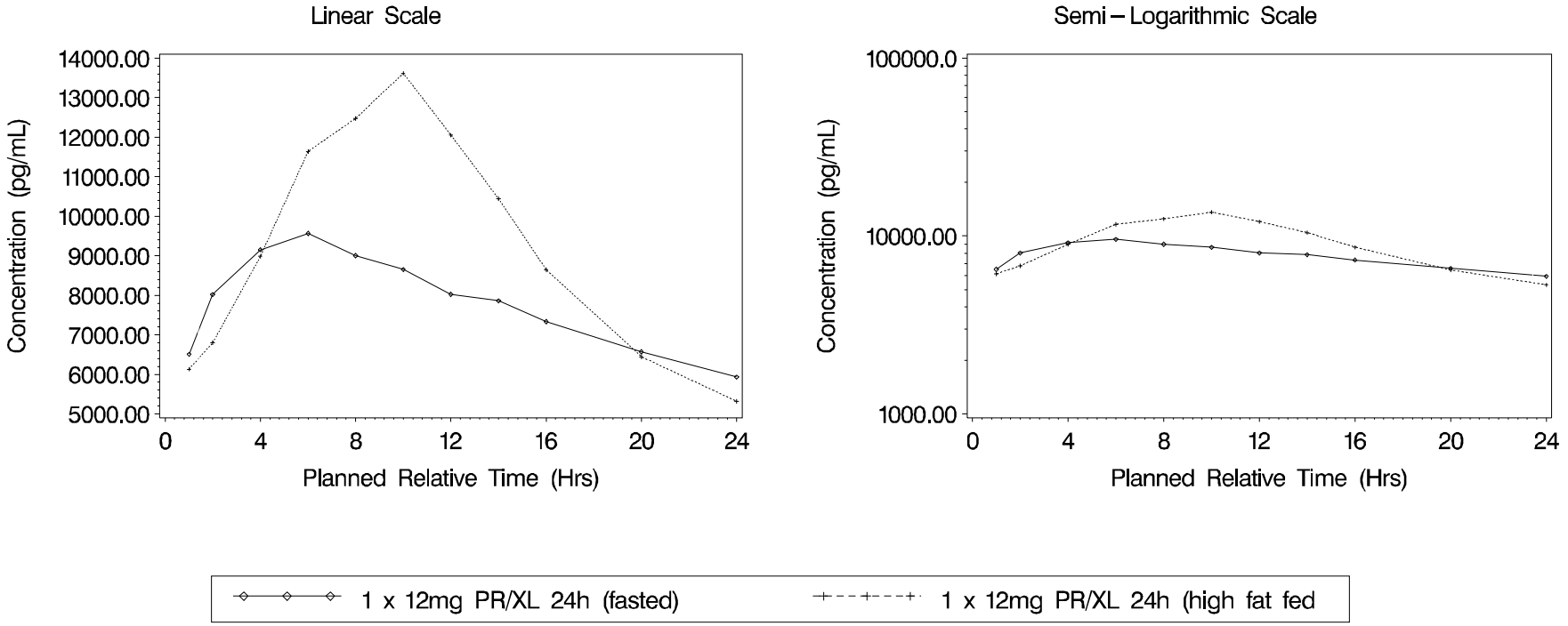
Figure 12.02
Mean Plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log) − E,F



NOTE: LLQ = 20 pg/mL
E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed)

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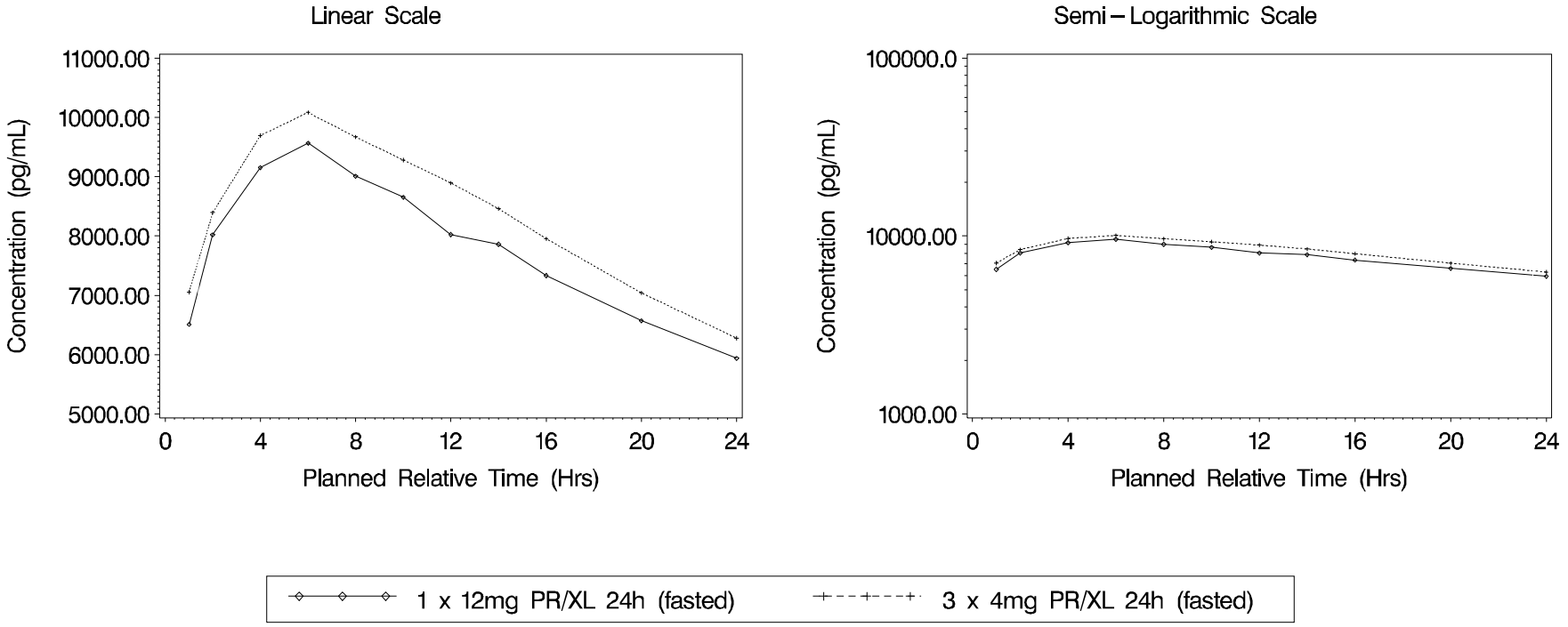
Figure 12.03
Mean Plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log) − E,G



NOTE: LLQ = 20 pg/mL
E=1 x 12 mg PR/XL 24h (fasted), G=3 x 4 mg PR/XL 24h (fasted)

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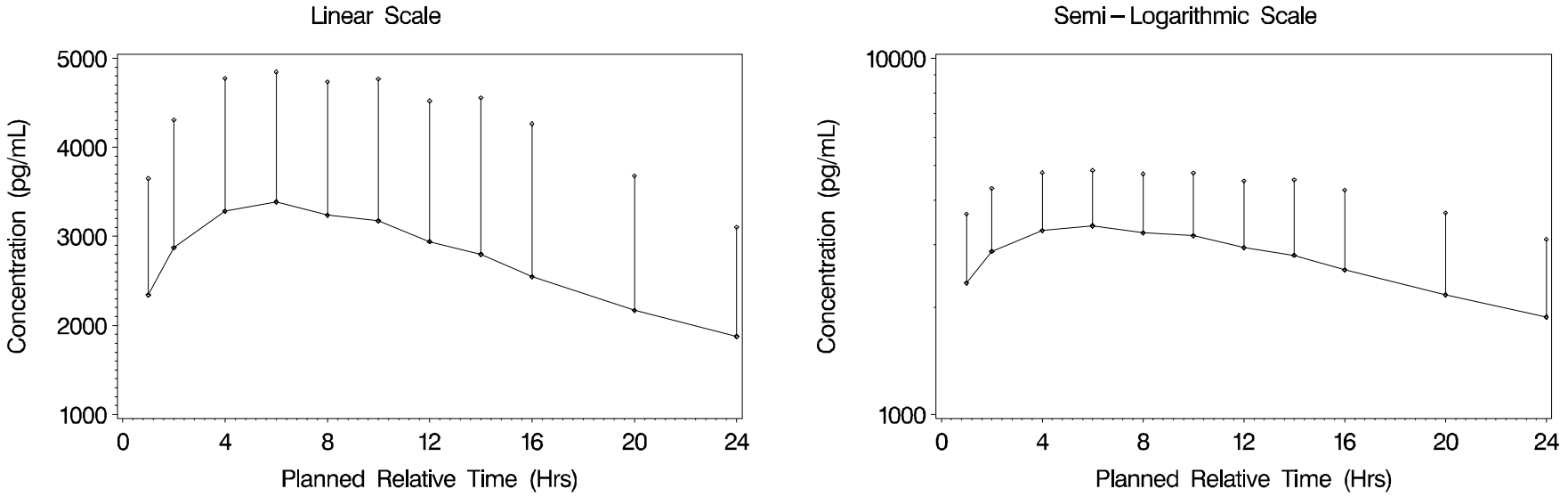
Figure 12.04
Mean + − SD Concentration − Time plots (SKF − 101468) − B,D,E,F,G
Period Treatment Group = 4 mg PR/XL 24h



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted),
F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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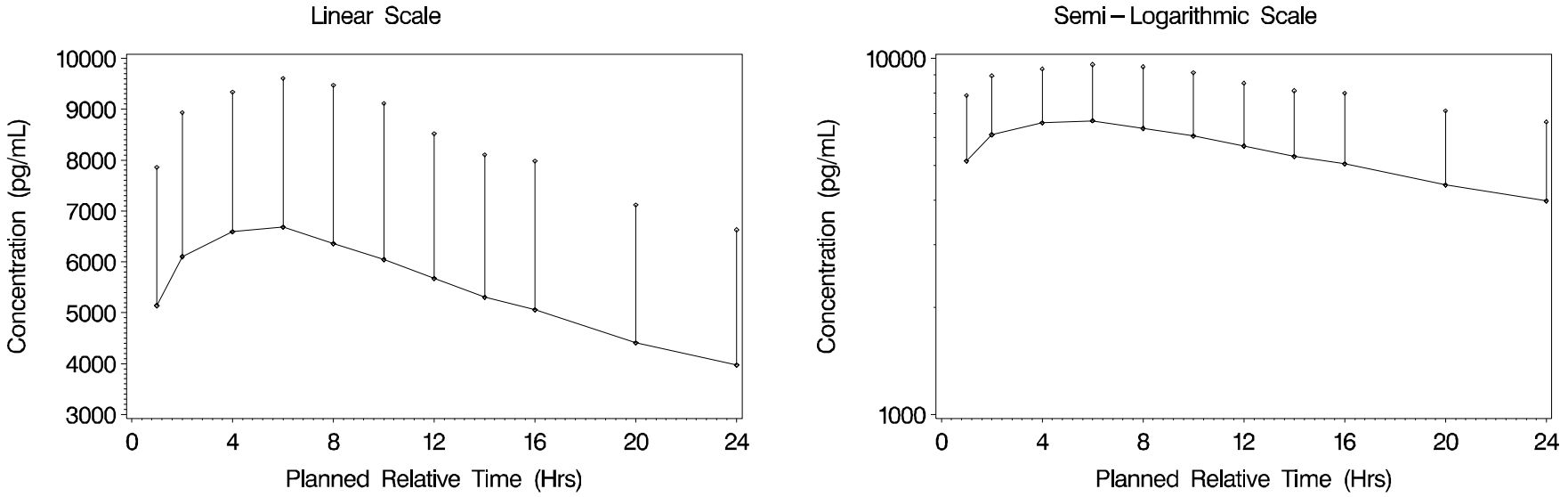
Figure 12.04
Mean + − SD Concentration − Time plots (SKF − 101468) − B,D,E,F,G
Period Treatment Group = 8 mg PR/XL 24h



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted),
F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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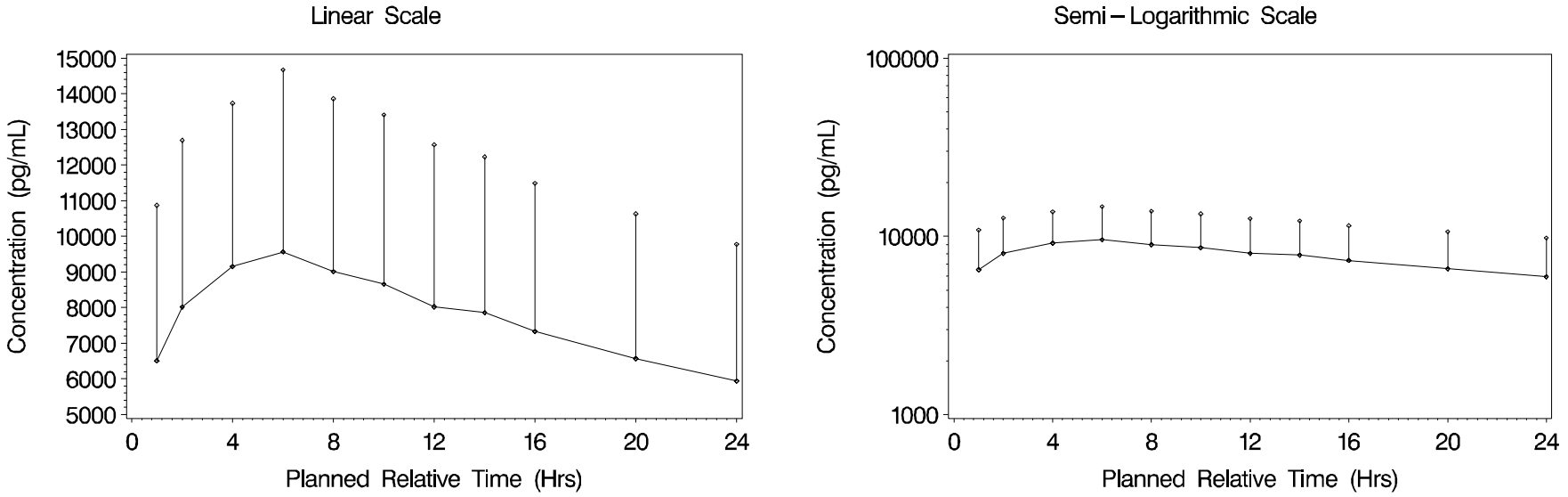
Figure 12.04
Mean + − SD Concentration − Time plots (SKF − 101468) − B,D,E,F,G
Period Treatment Group = 1 x 12mg PR/XL 24h (fasted)



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted),
F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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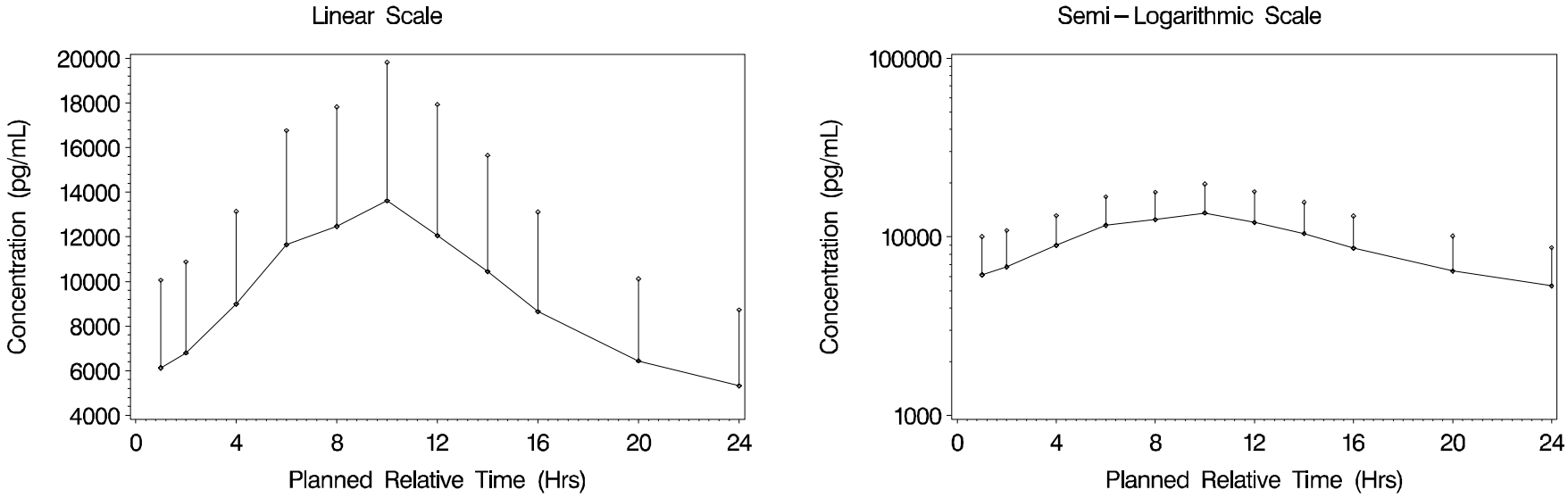
Figure 12.04
Mean + − SD Concentration − Time plots (SKF − 101468) − B,D,E,F,G
Period Treatment Group = 1 x 12mg PR/XL 24h (high fat fed)



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted),
F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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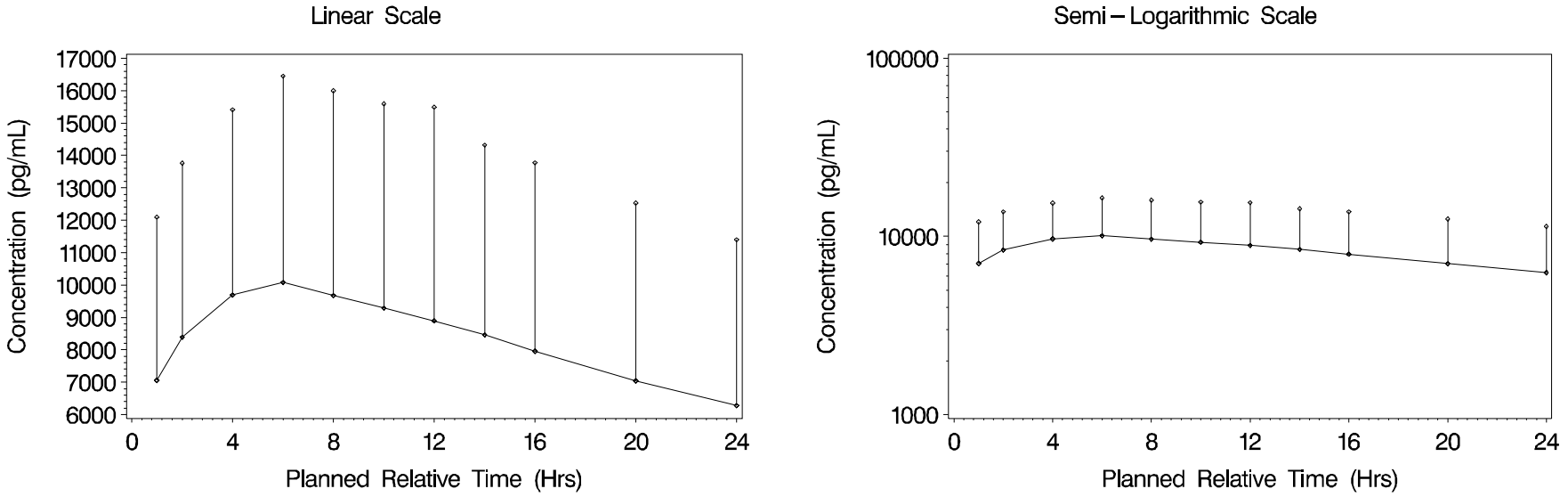
Figure 12.04
Mean + − SD Concentration − Time plots (SKF − 101468) − B,D,E,F,G
Period Treatment Group = 3 x 4mg PR/XL 24h (fasted)



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted),
F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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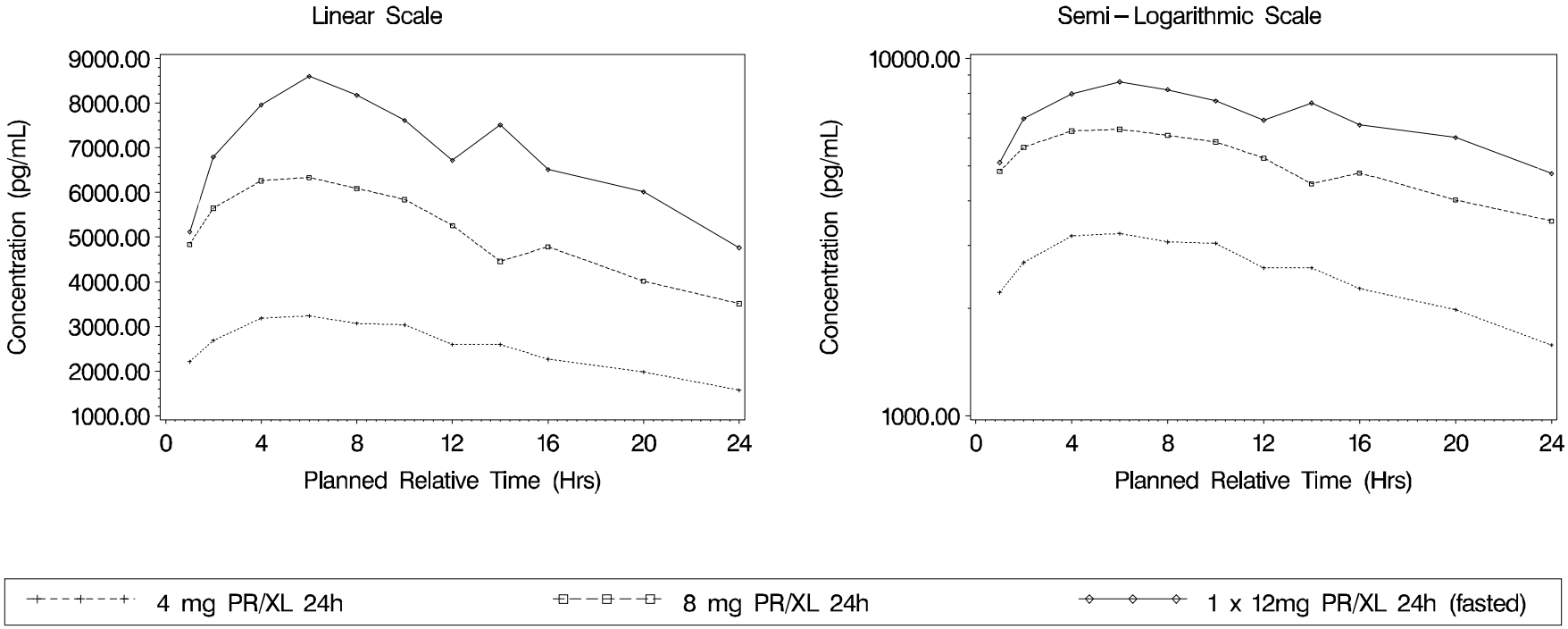
Figure 12.05
Median plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log) − B,D,E



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted)

[redacted]

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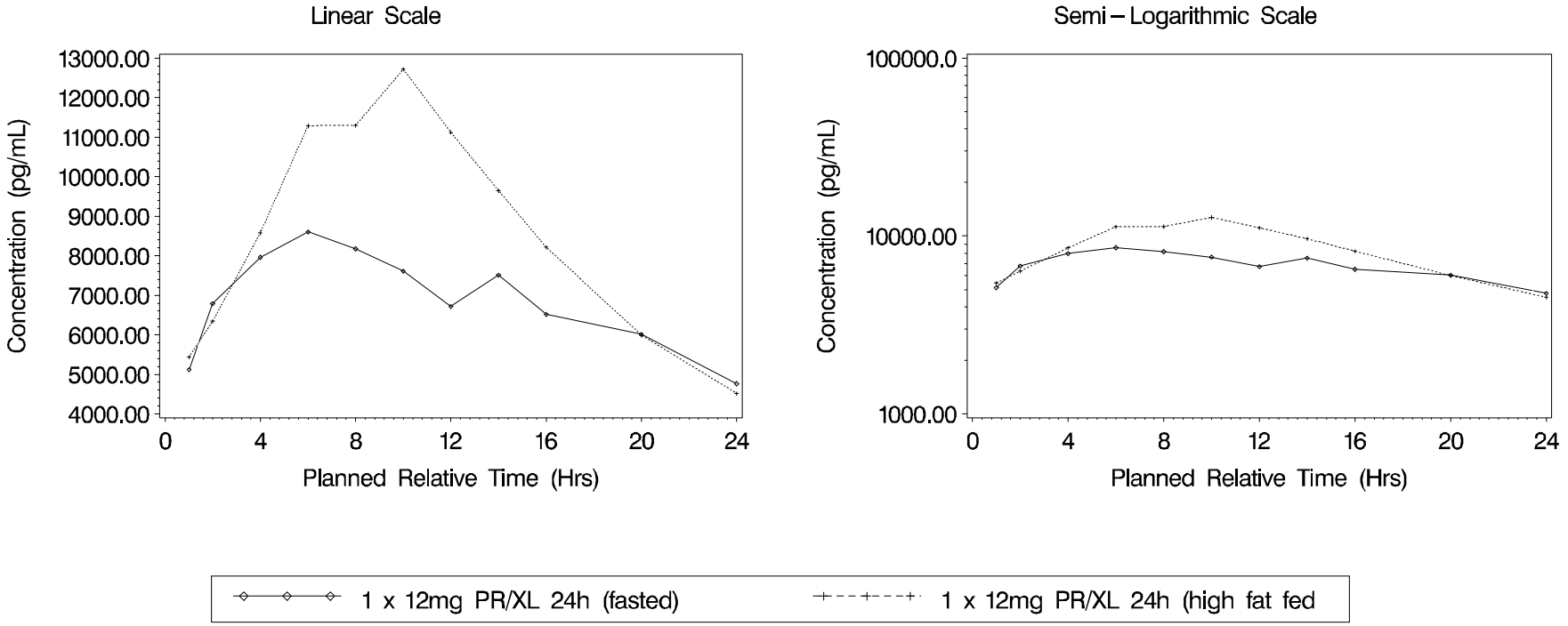
Figure 12.06
Median Plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log) − E, F



NOTE: LLQ = 20 pg/mL
E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed)

[redacted]

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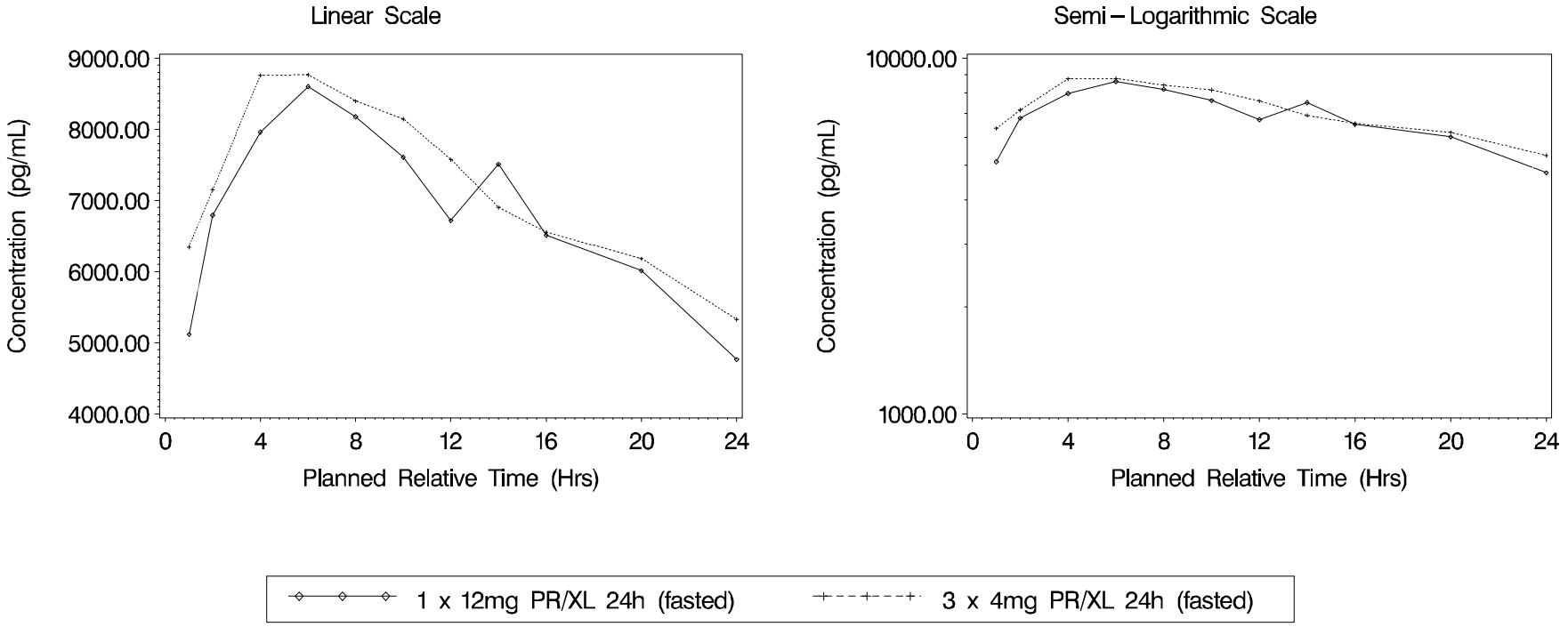
Figure 12.07
Median Plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log) − E,G



NOTE: LLQ = 20 pg/mL
E=1 x 12 mg PR/XL 24h (fasted), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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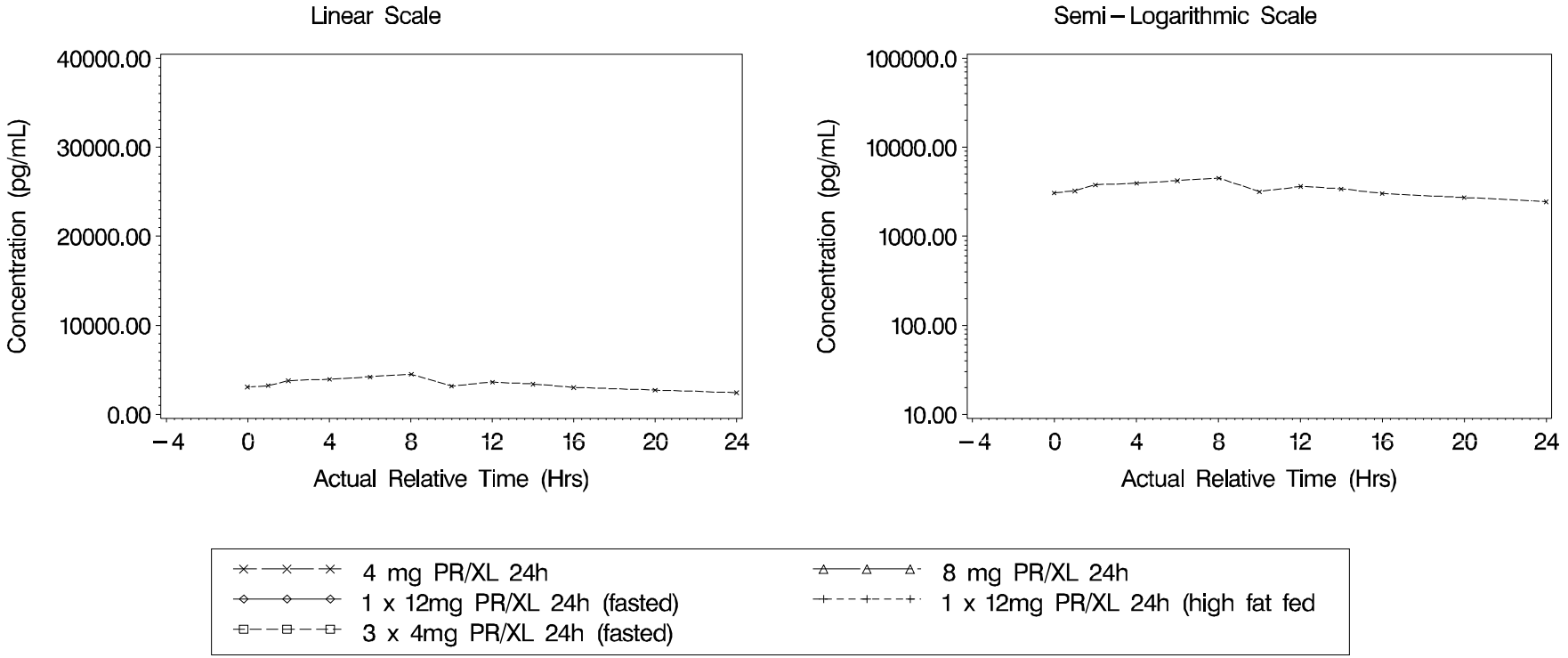
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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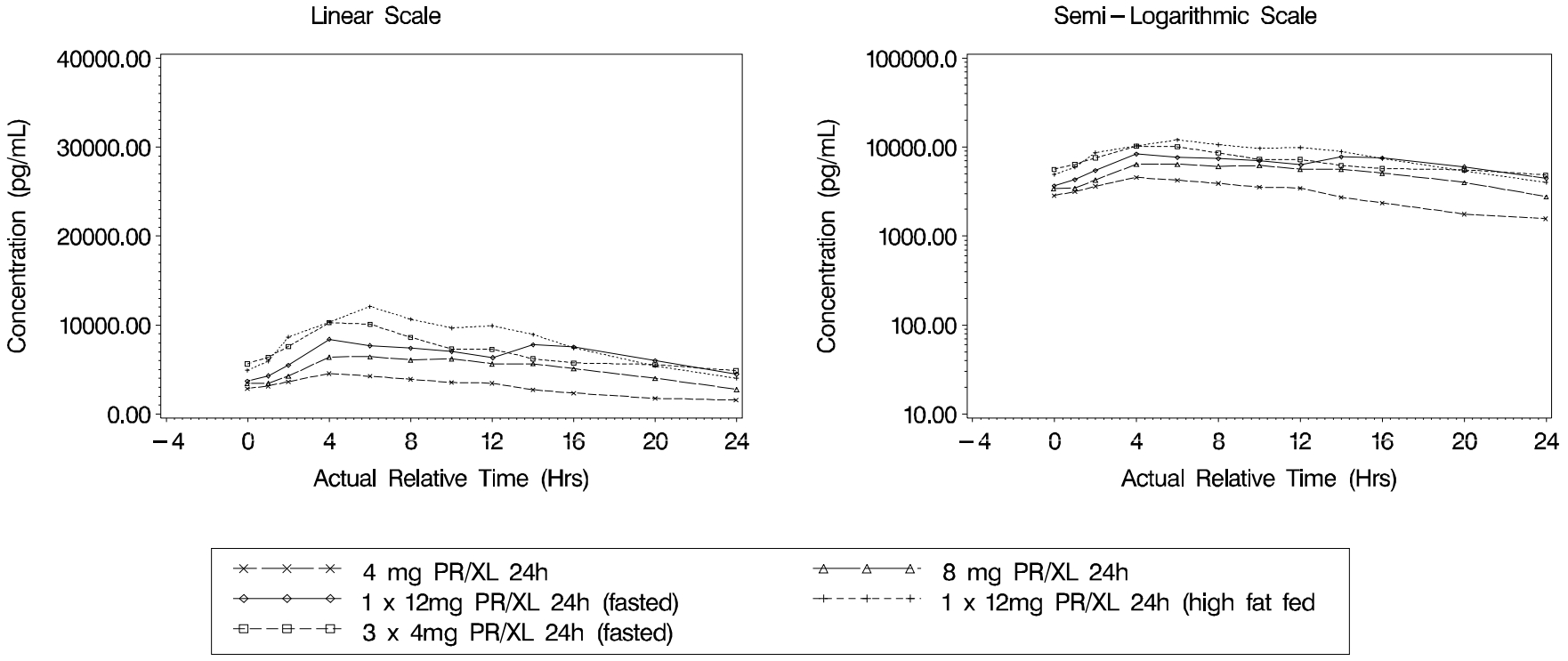
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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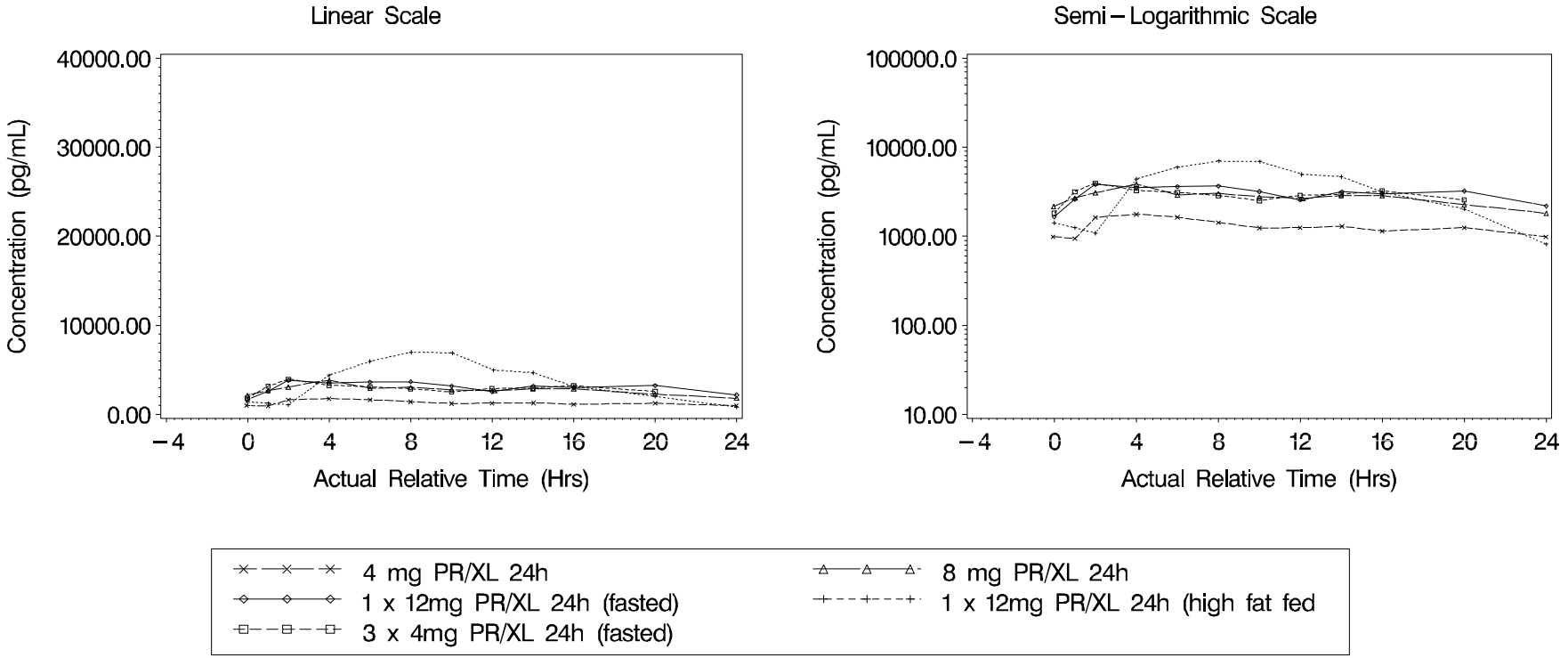
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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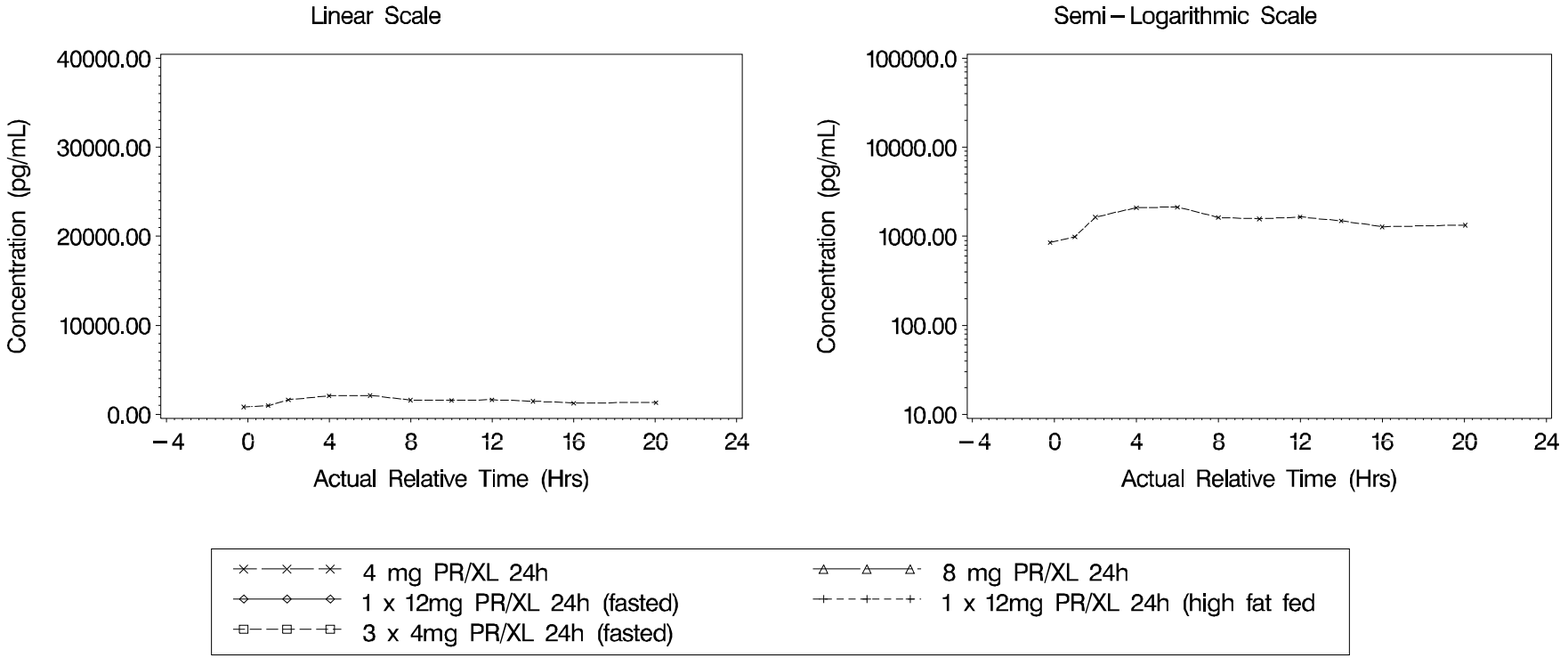
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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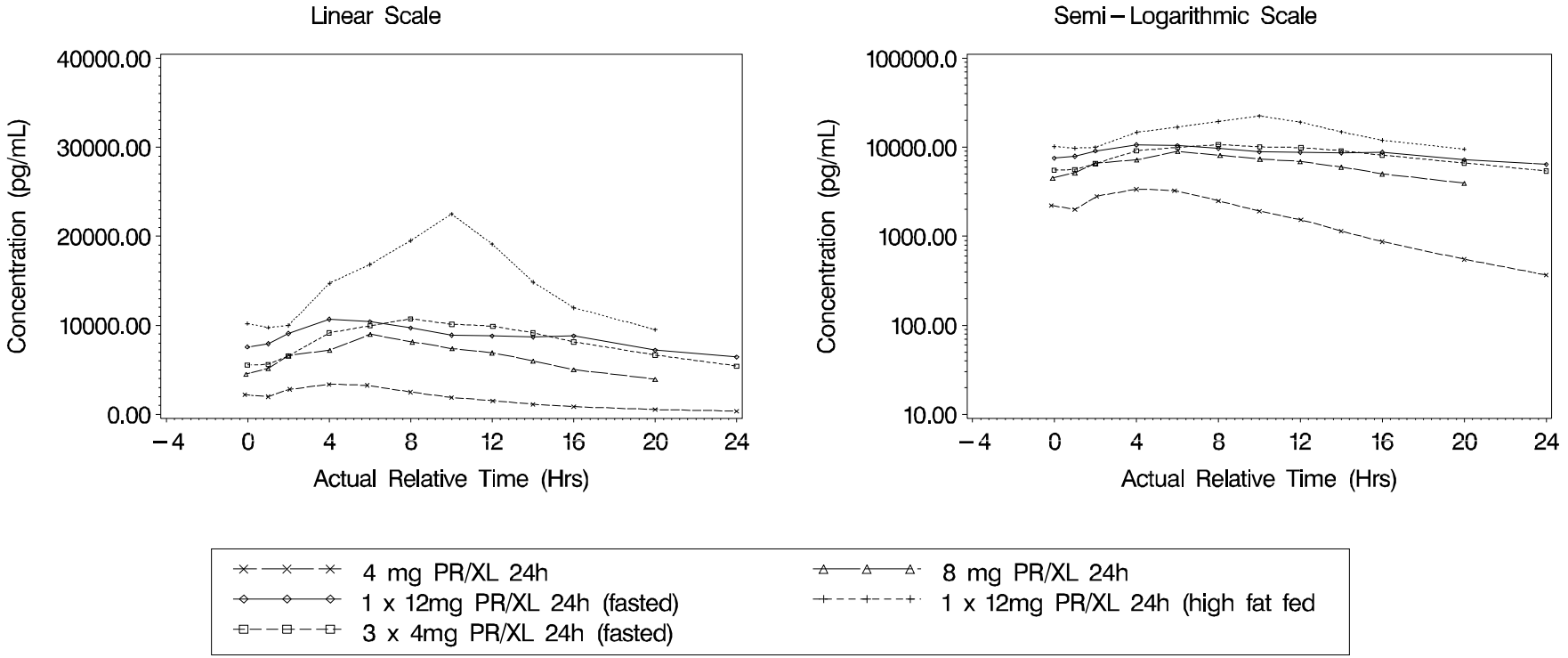
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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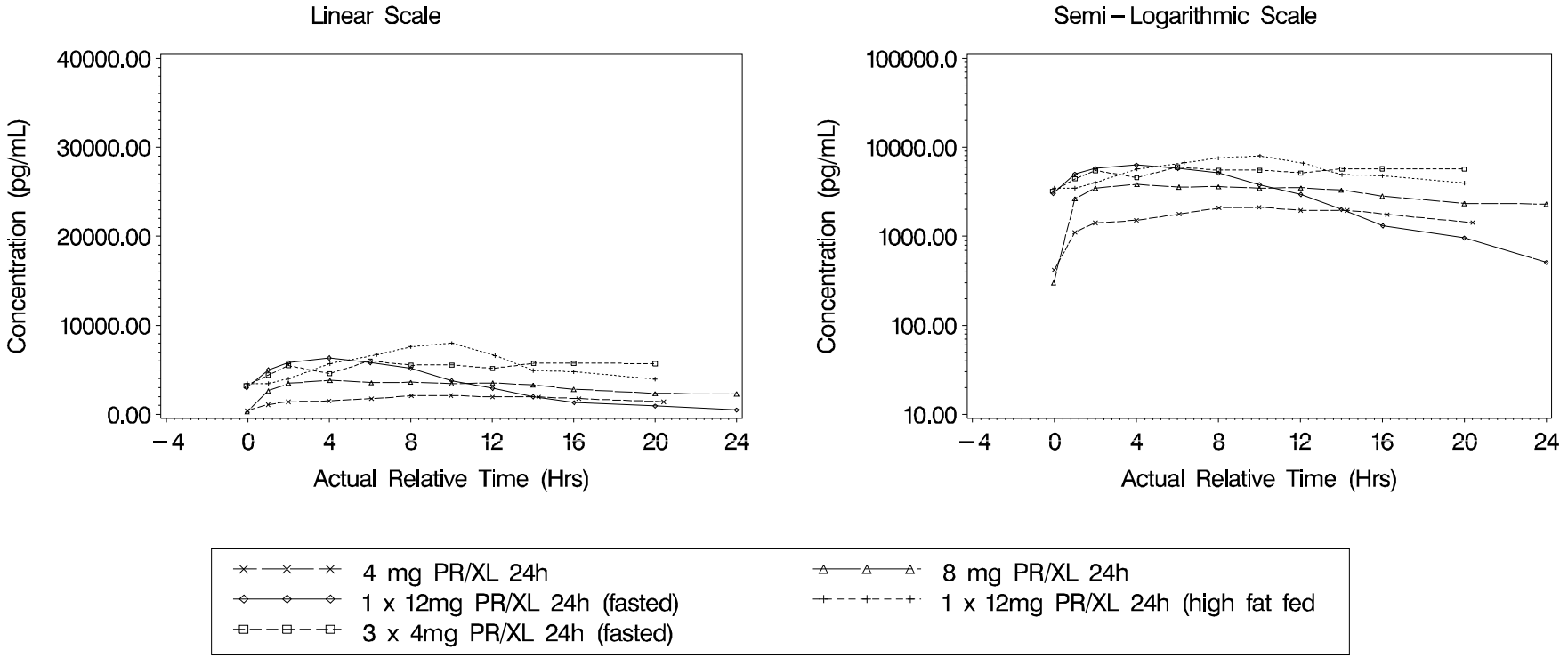
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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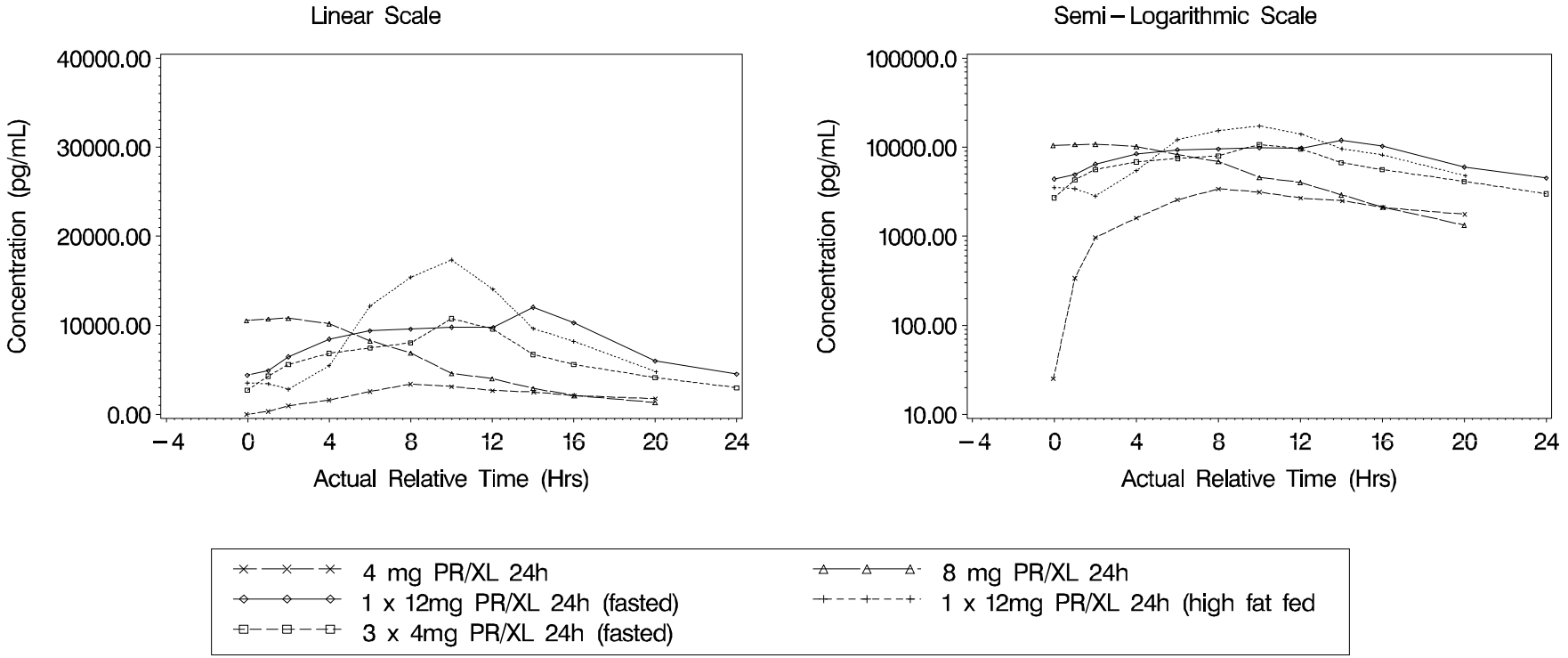
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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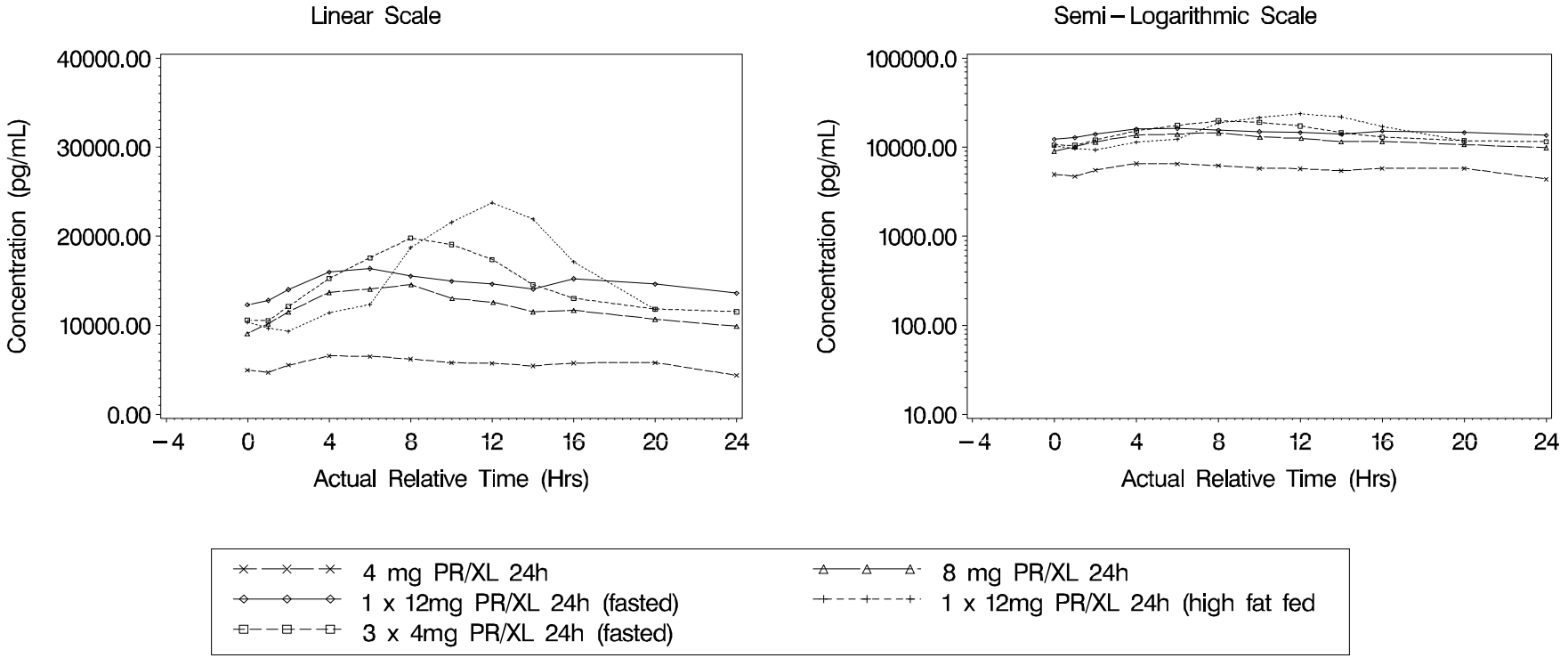
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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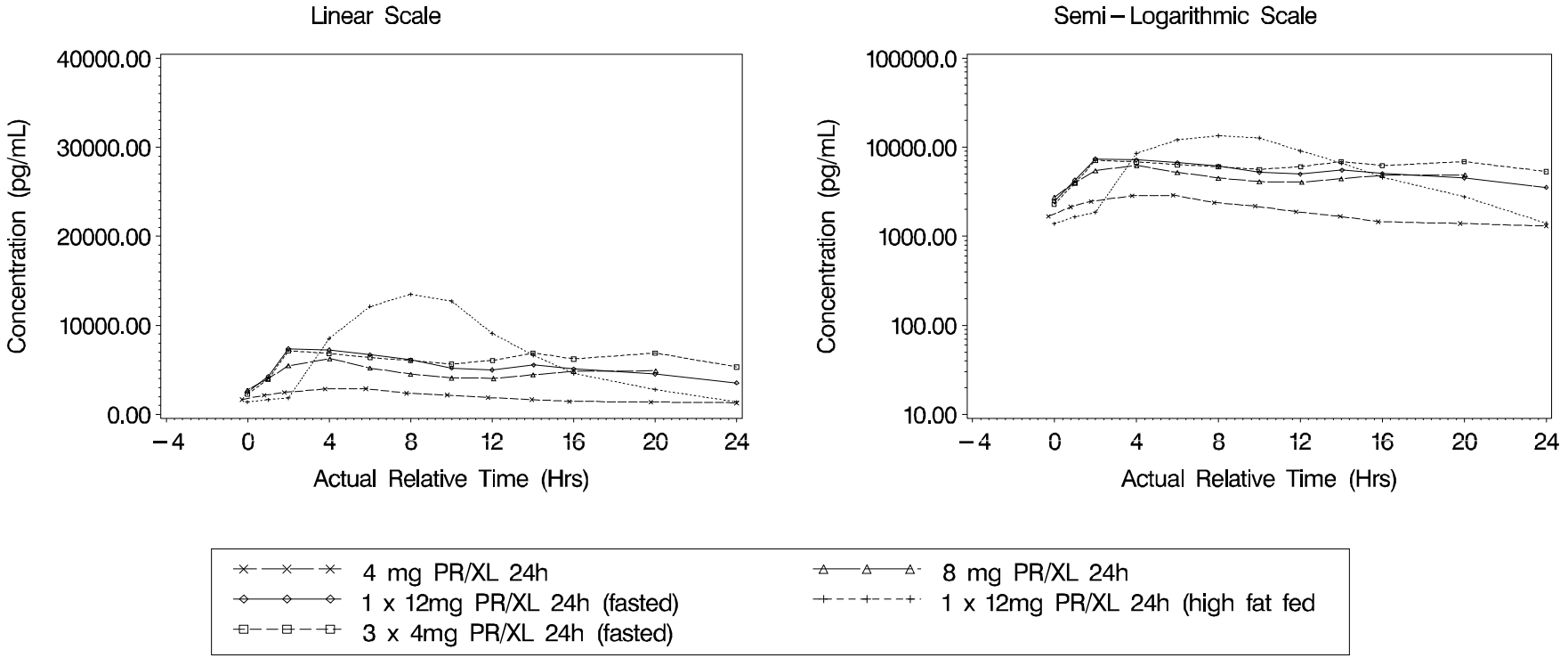
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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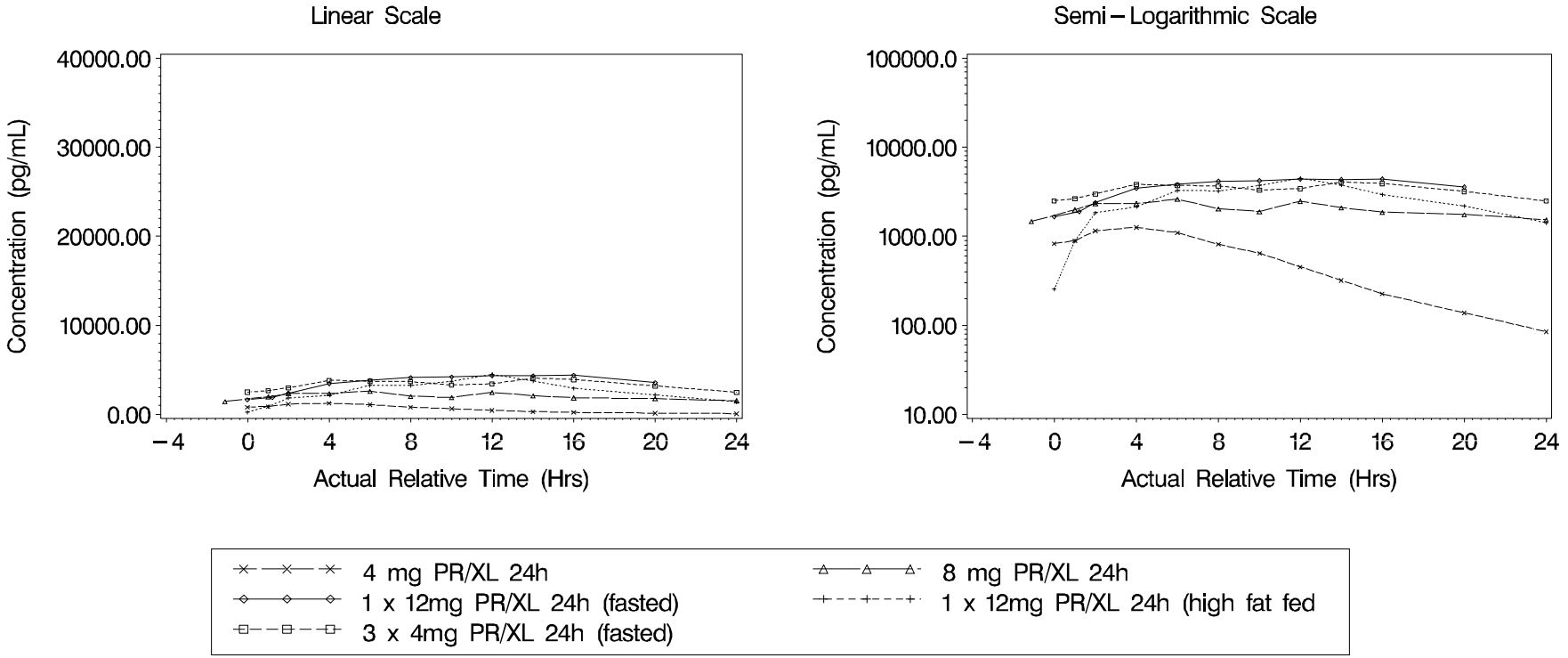
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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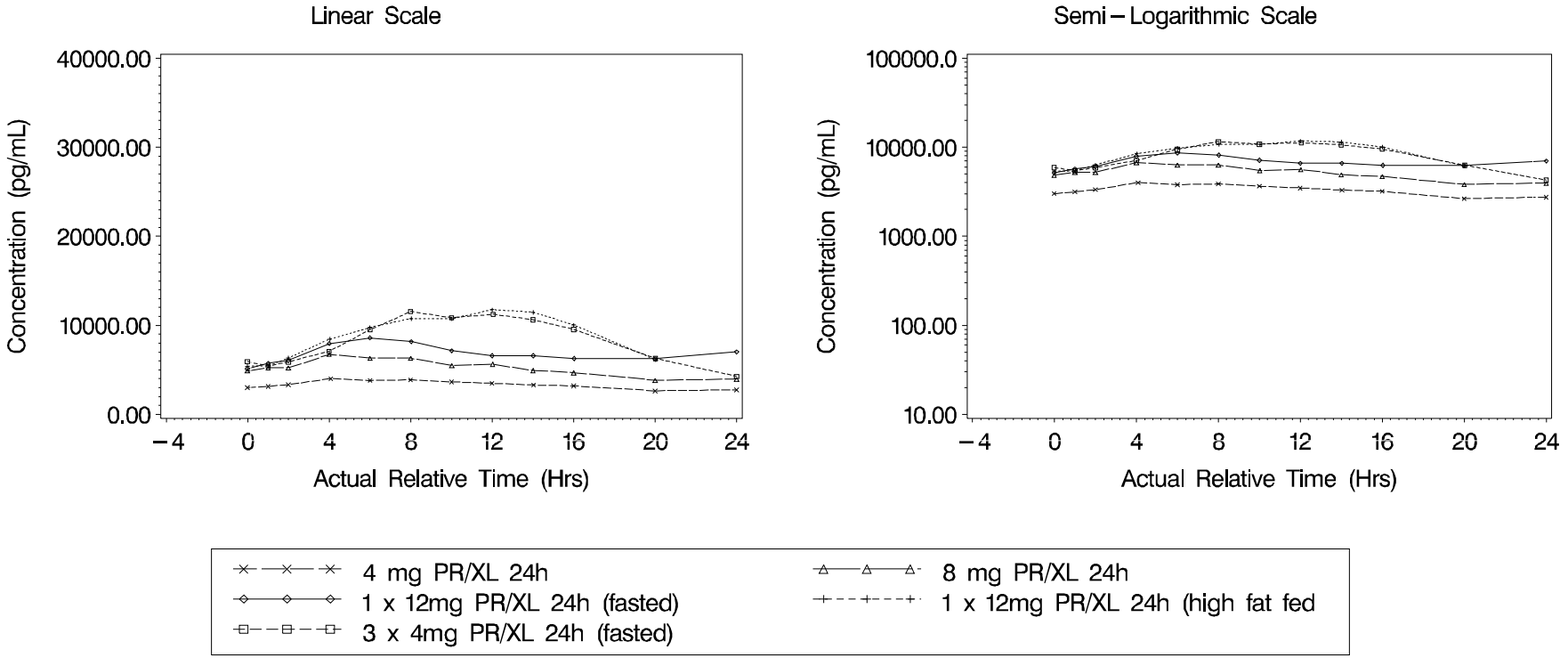
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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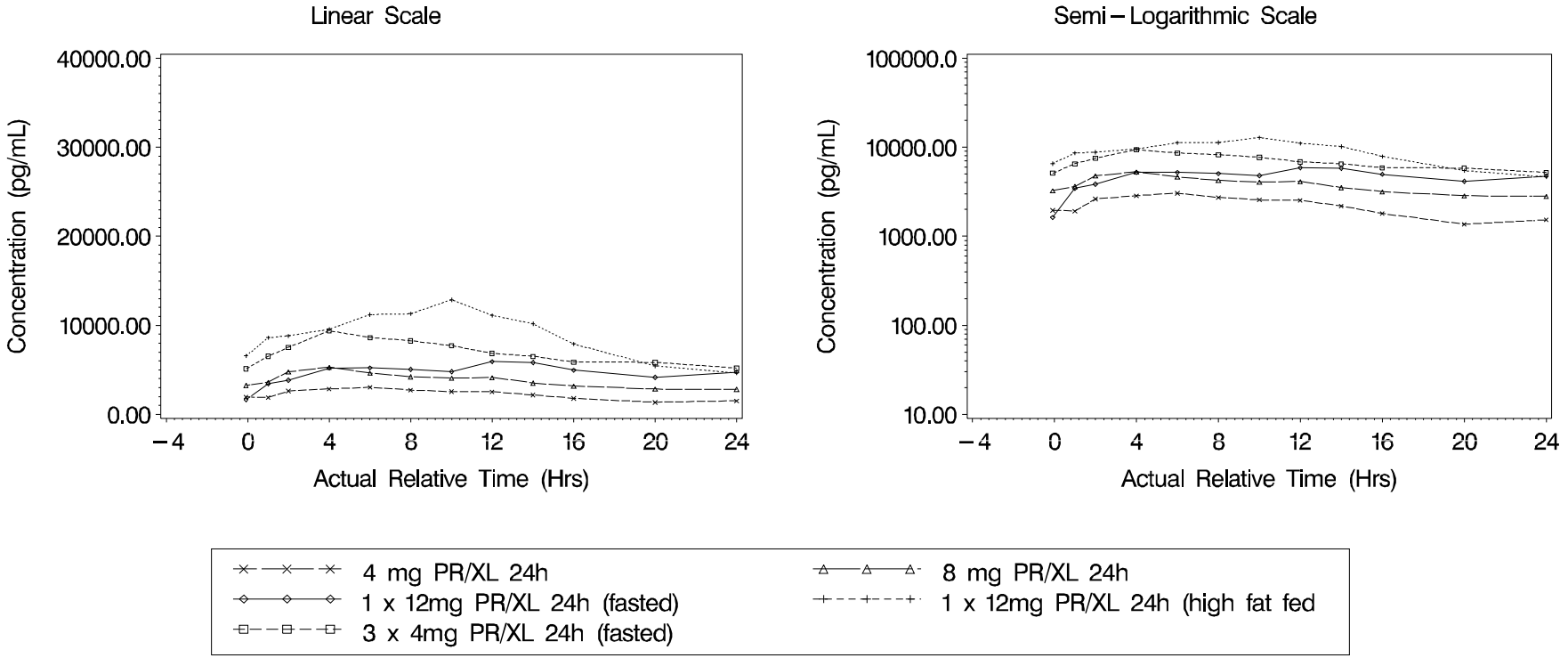
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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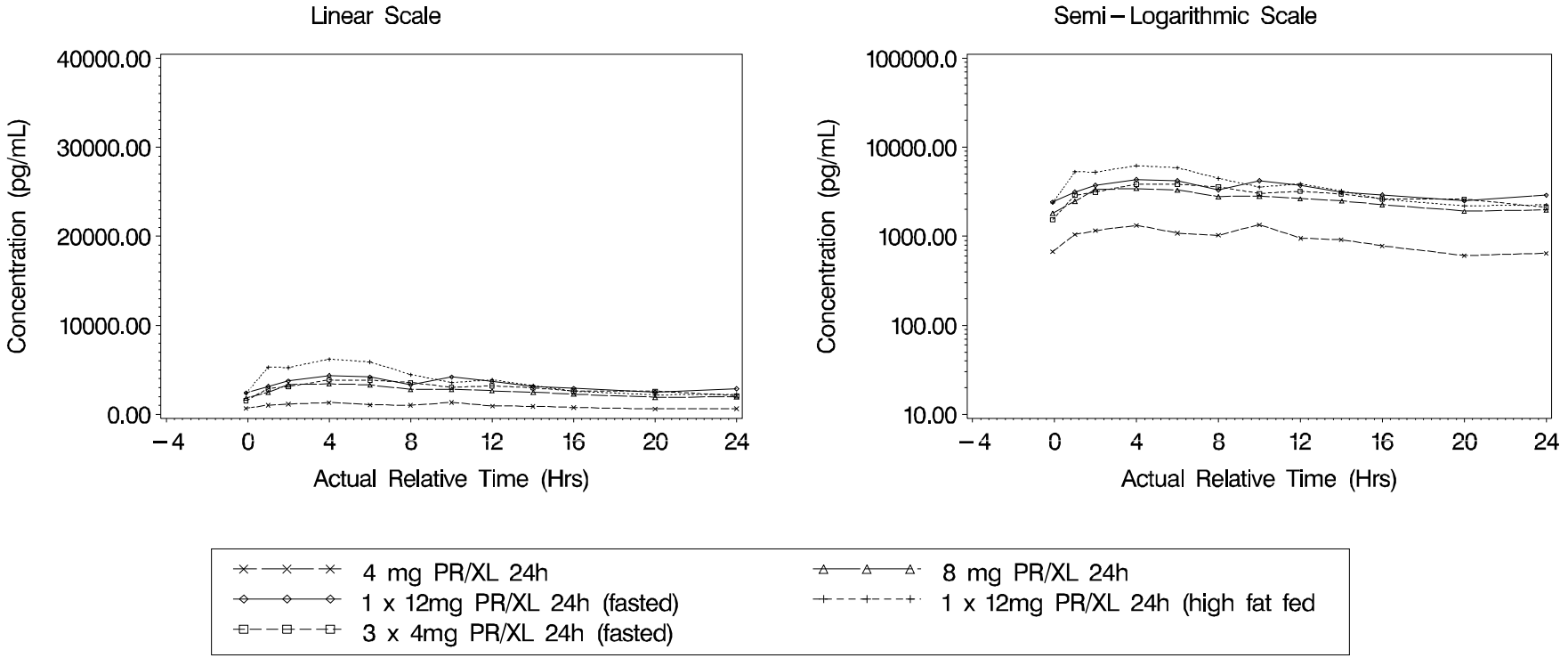
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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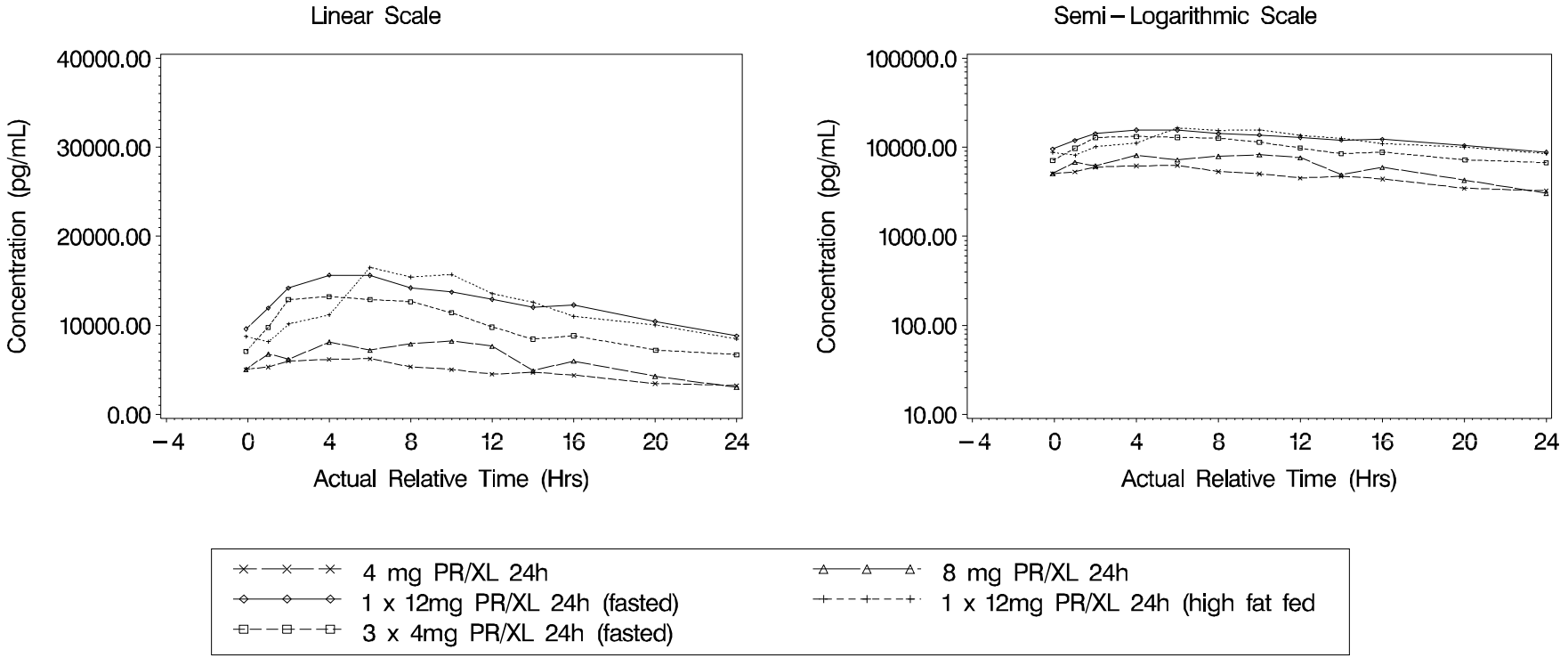
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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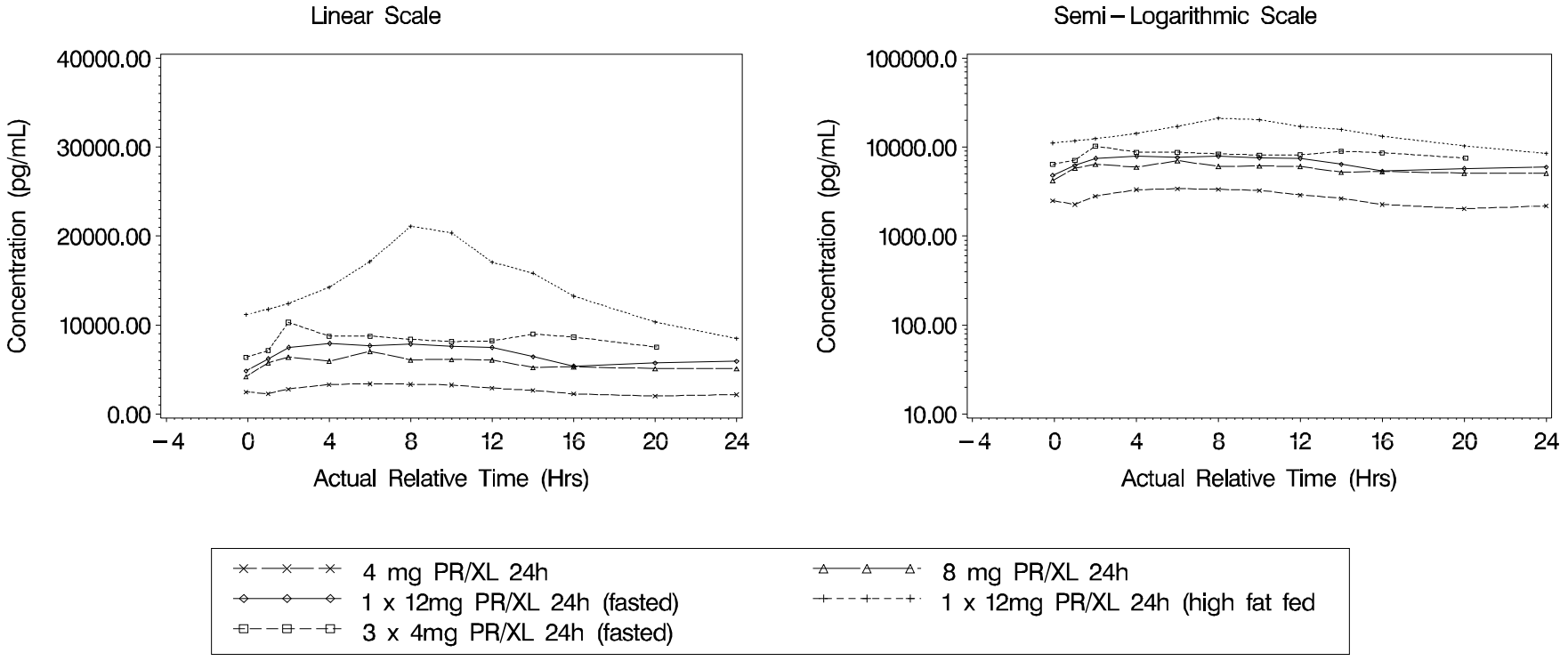
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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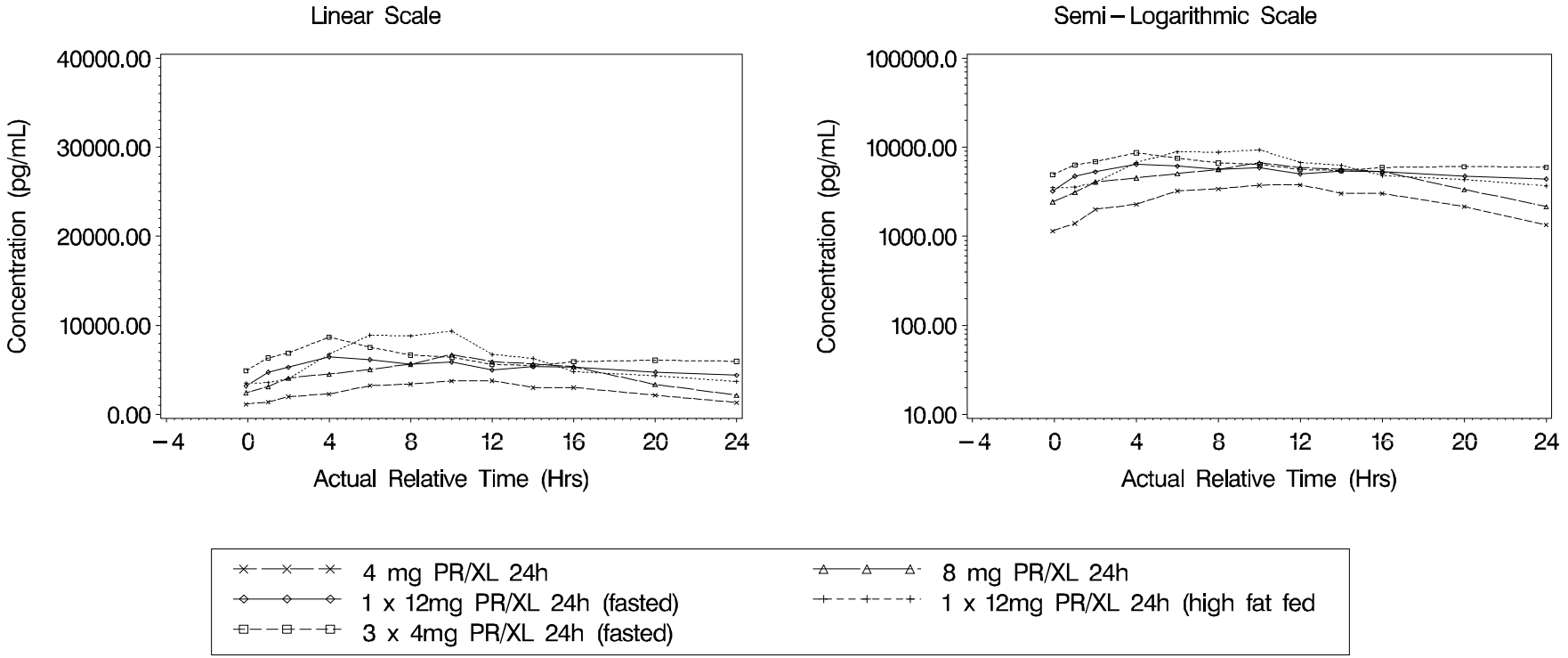
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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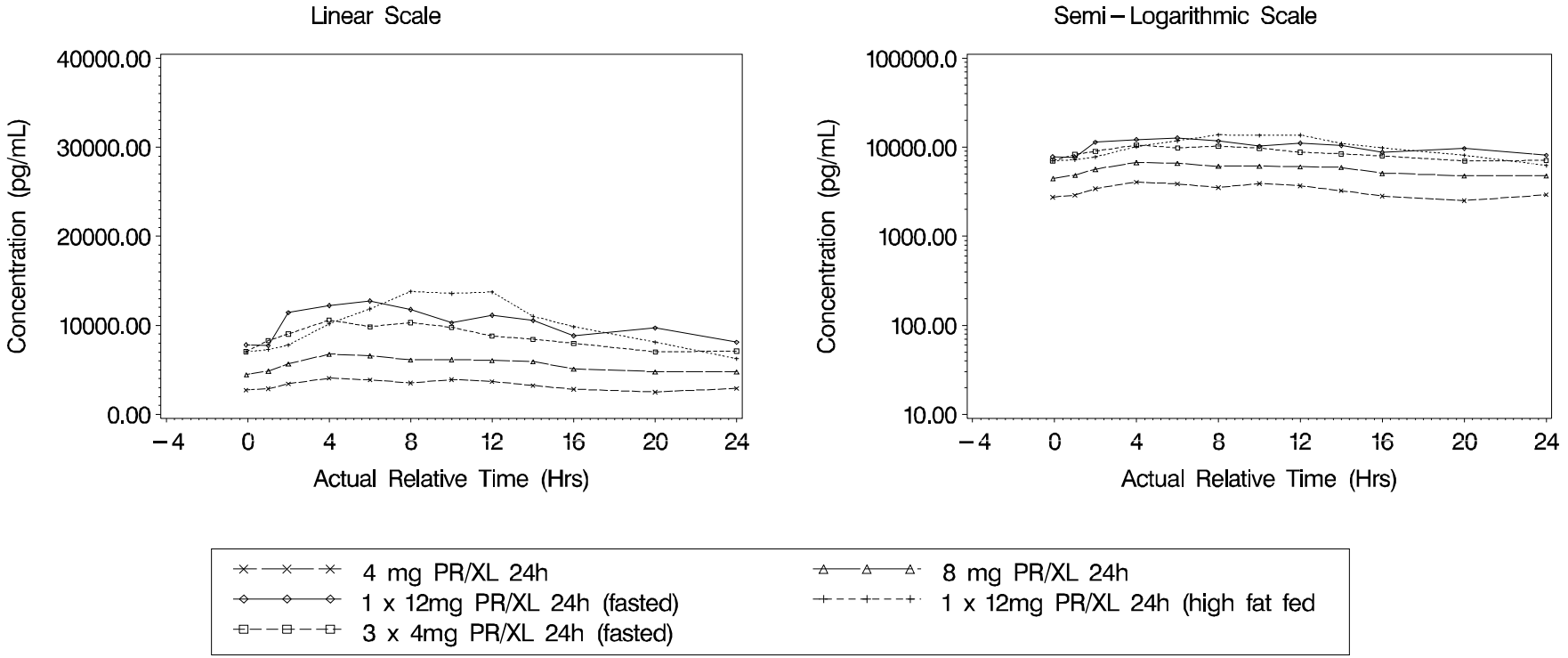
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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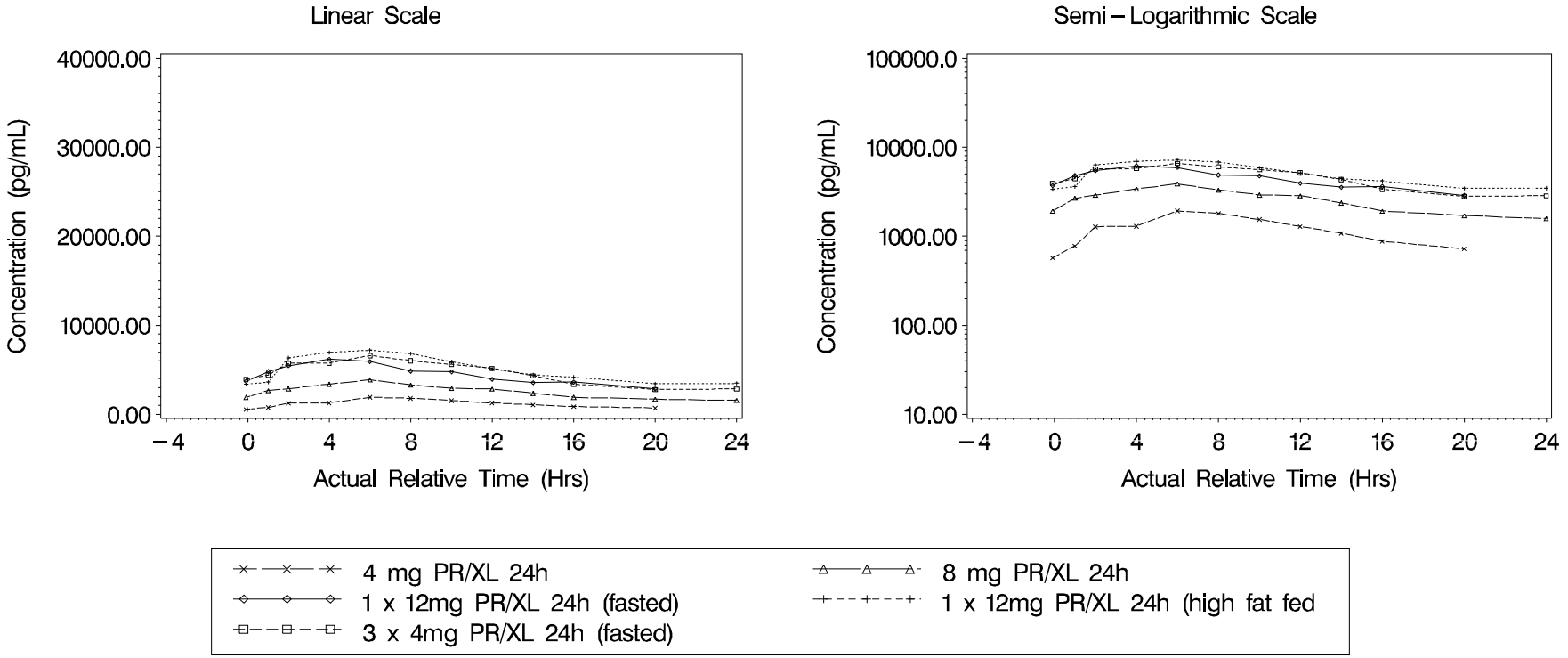
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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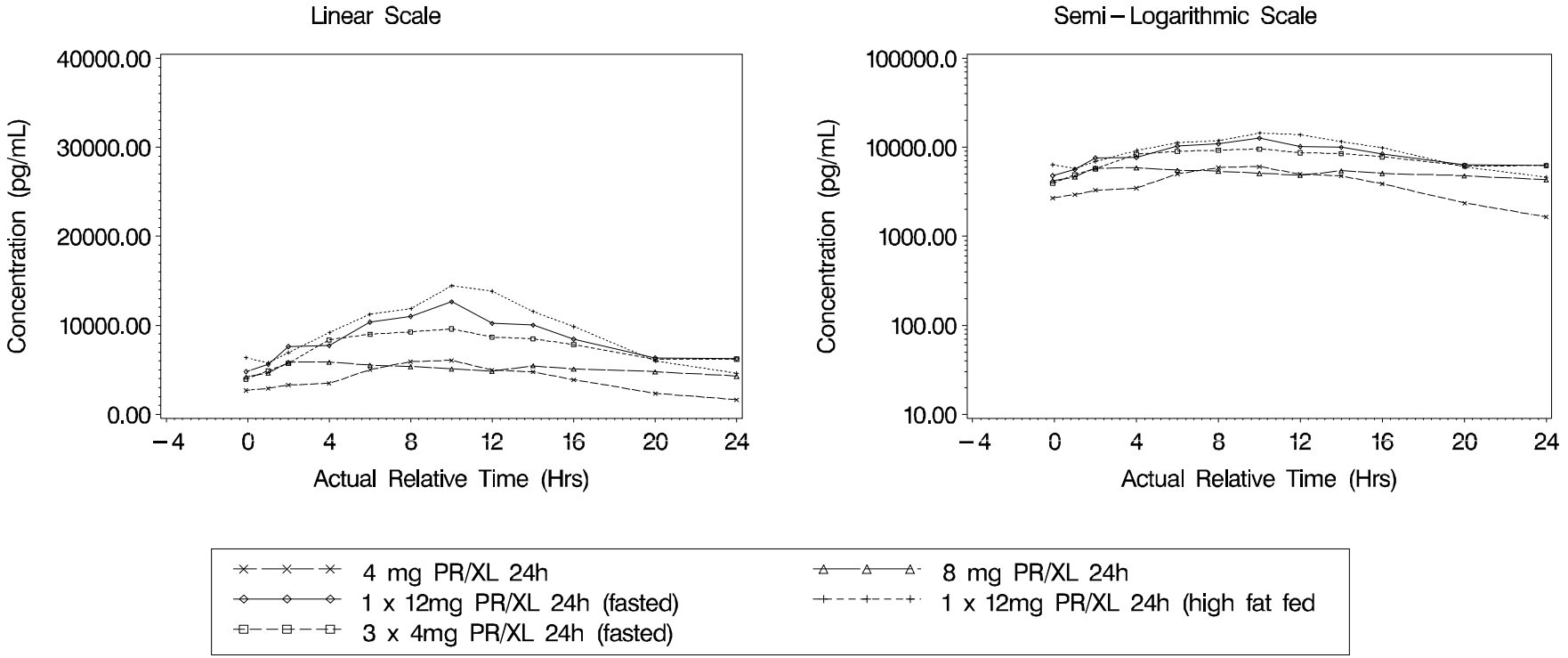
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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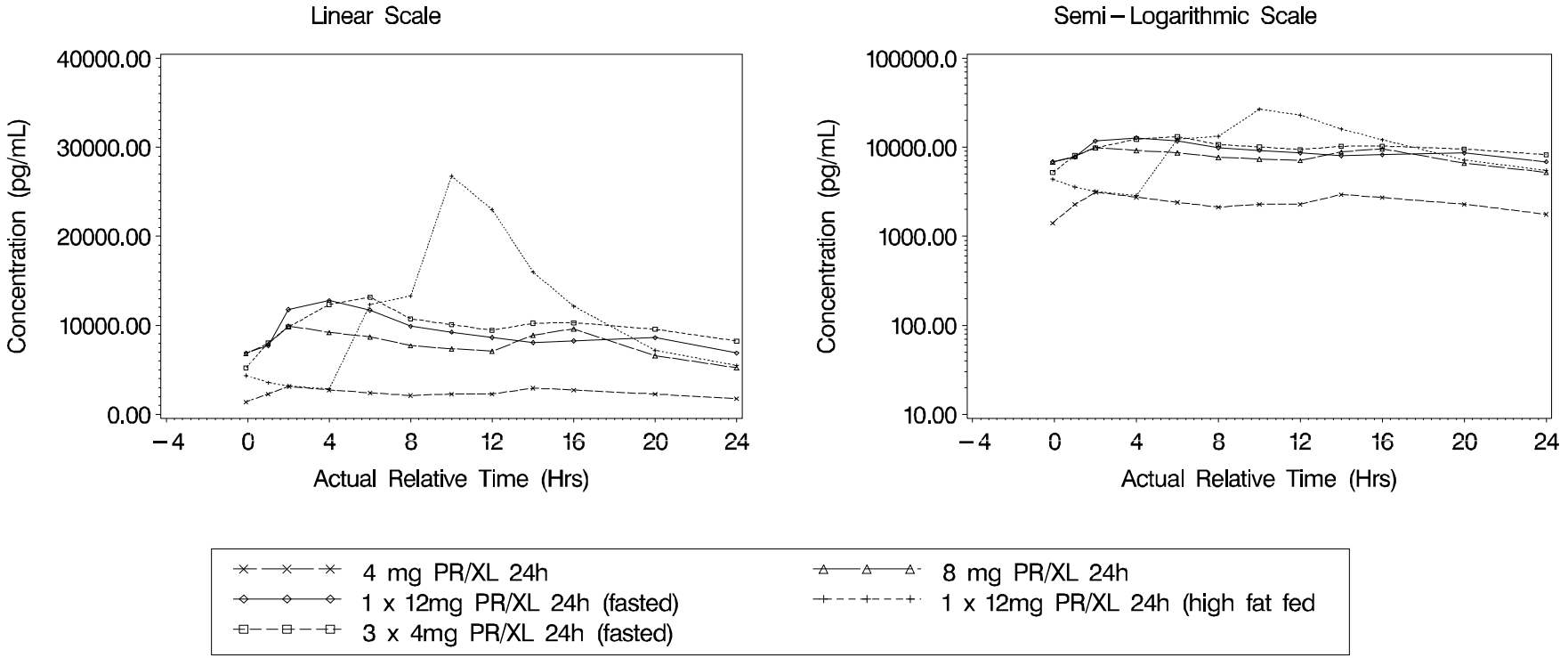
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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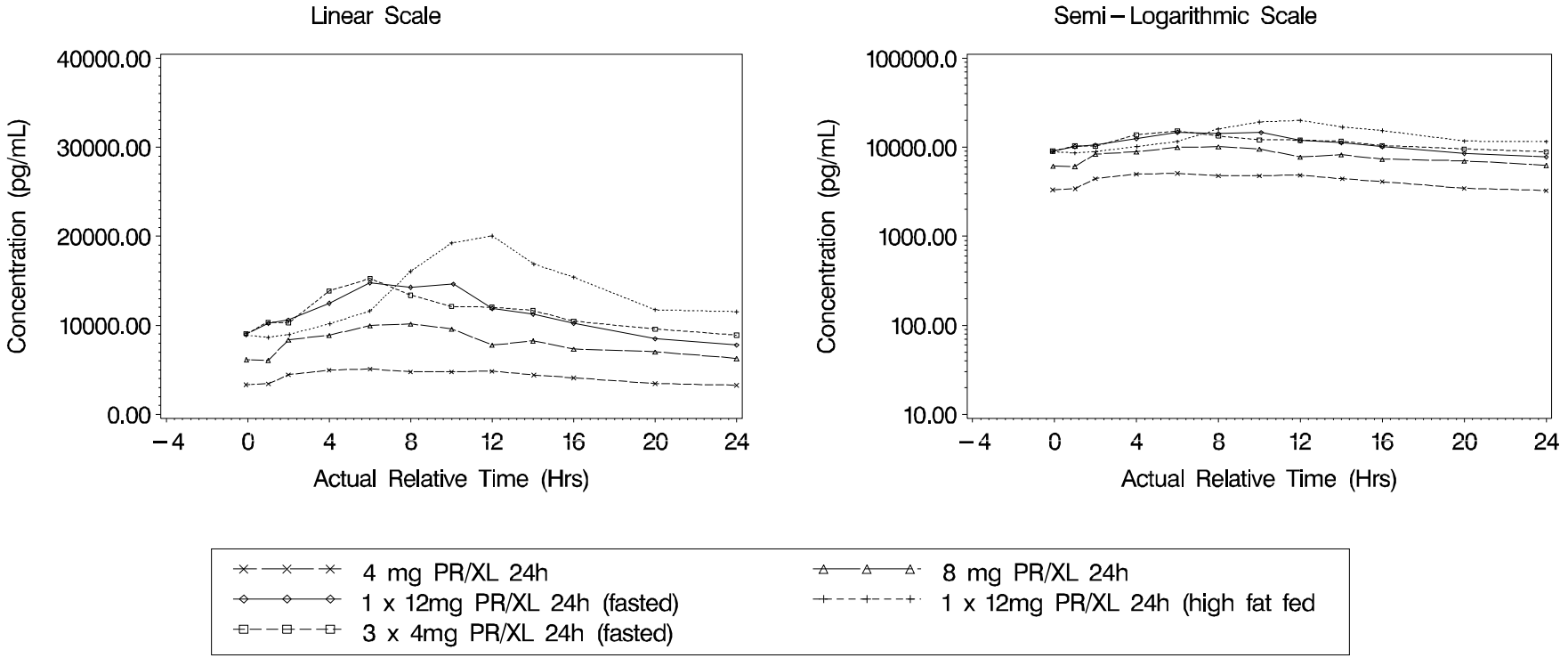
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

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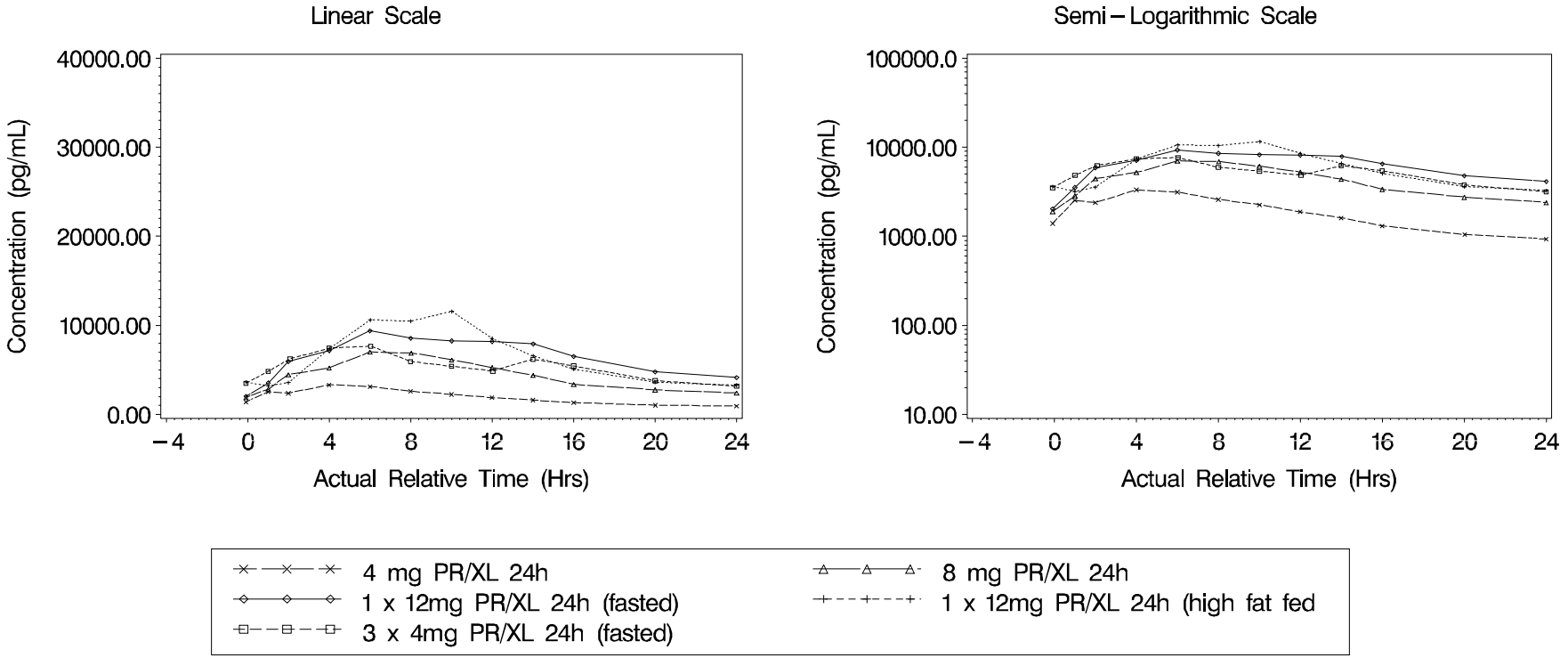
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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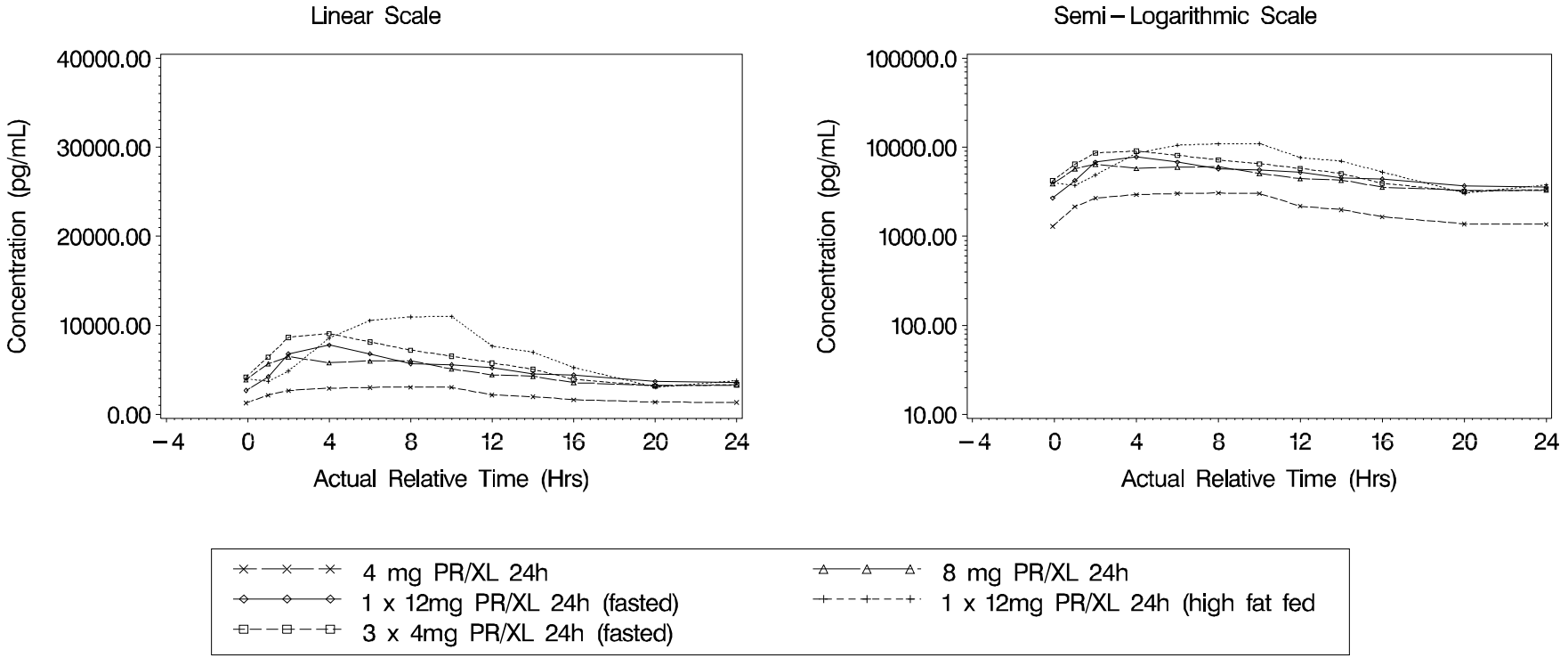
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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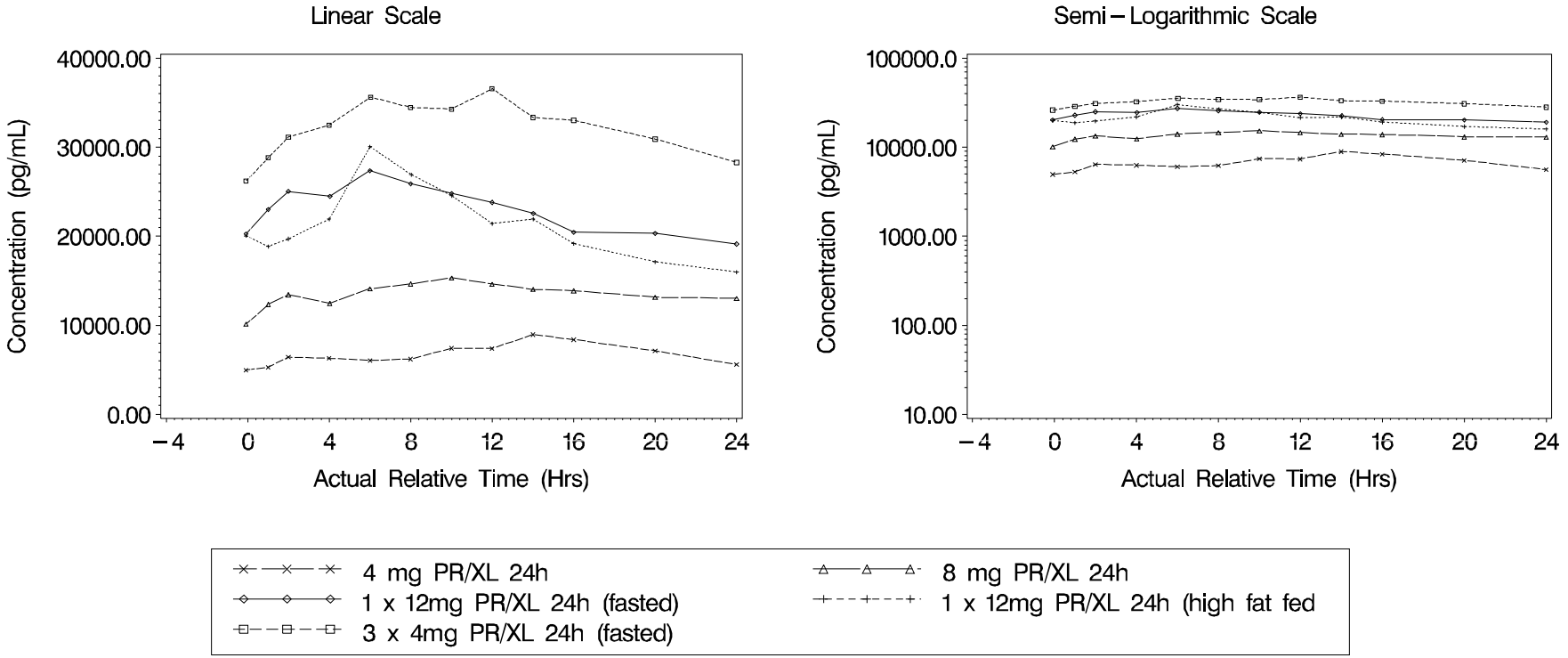
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
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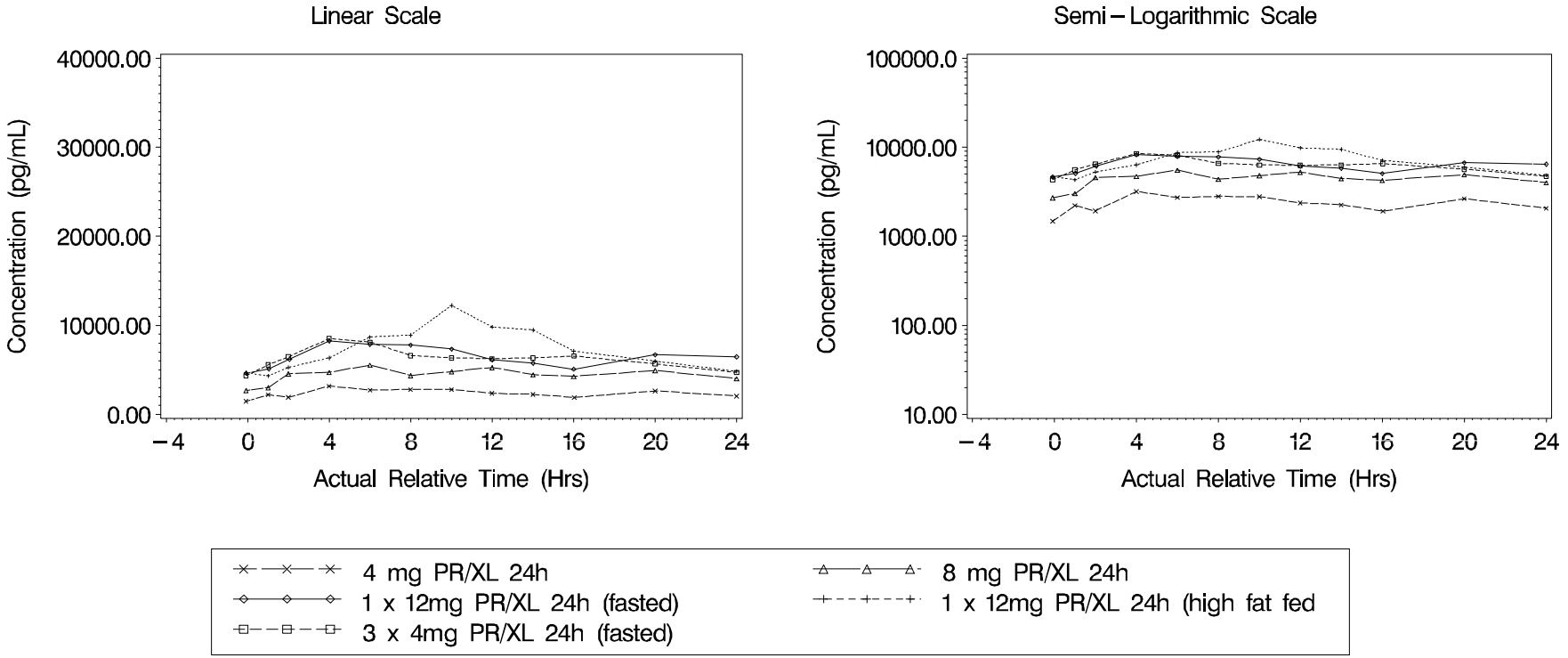
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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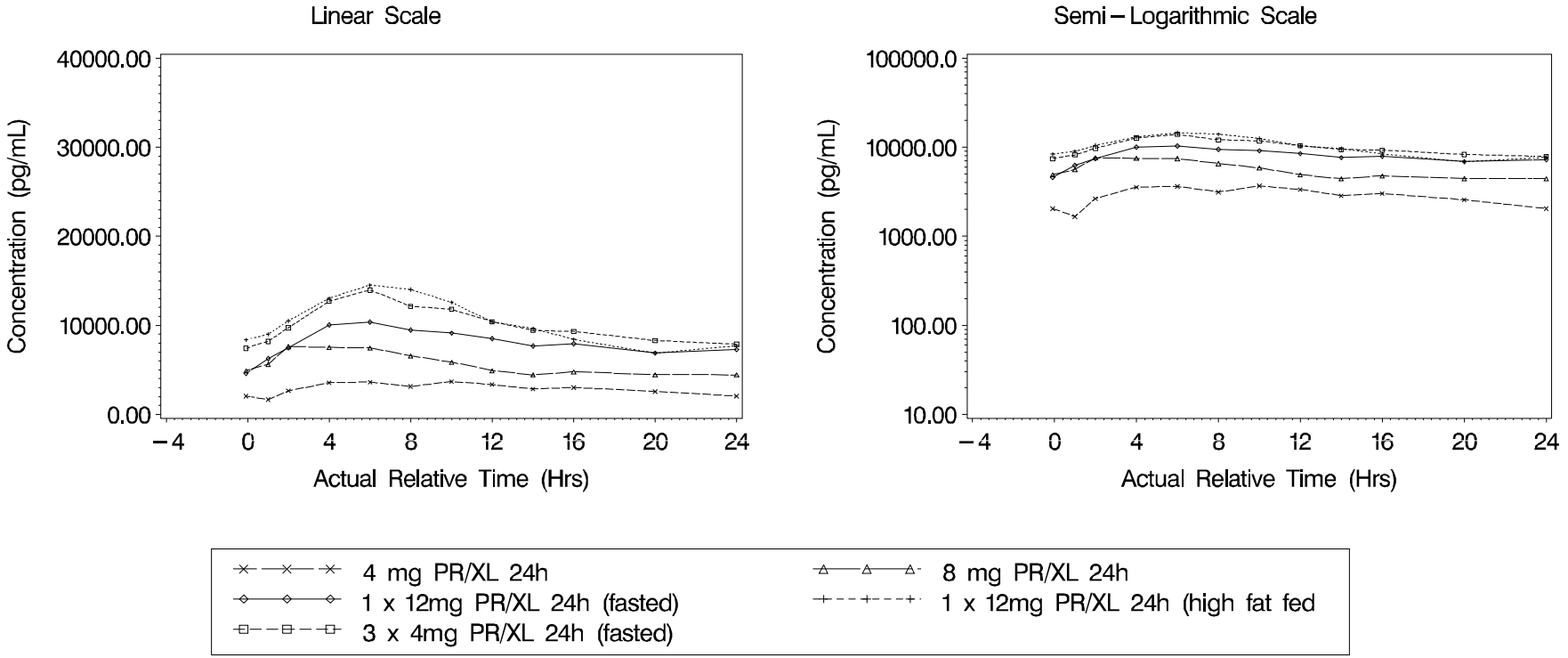
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)
[redacted]



NOTE: LLQ = 20 pg/mL
[redacted]

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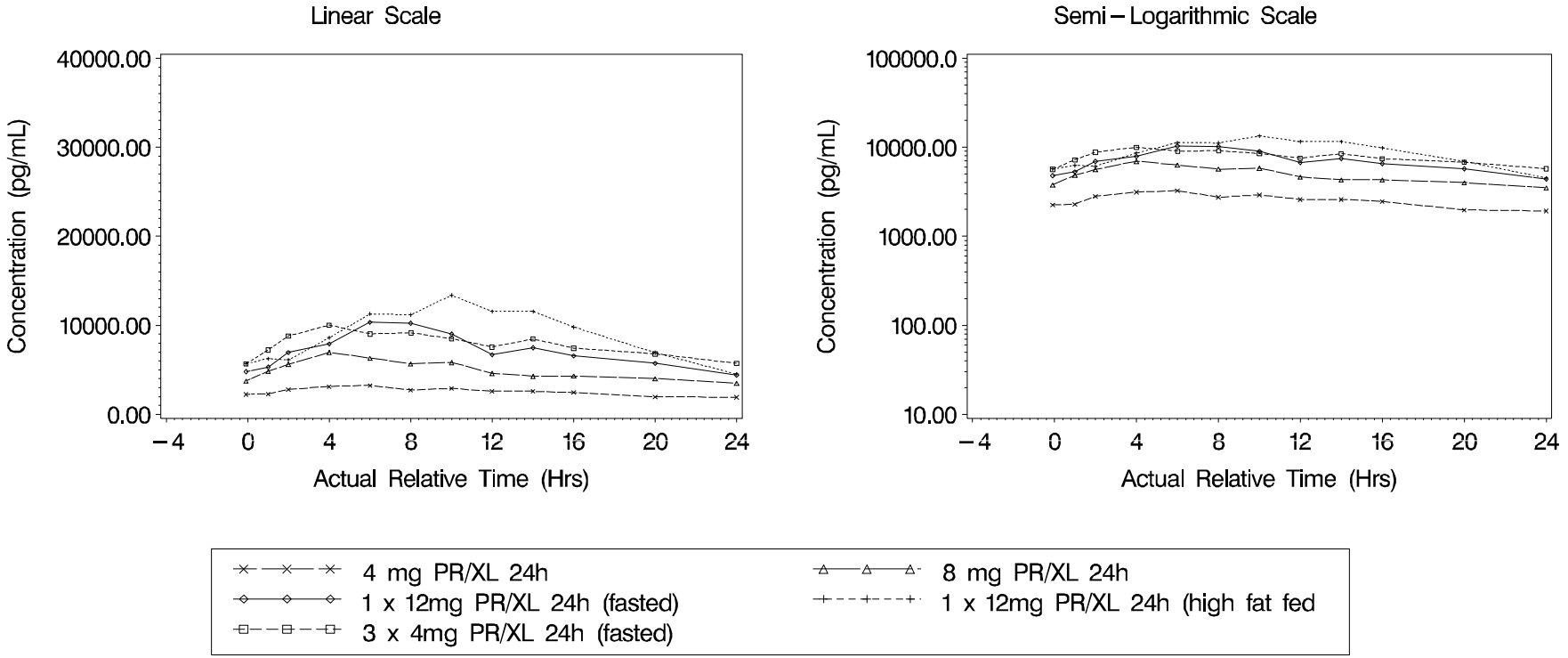
Figure 12.08
Individual plasma Ropinirole (SKF−101468) Concentration−Time Plots (Linear and Semi−log)



NOTE: LLQ = 20 pg/mL

[redacted]

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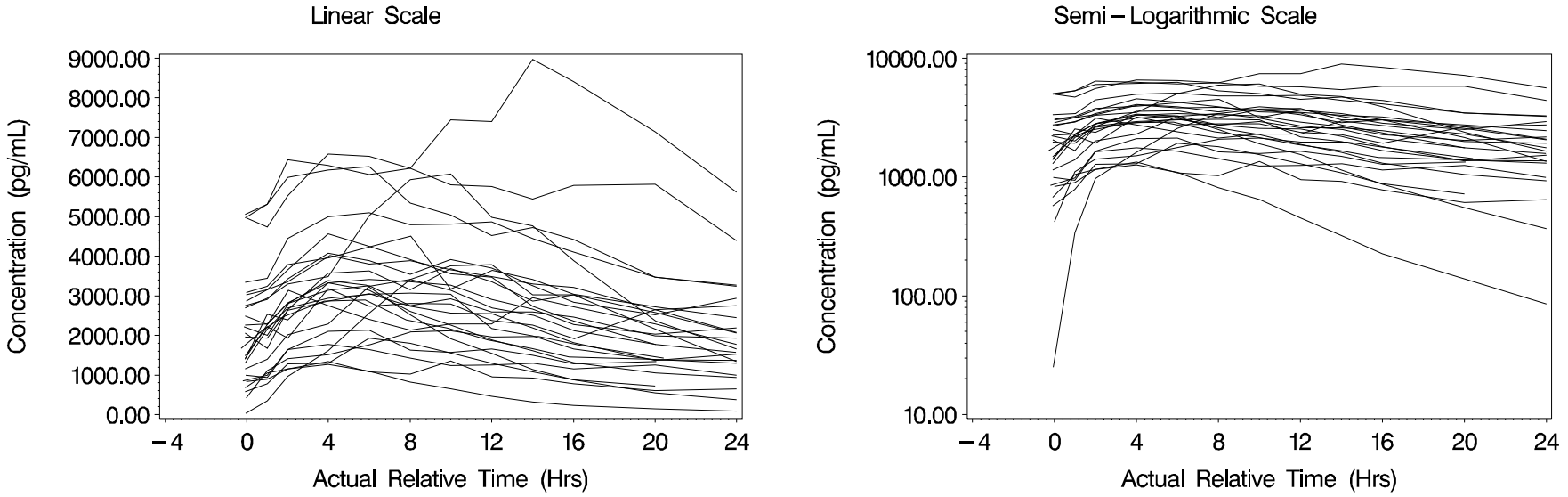
Figure 12.09
Individual Plasma Ropinirole (SKF−101468) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=4 mg PR/XL 24h



NOTE: LLQ = 20 pg/mL

[redacted]

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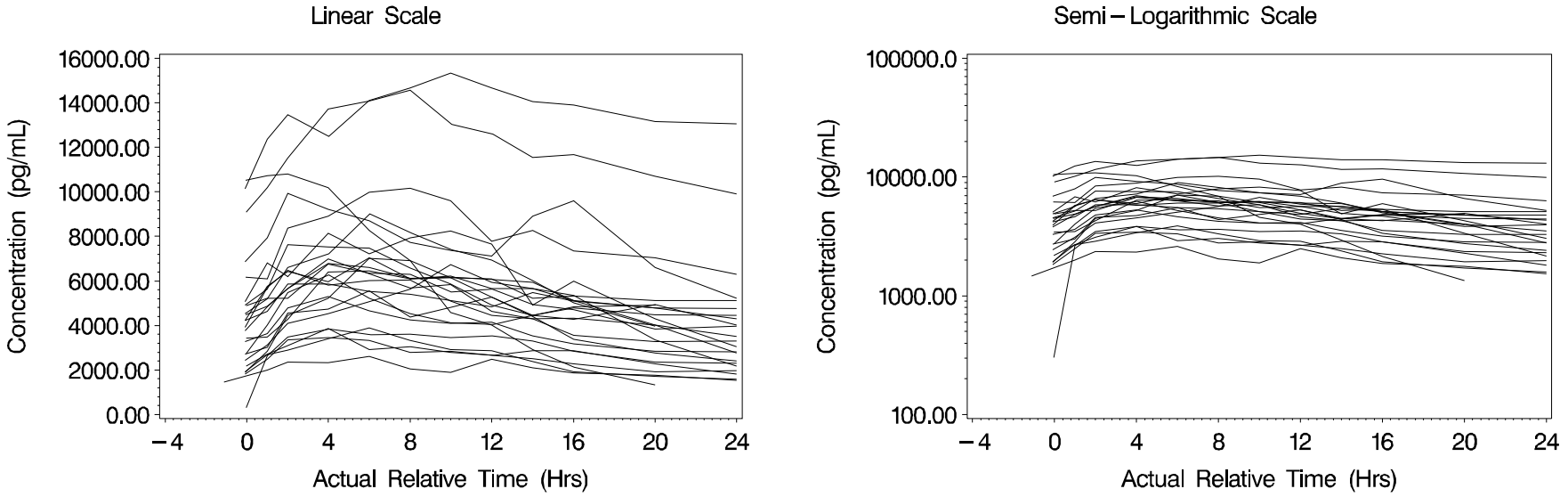
Figure 12.09
Individual Plasma Ropinirole (SKF−101468) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=8 mg PR/XL 24h



NOTE: LLQ = 20 pg/mL

[redacted]

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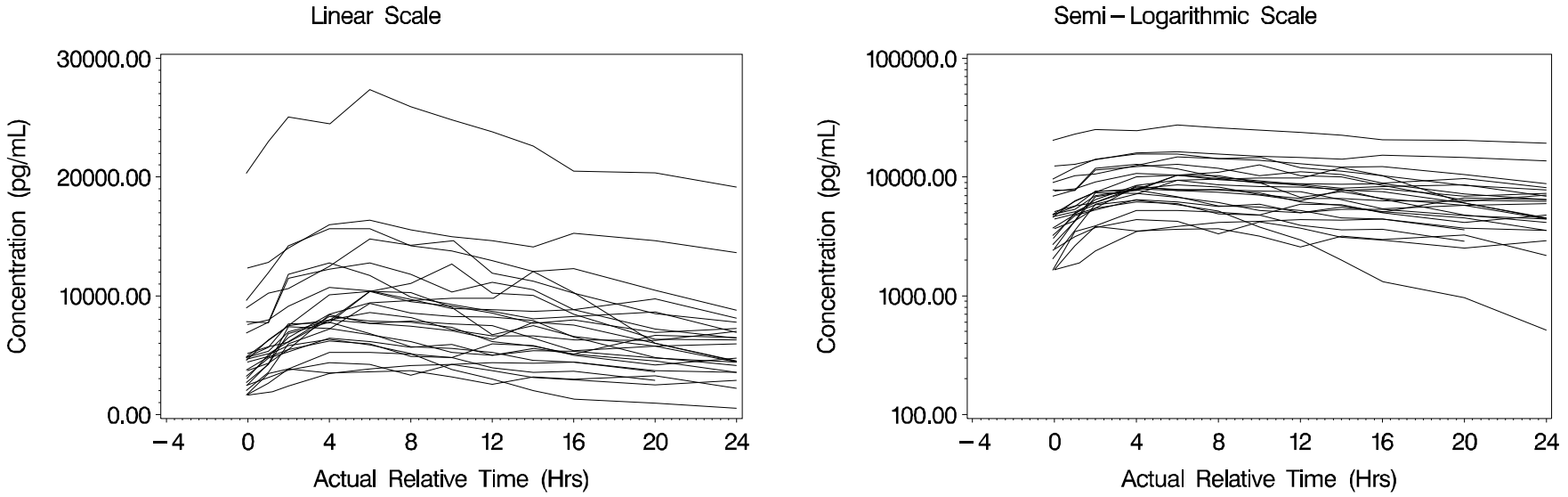
Figure 12.09
Individual Plasma Ropinirole (SKF−101468) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=1 x 12mg PR/XL 24h (fasted)



NOTE: LLQ = 20 pg/mL

[redacted]

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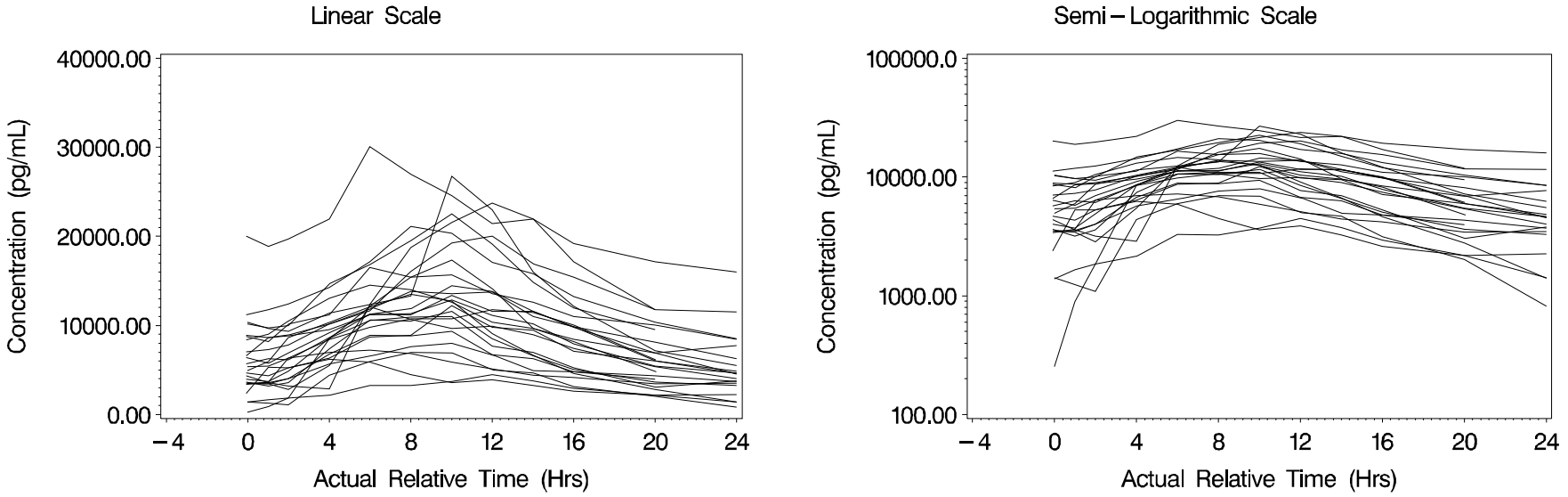
Figure 12.09
Individual Plasma Ropinirole (SKF−101468) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=1 x 12mg PR/XL 24h (high fat fed)



NOTE: LLQ = 20 pg/mL

[redacted]

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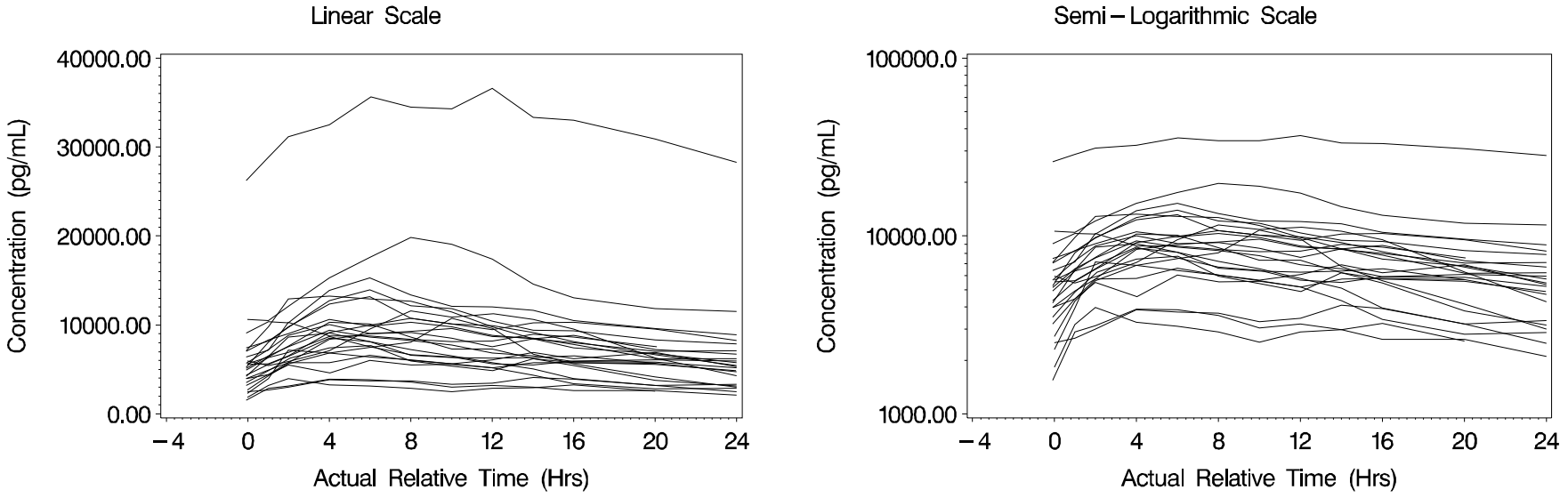
Figure 12.09
Individual Plasma Ropinirole (SKF−101468) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=3 x 4mg PR/XL 24h (fasted)



NOTE: LLQ = 20 pg/mL

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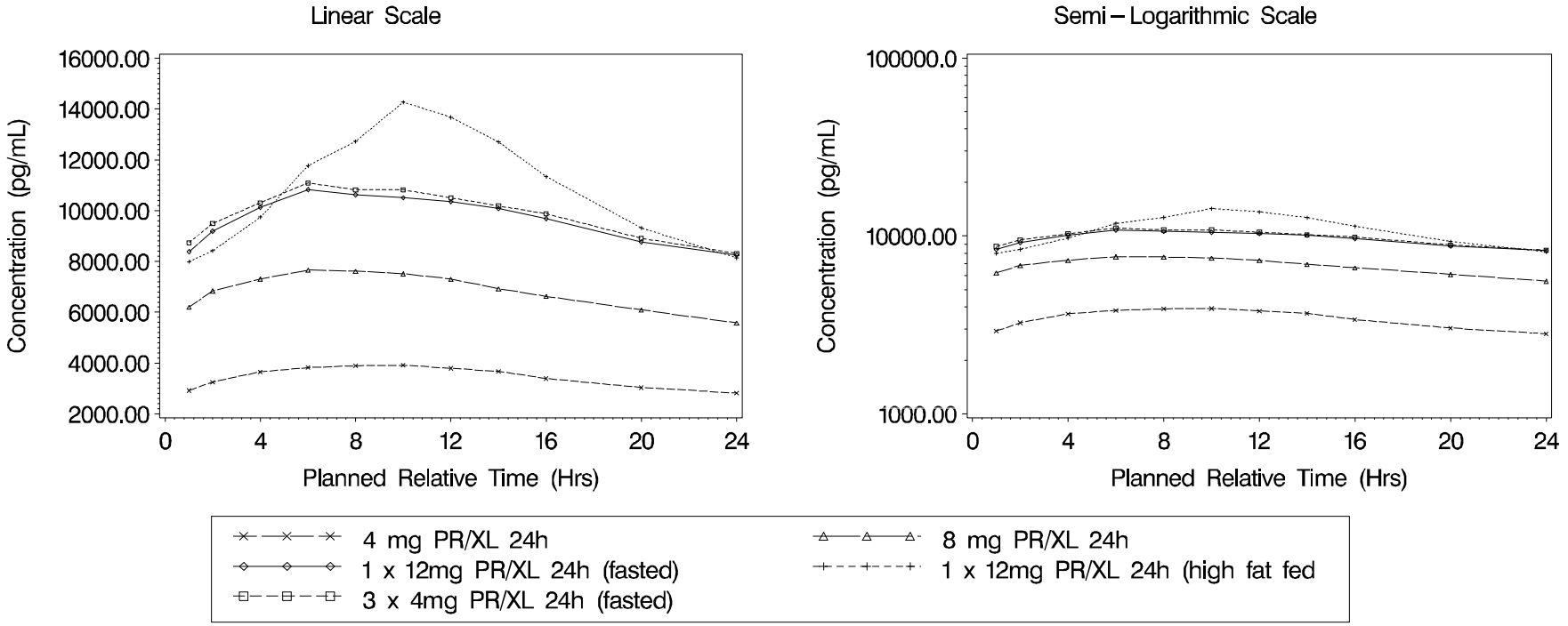
Figure 12.10
Mean Plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log)− B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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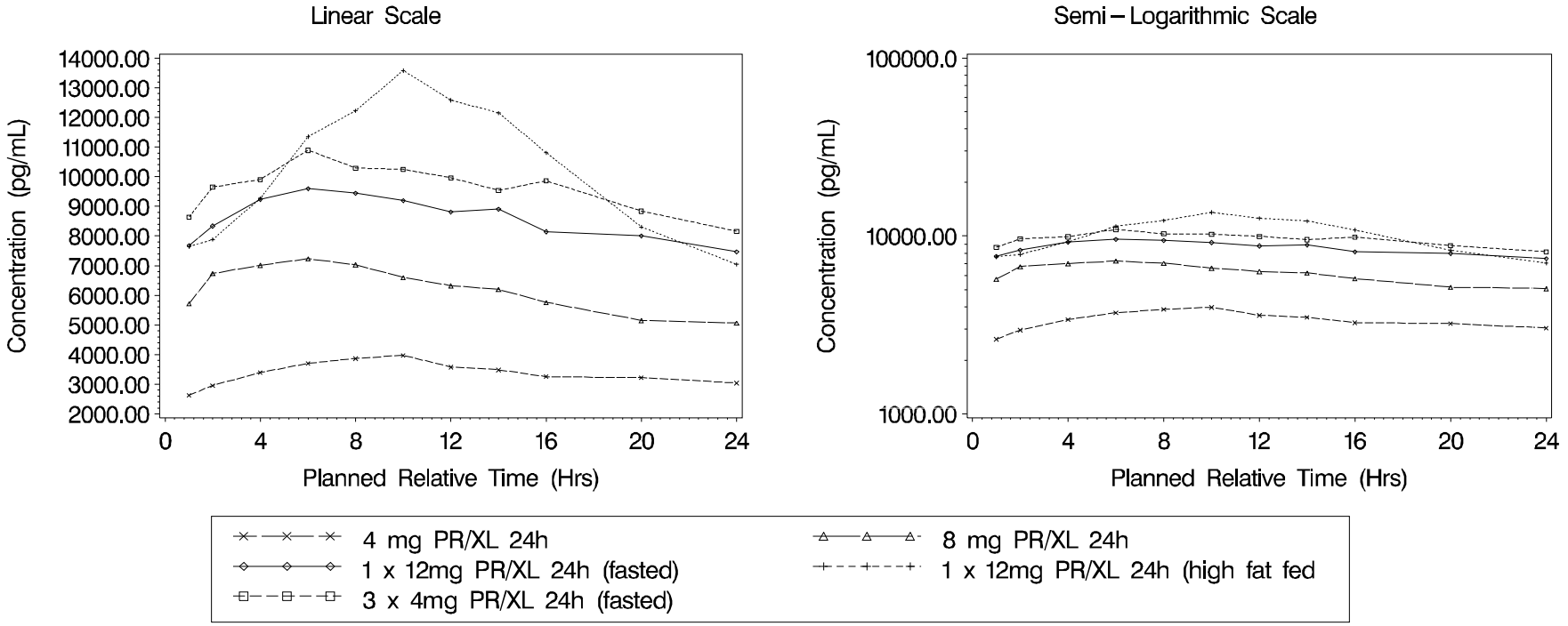
Figure 12.11
Median plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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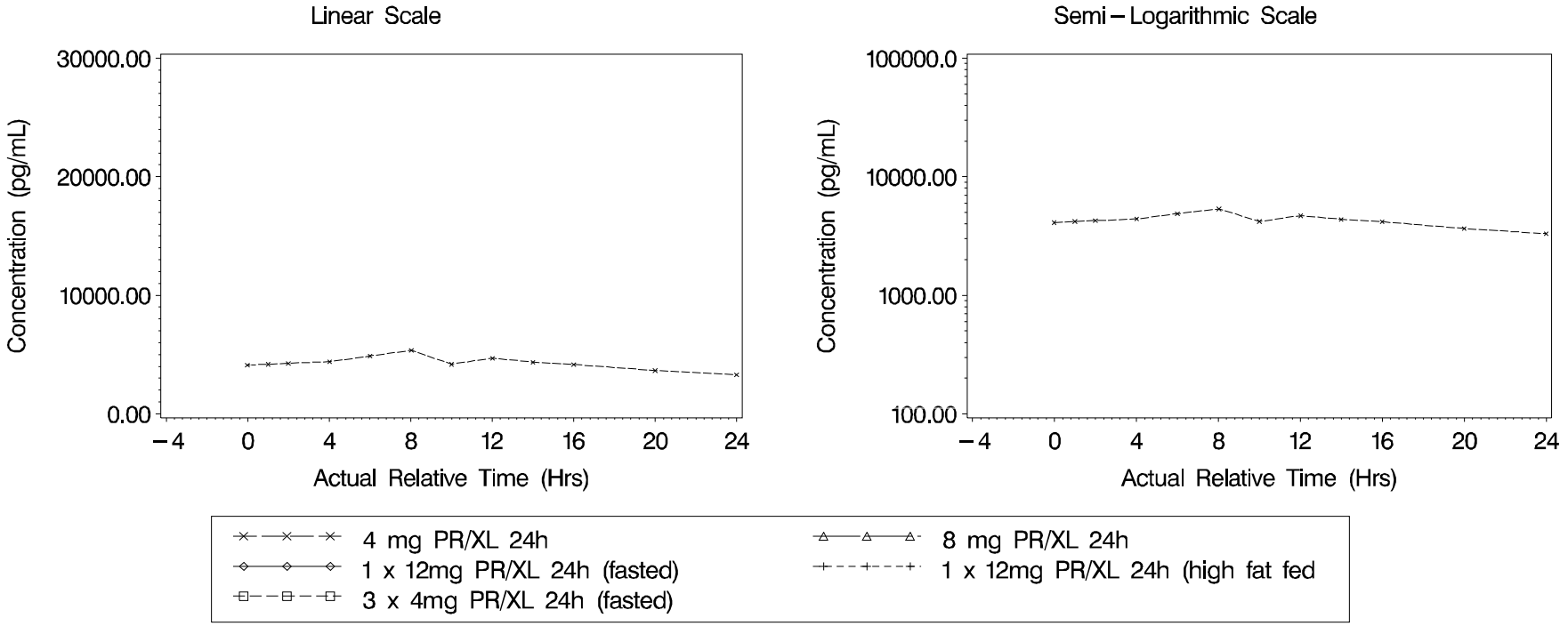
Figure 12.12

Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G [redacted]



NOTE: LLQ = 50 pg/mL

B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted) [redacted]

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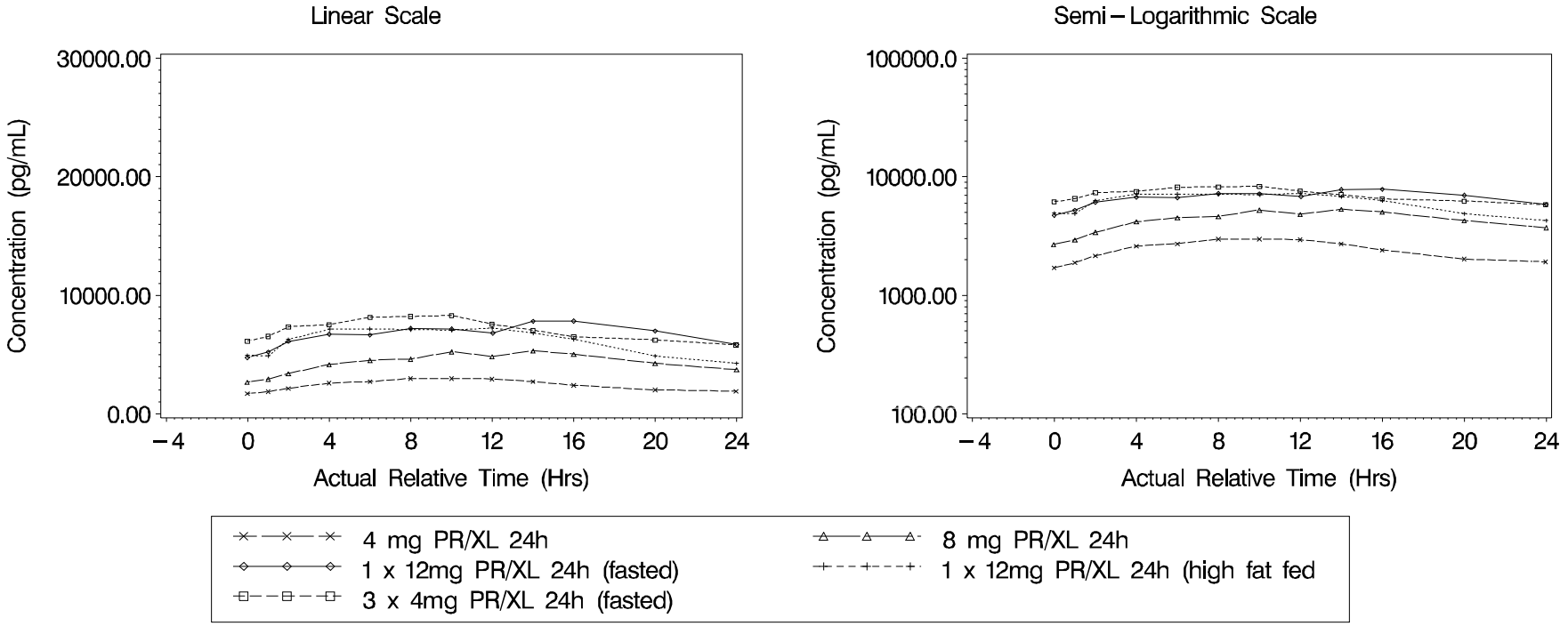
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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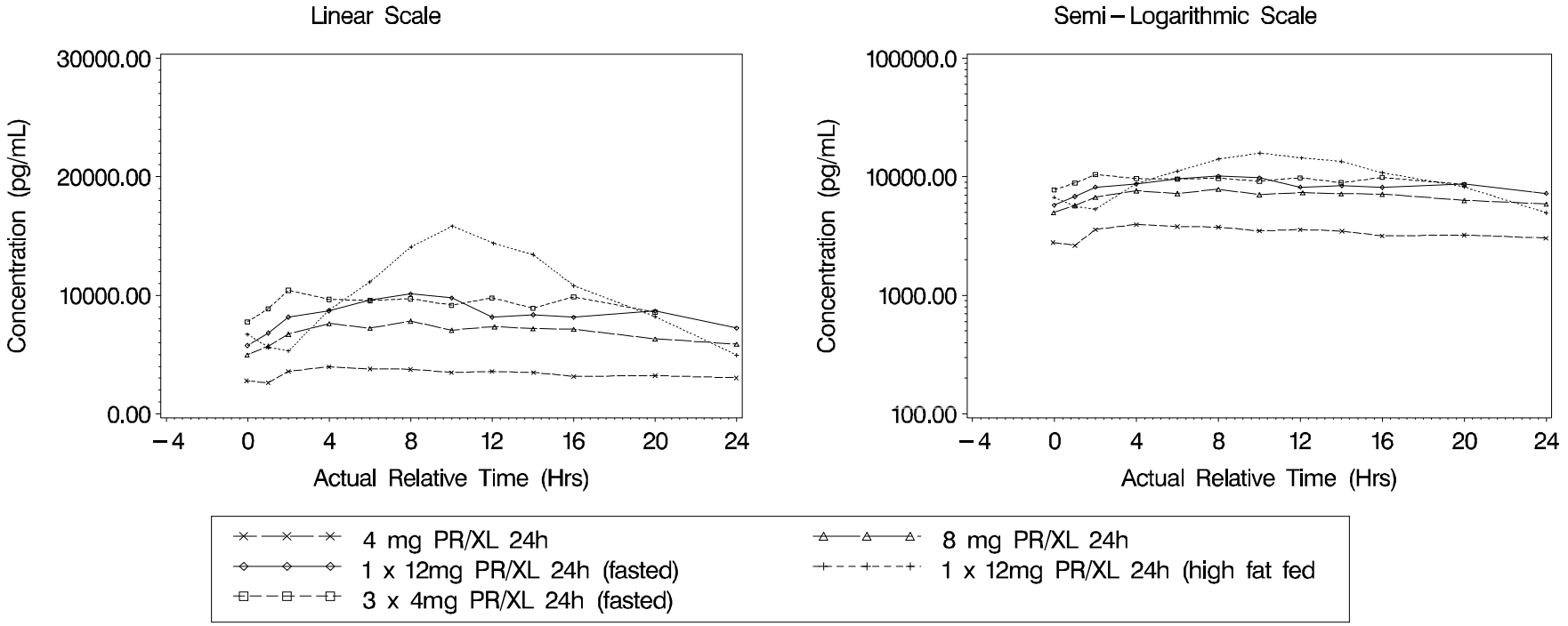
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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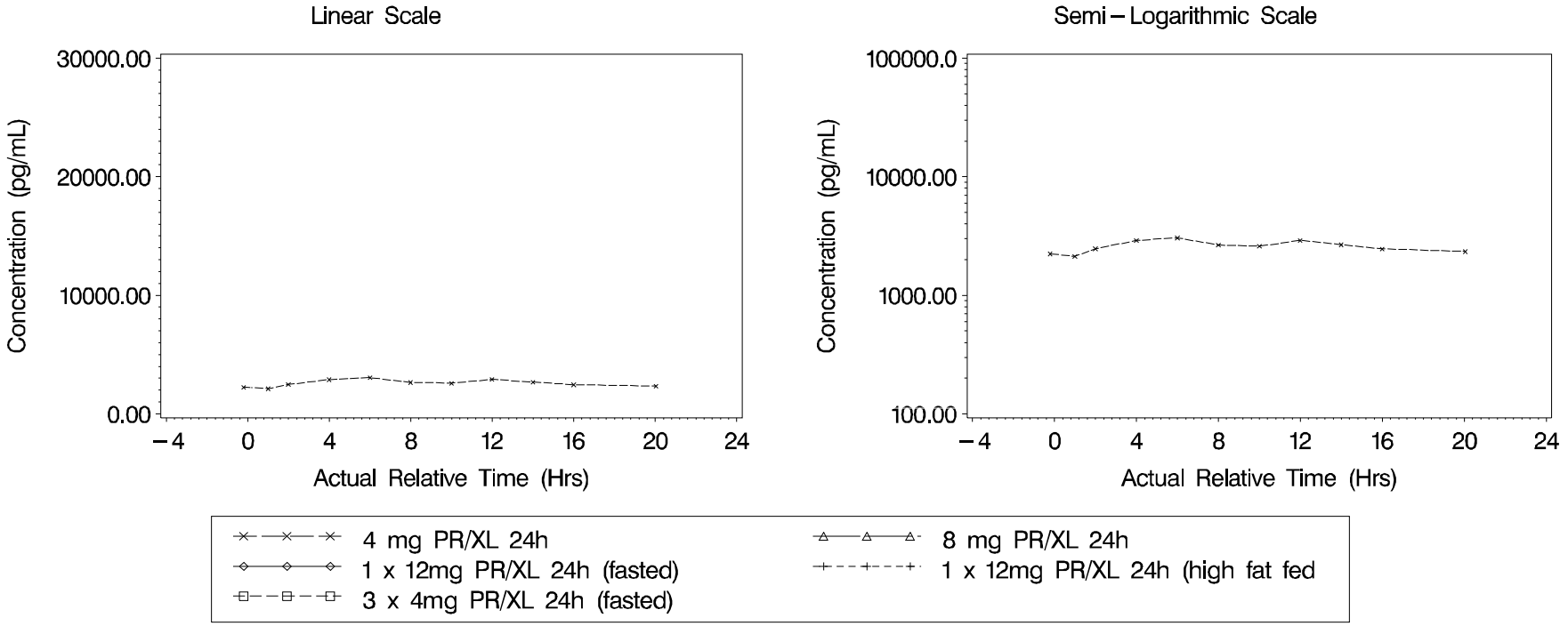
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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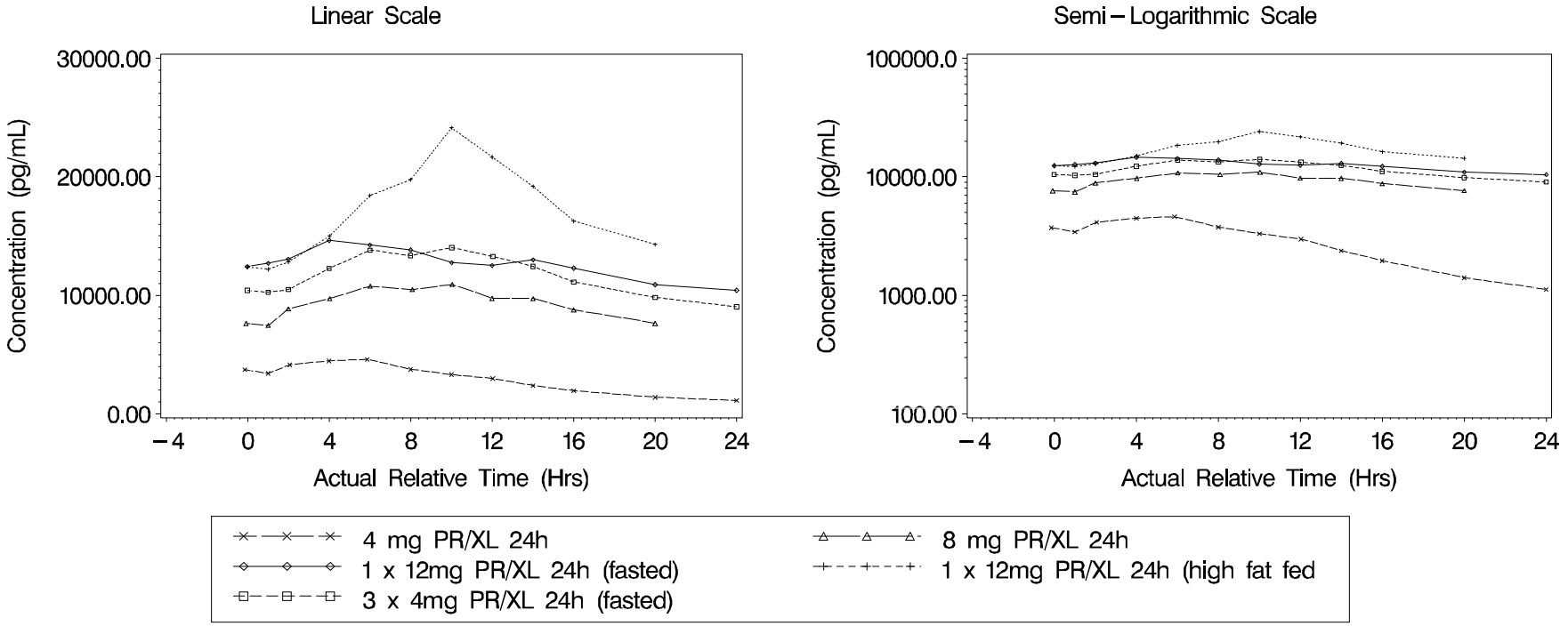
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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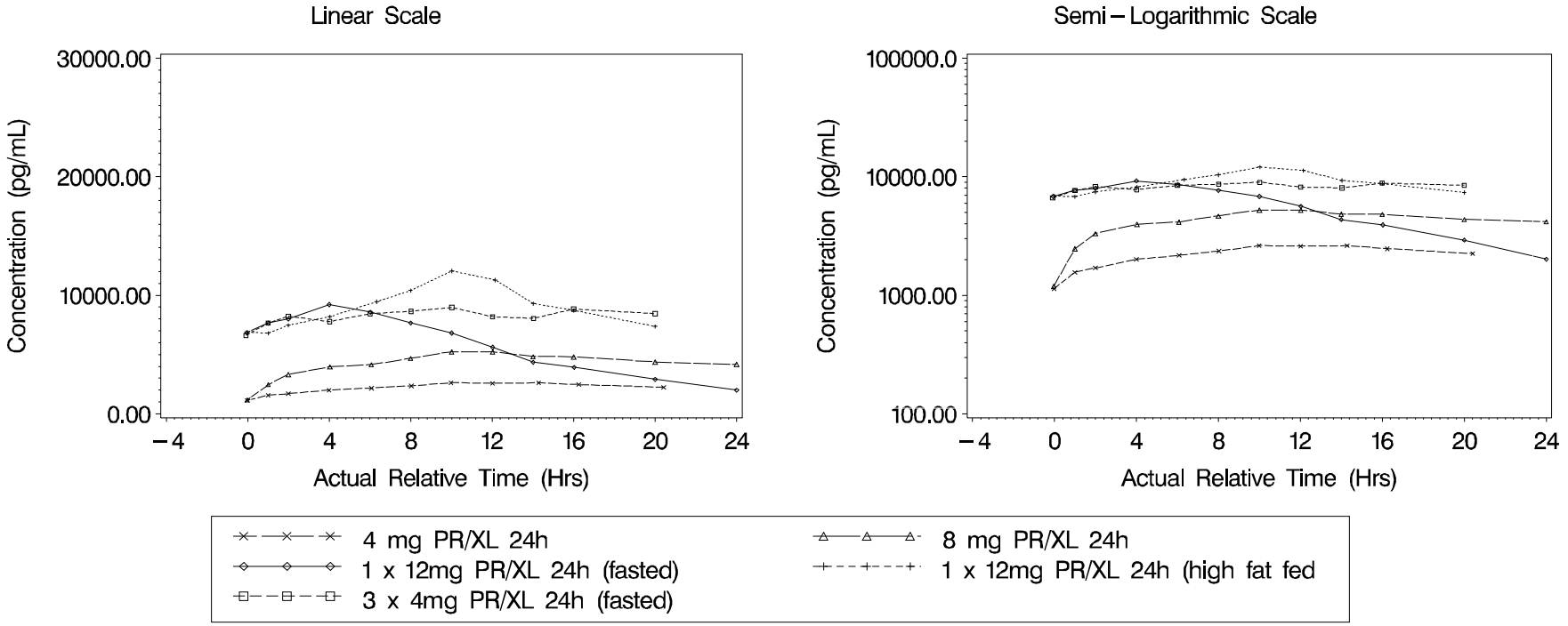
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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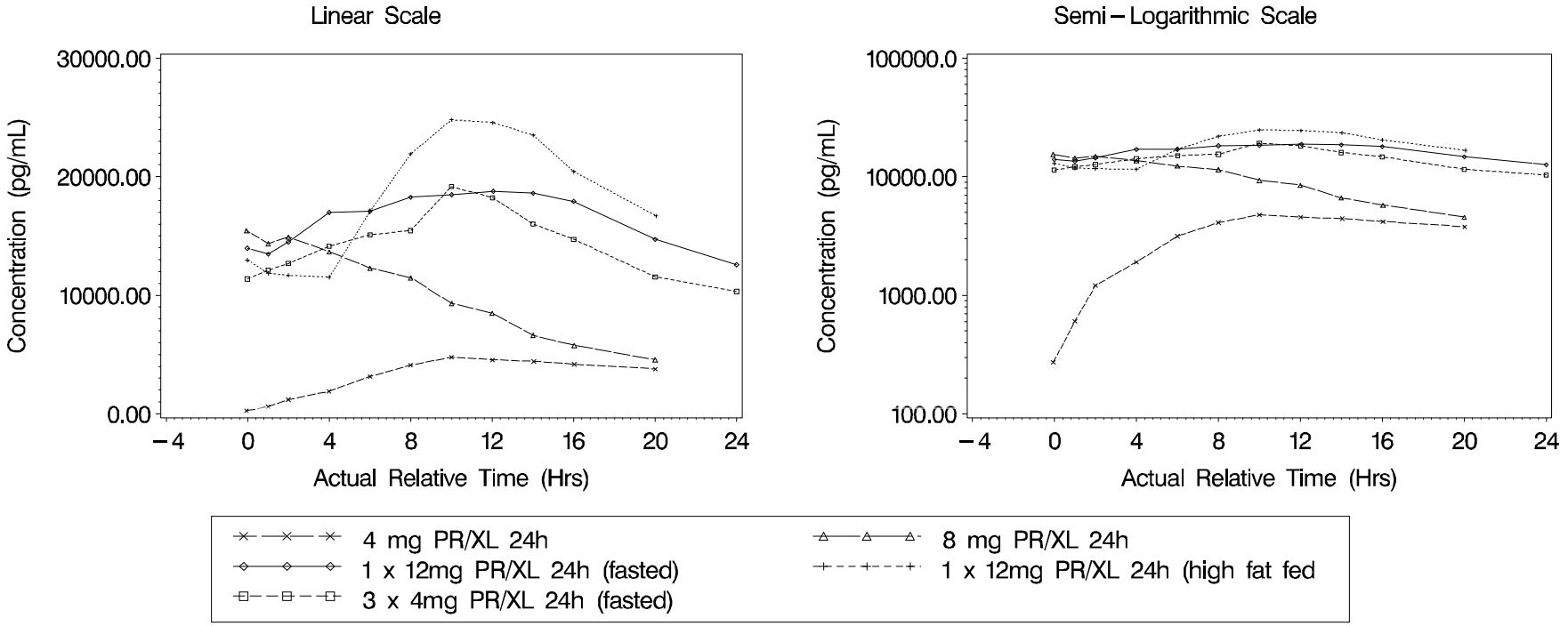
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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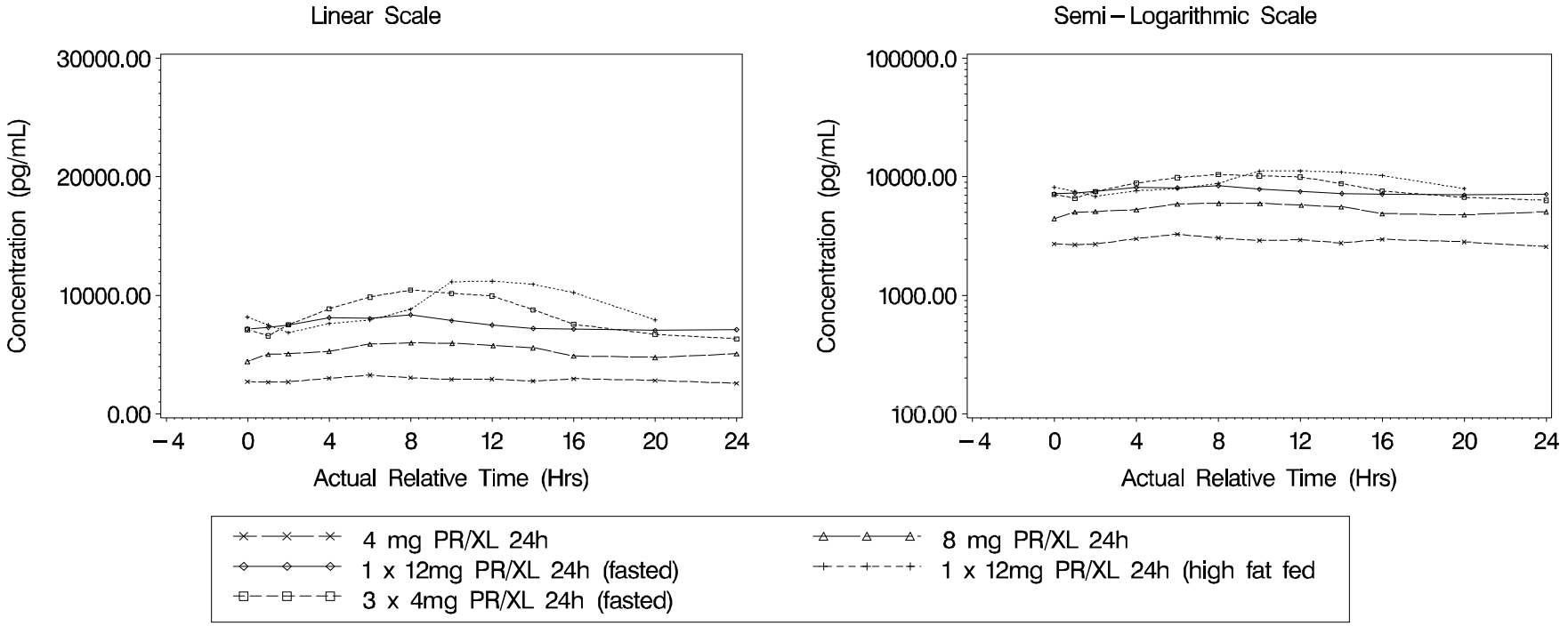
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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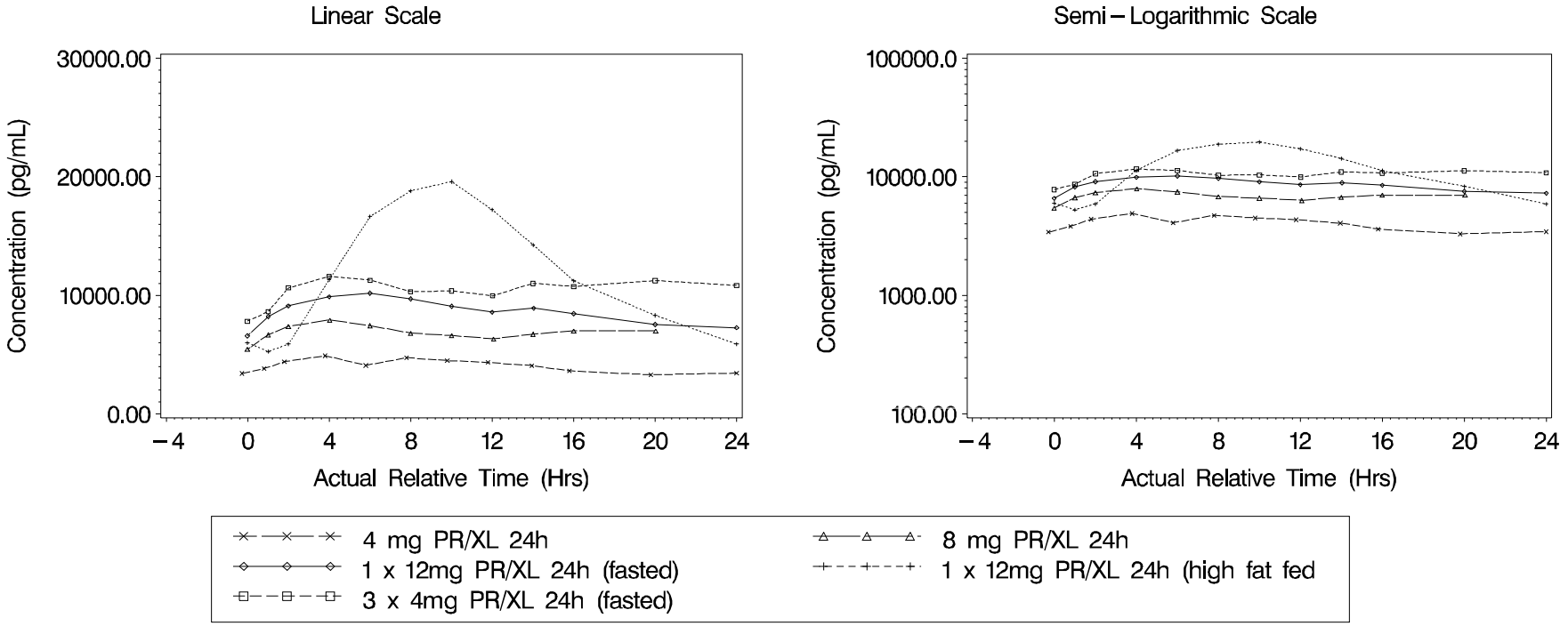
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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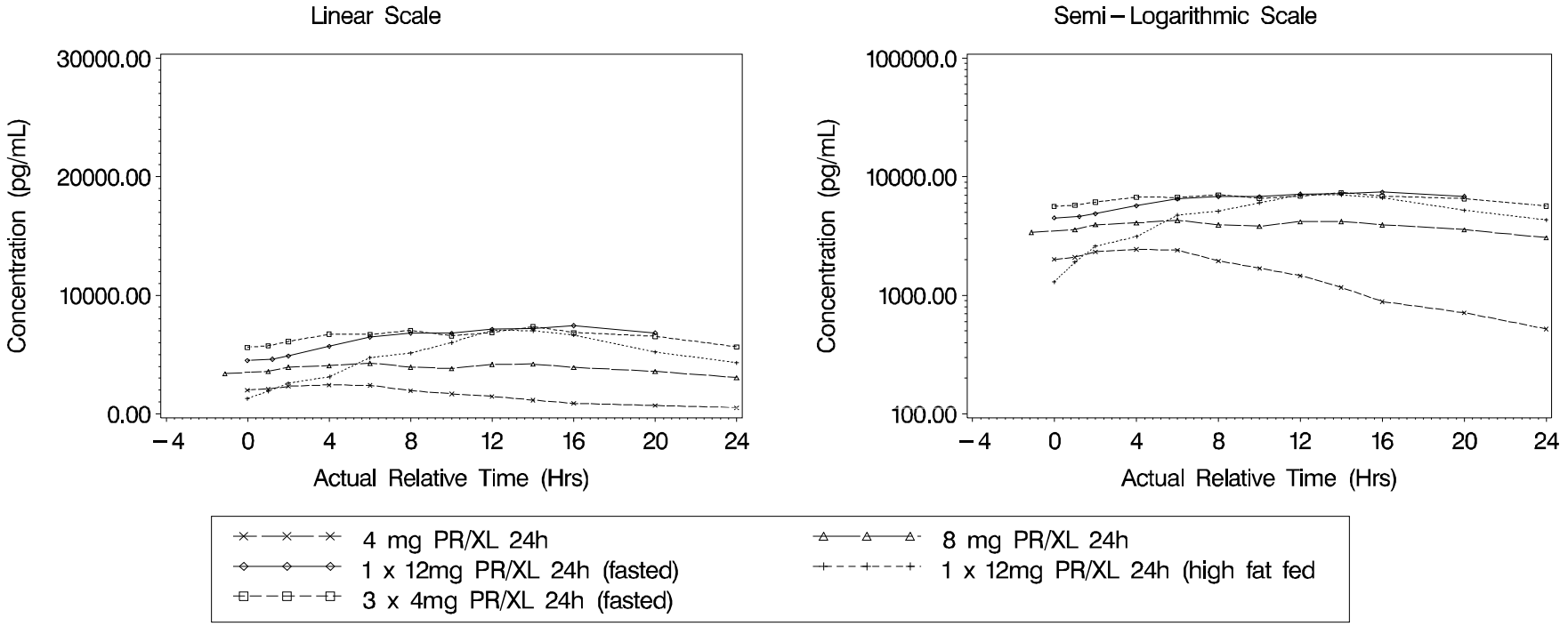
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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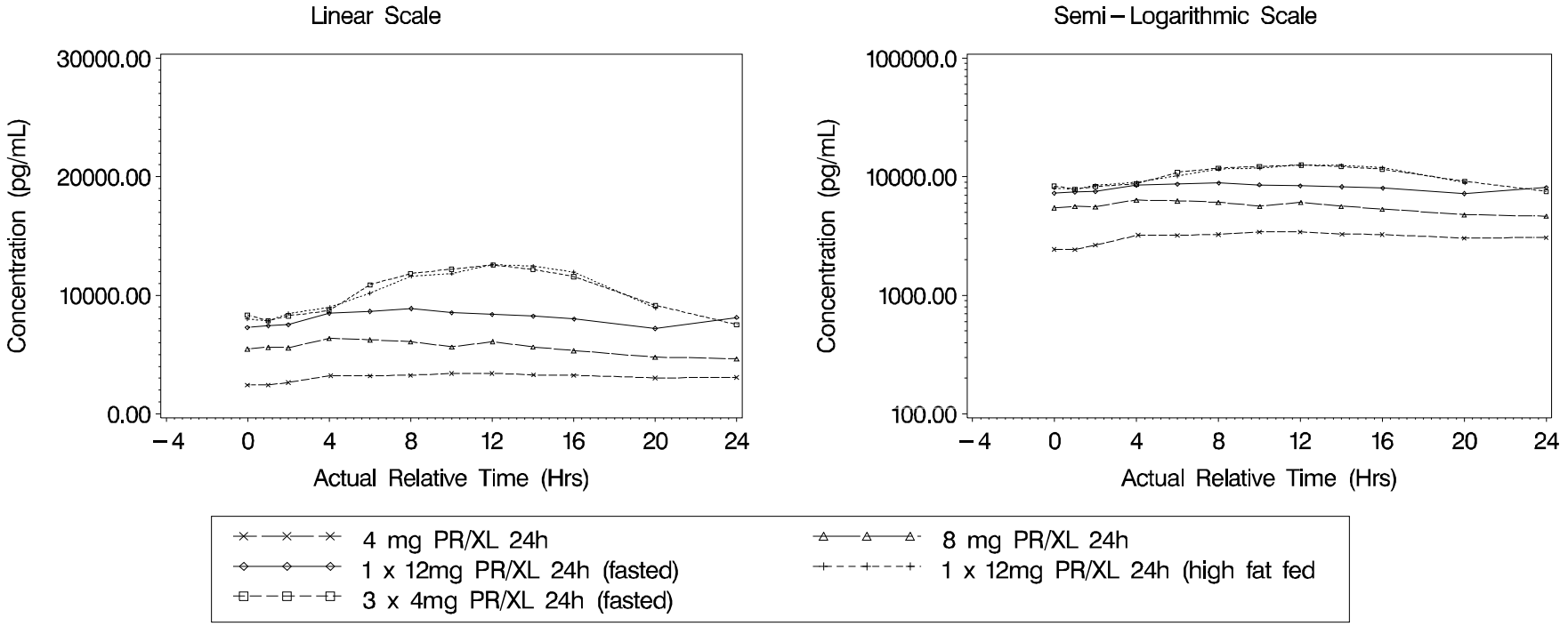
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
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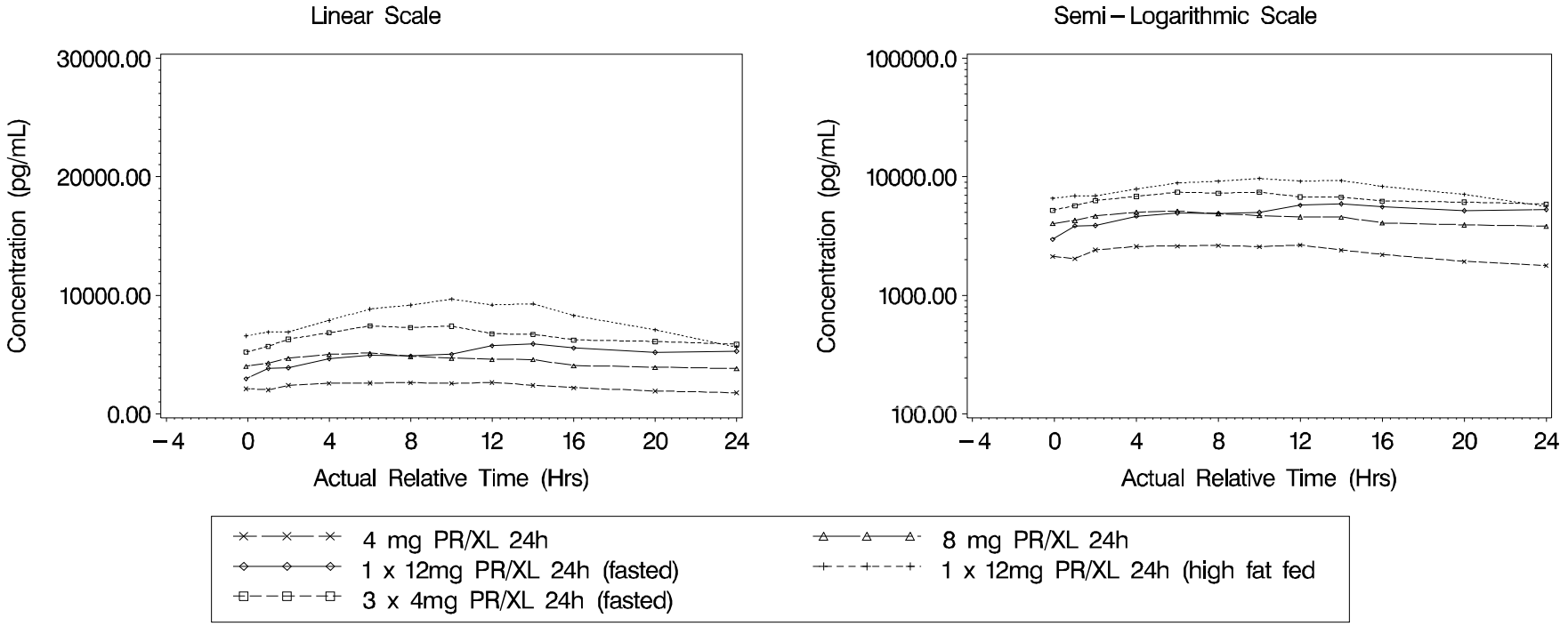
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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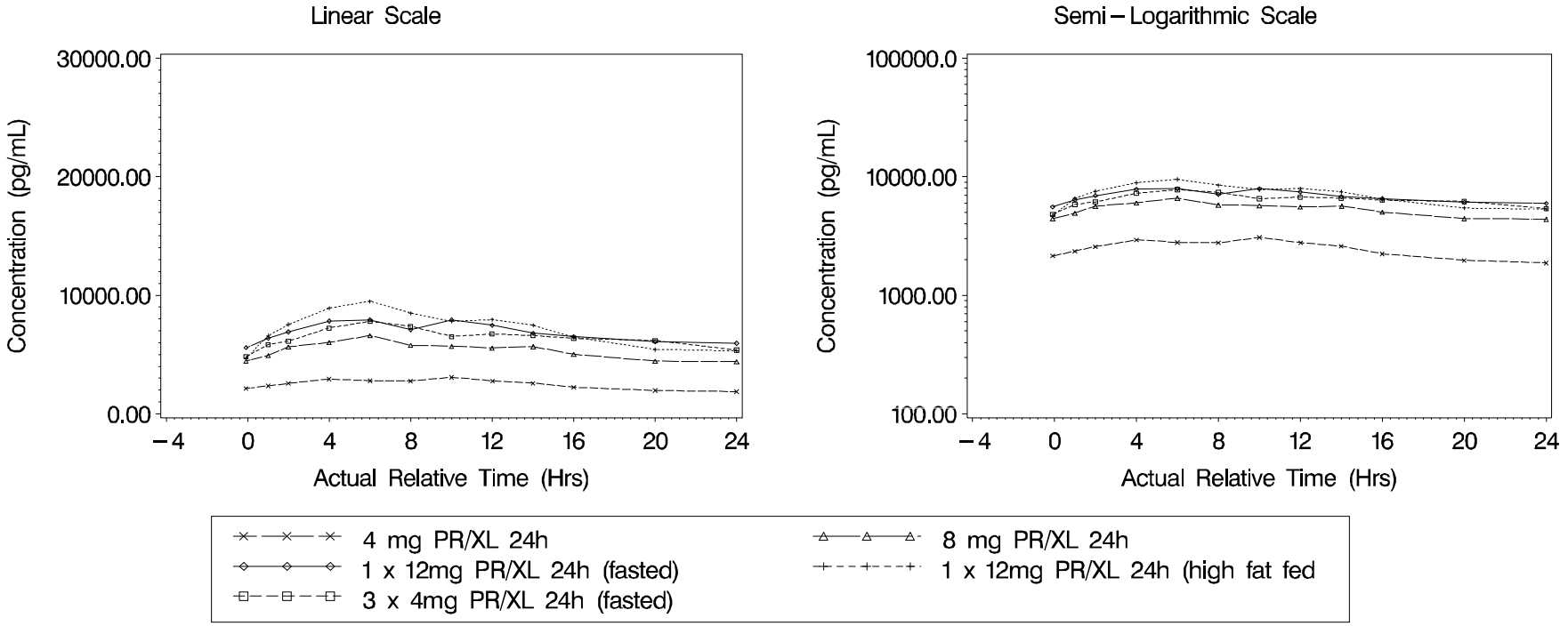
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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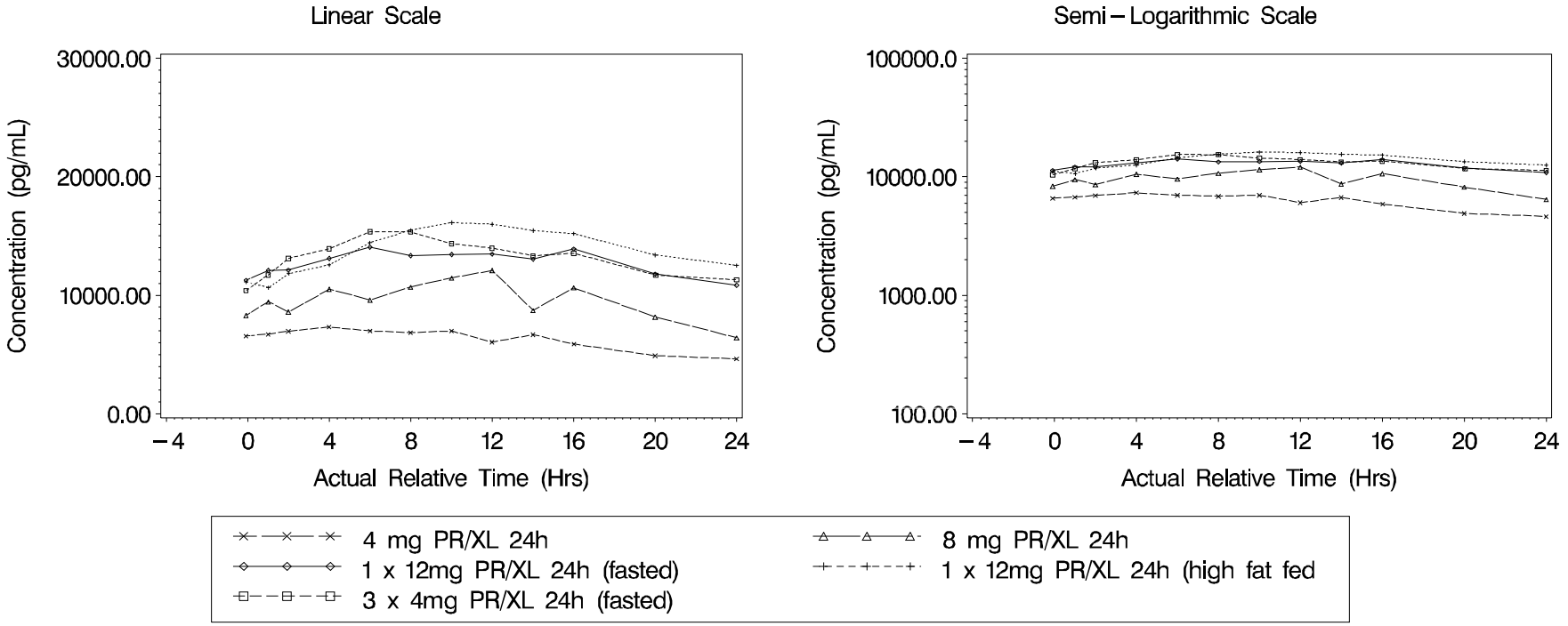
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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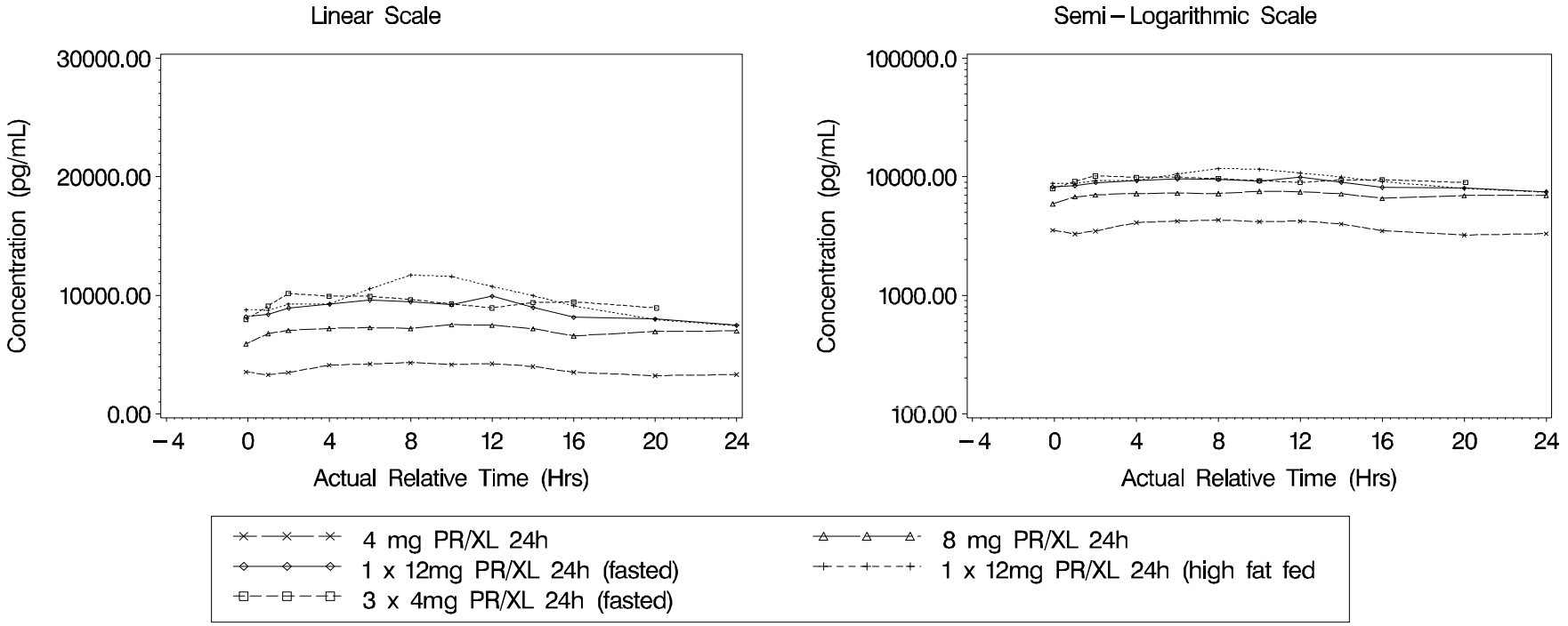
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
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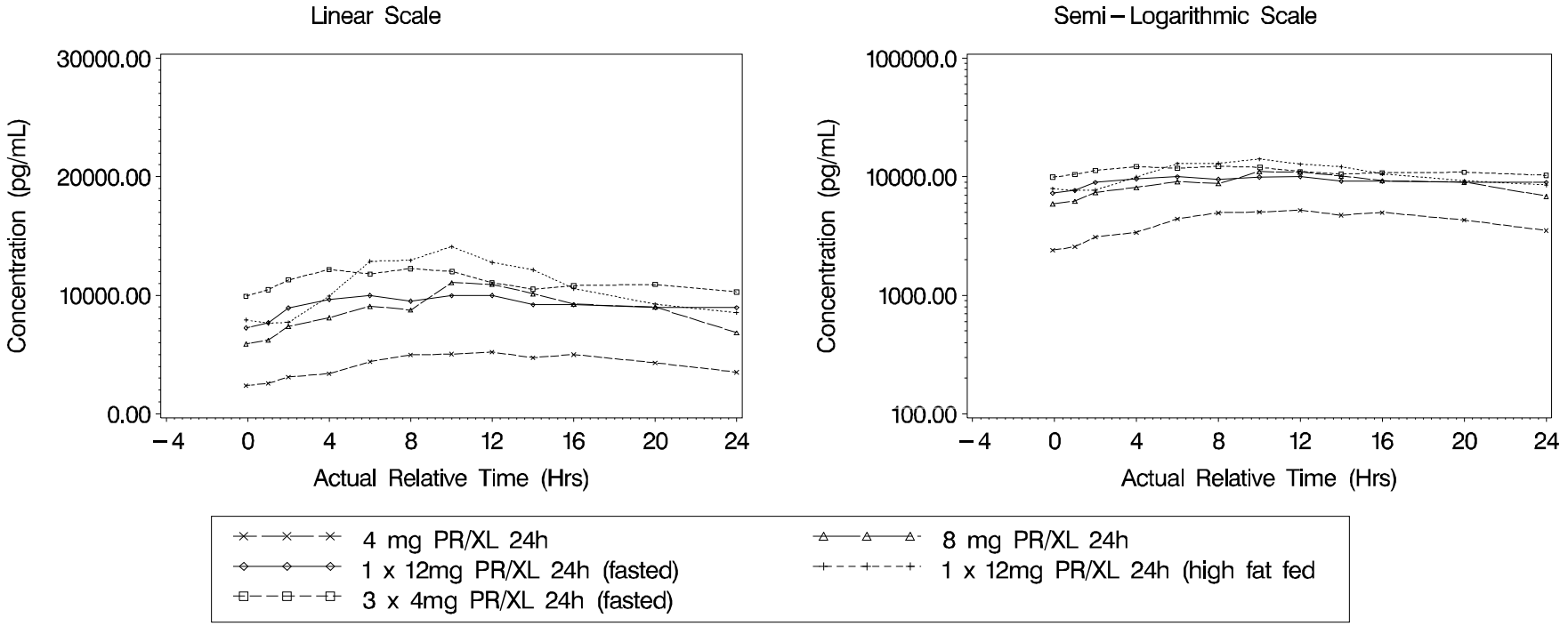
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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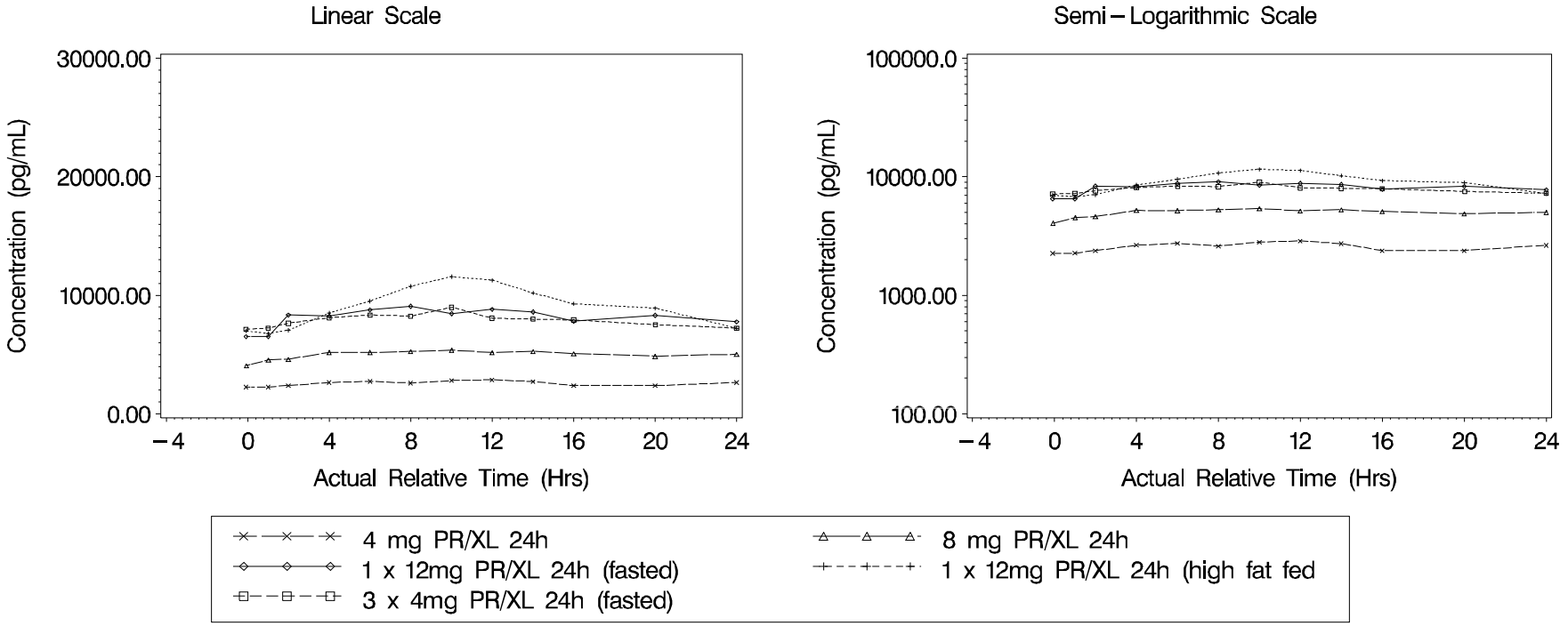
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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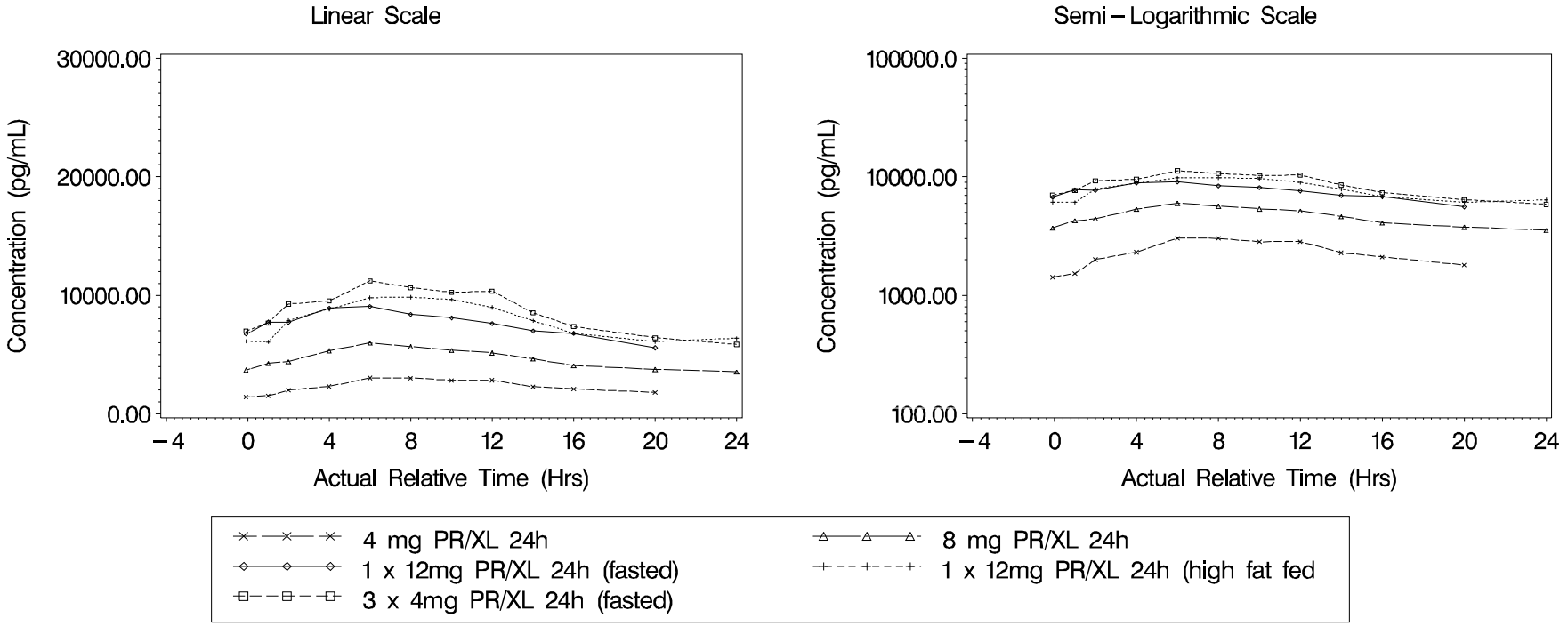
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
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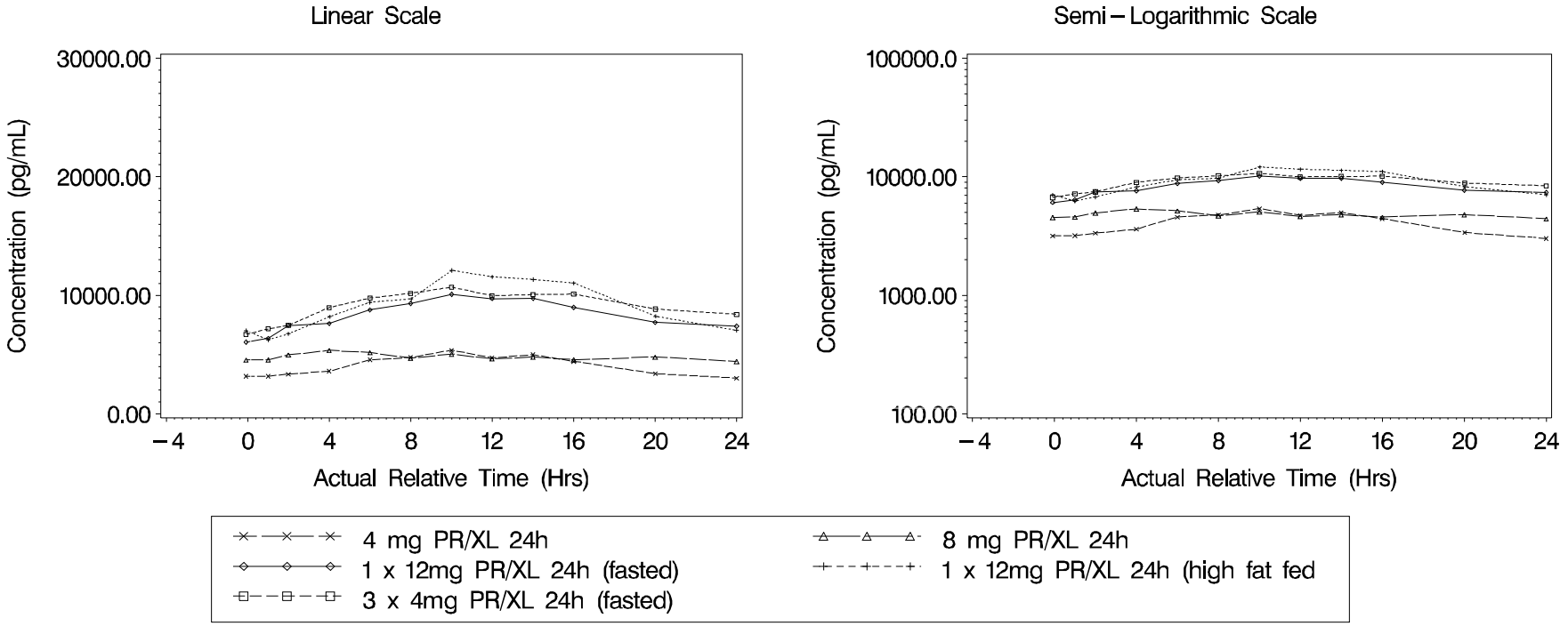
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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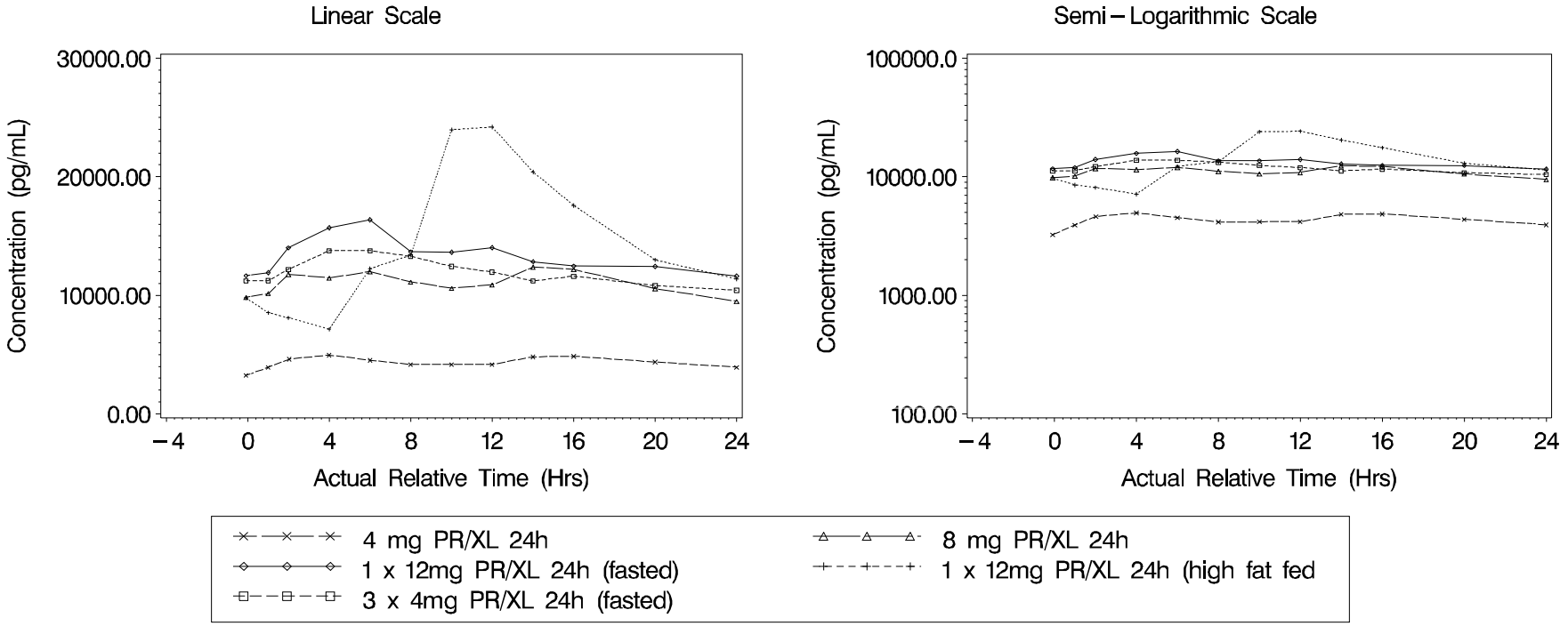
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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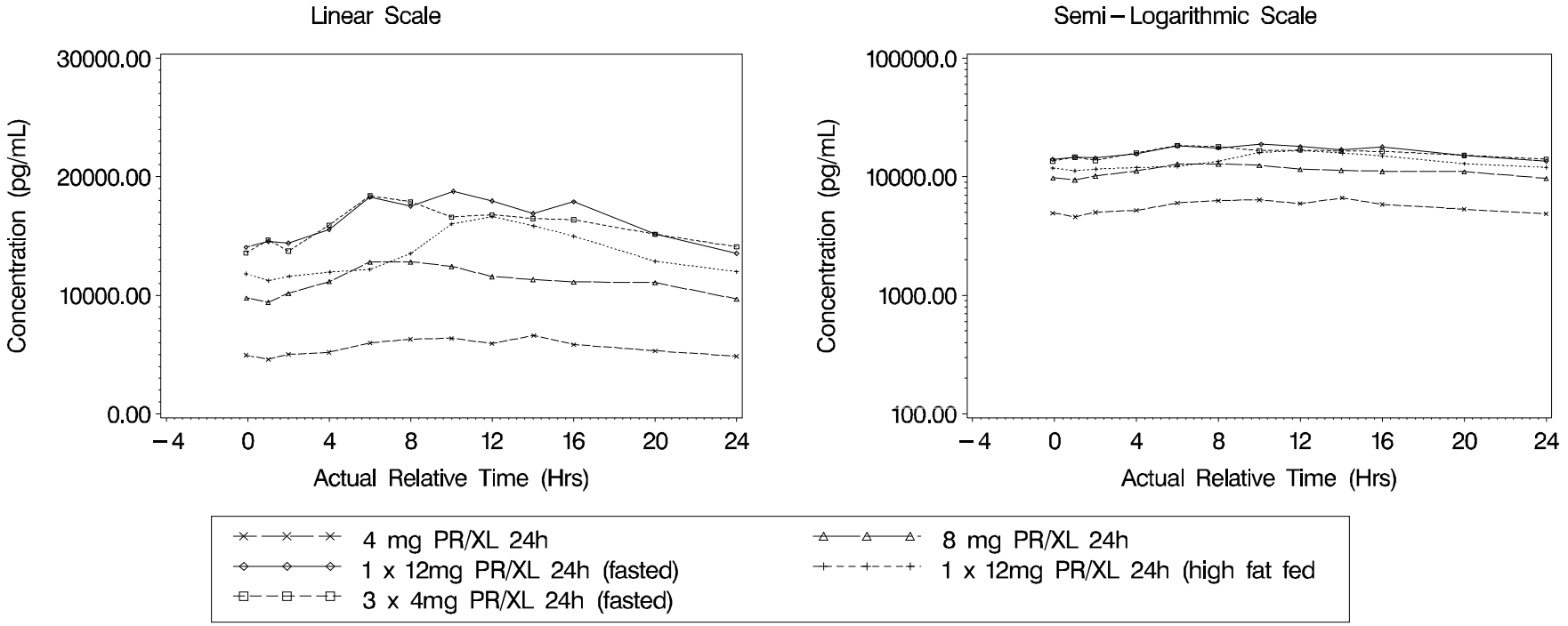
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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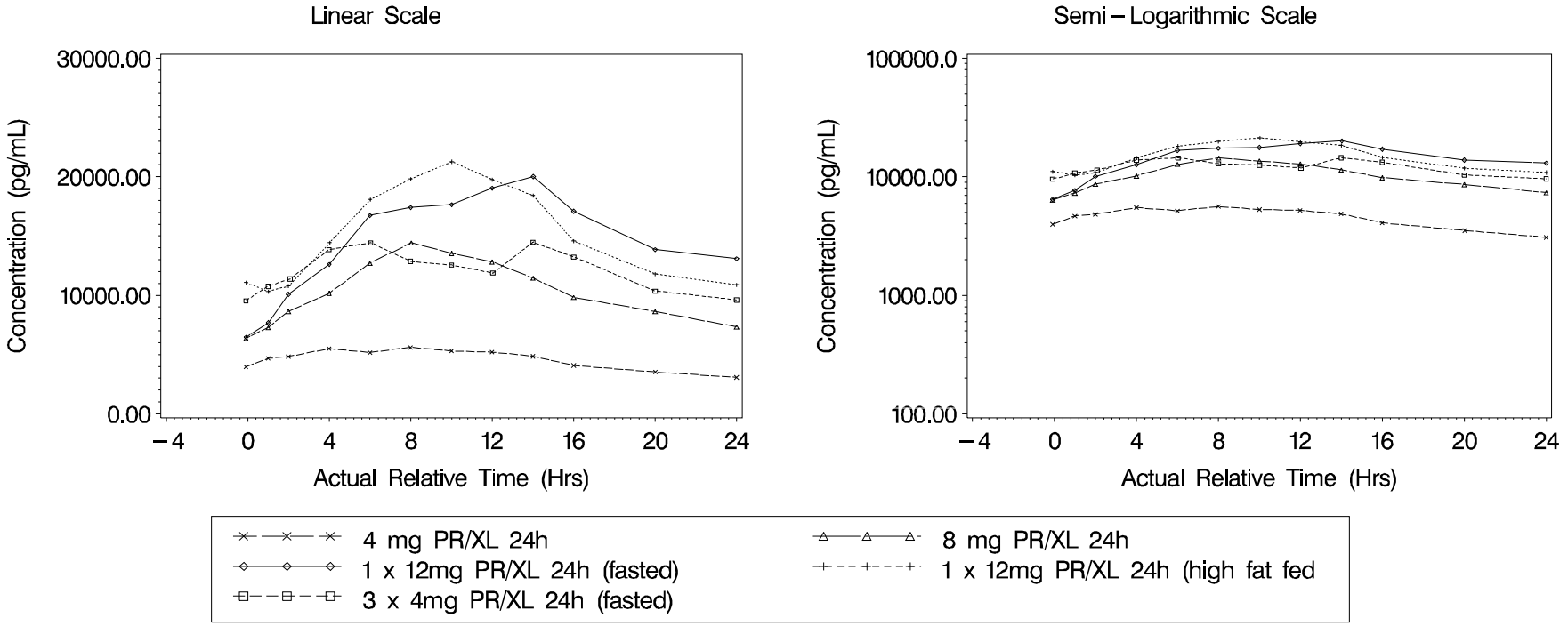
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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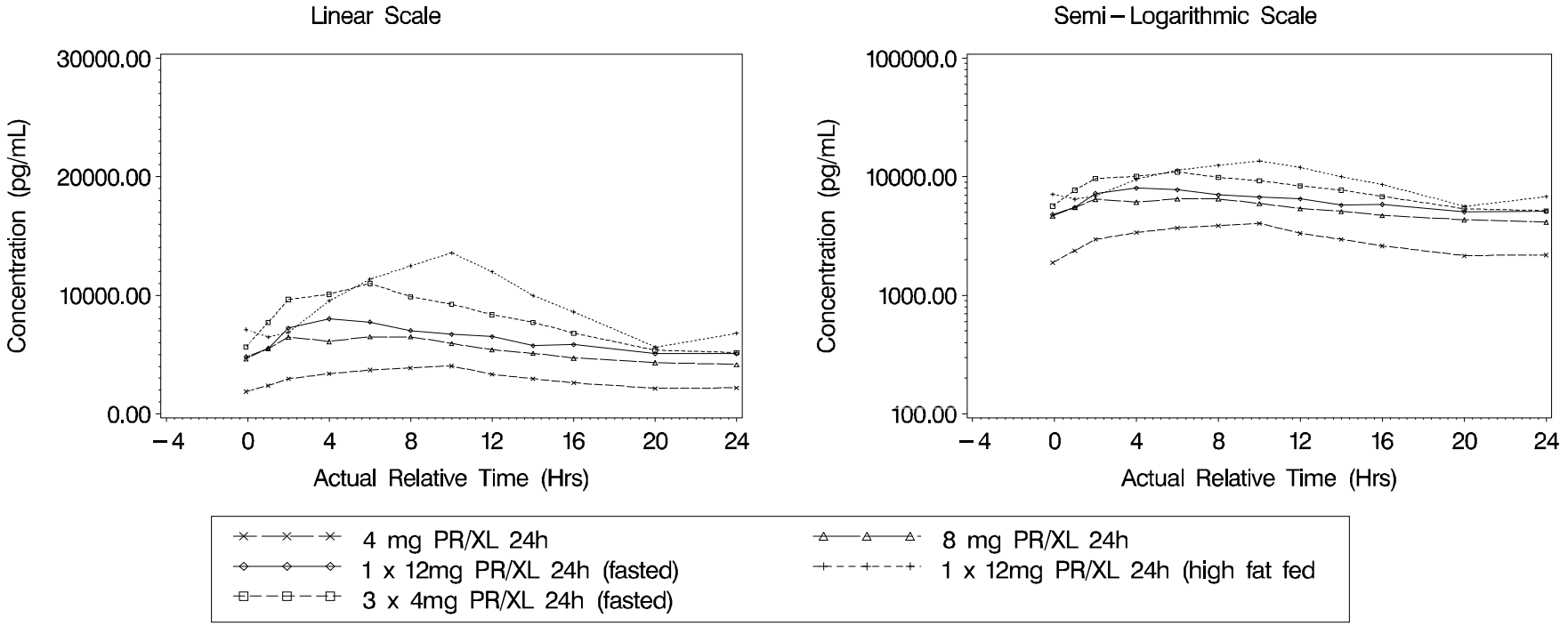
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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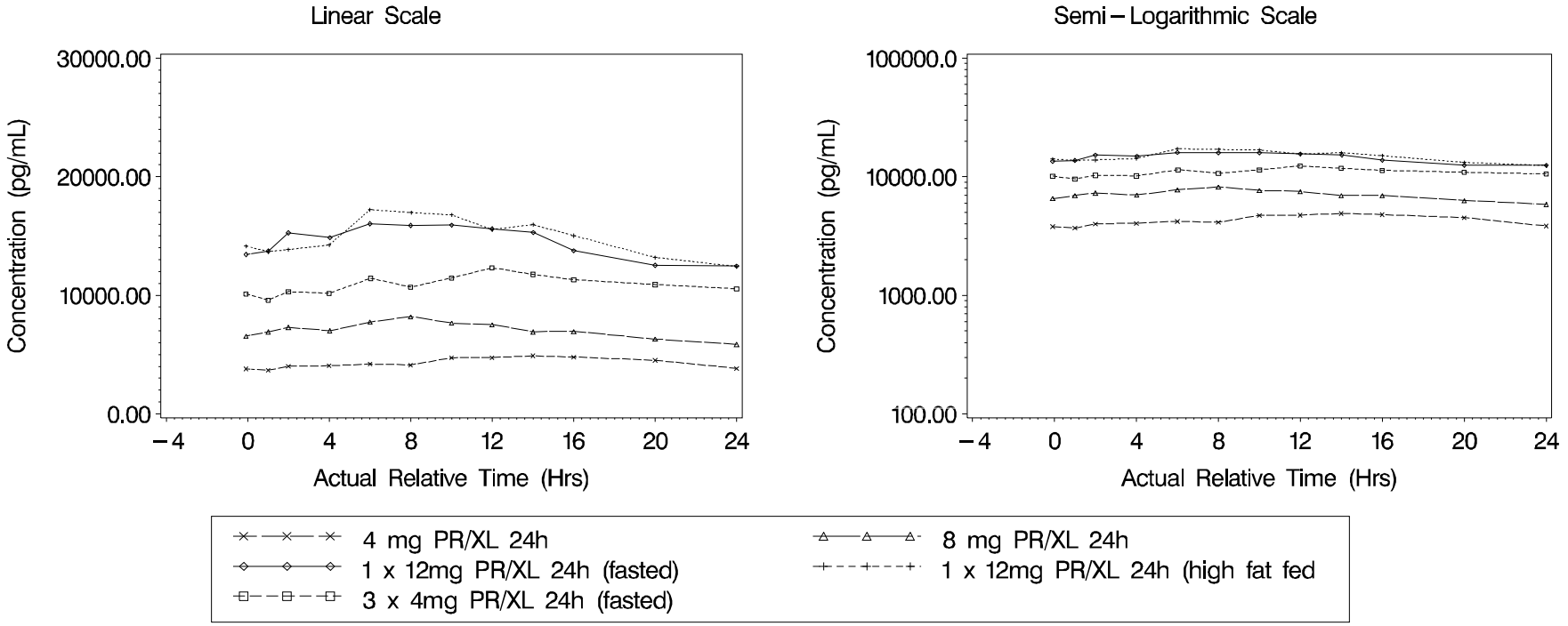
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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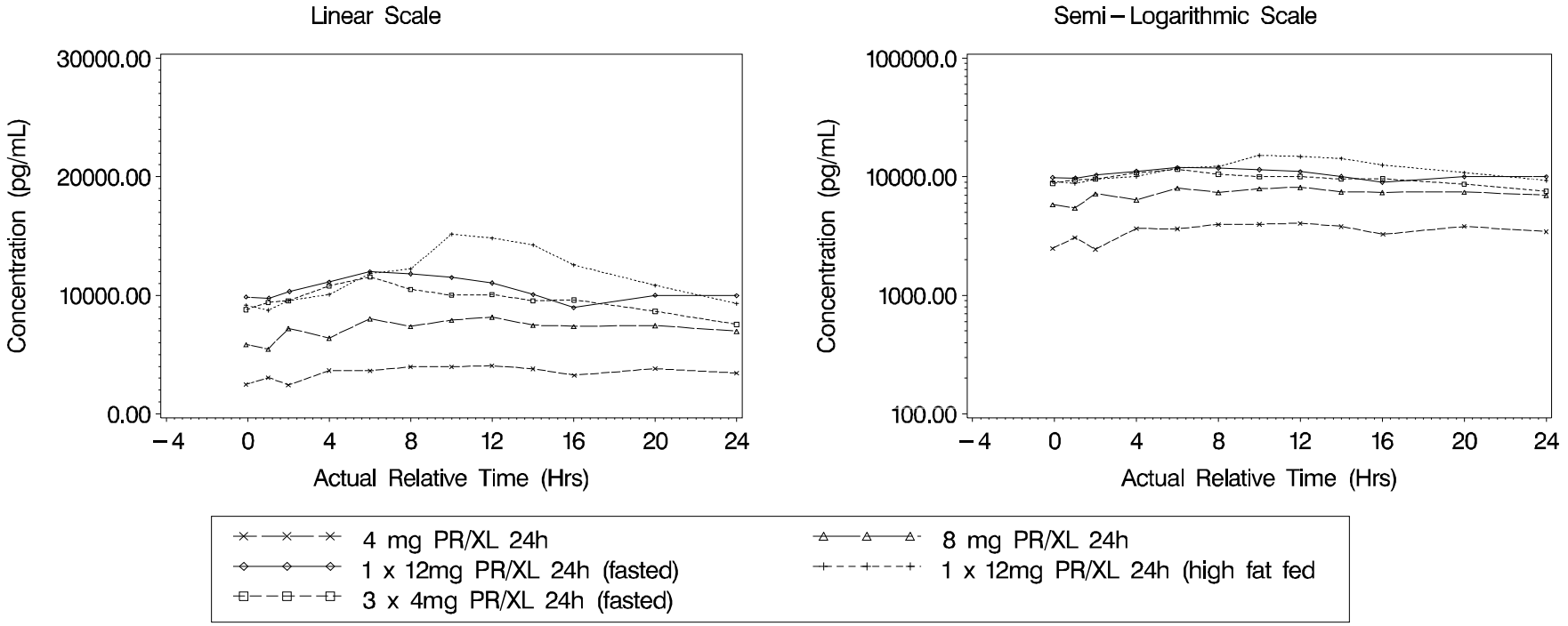
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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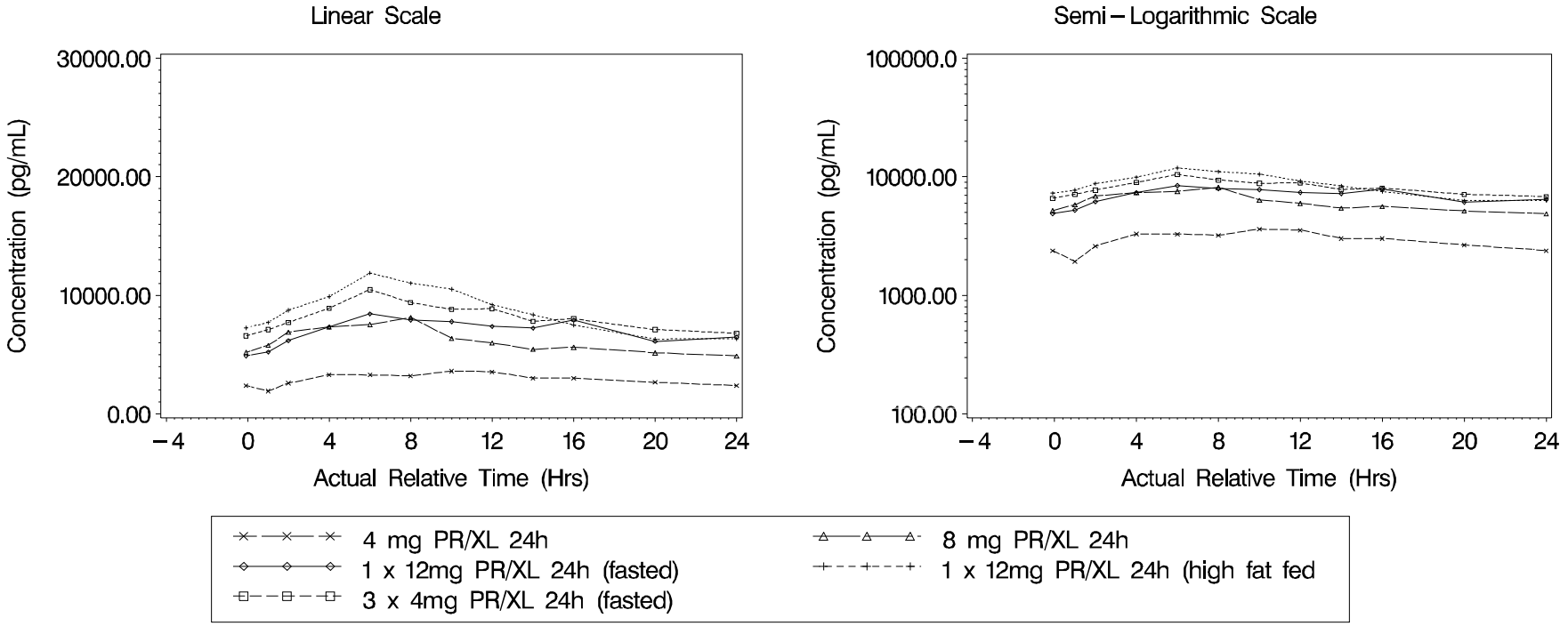
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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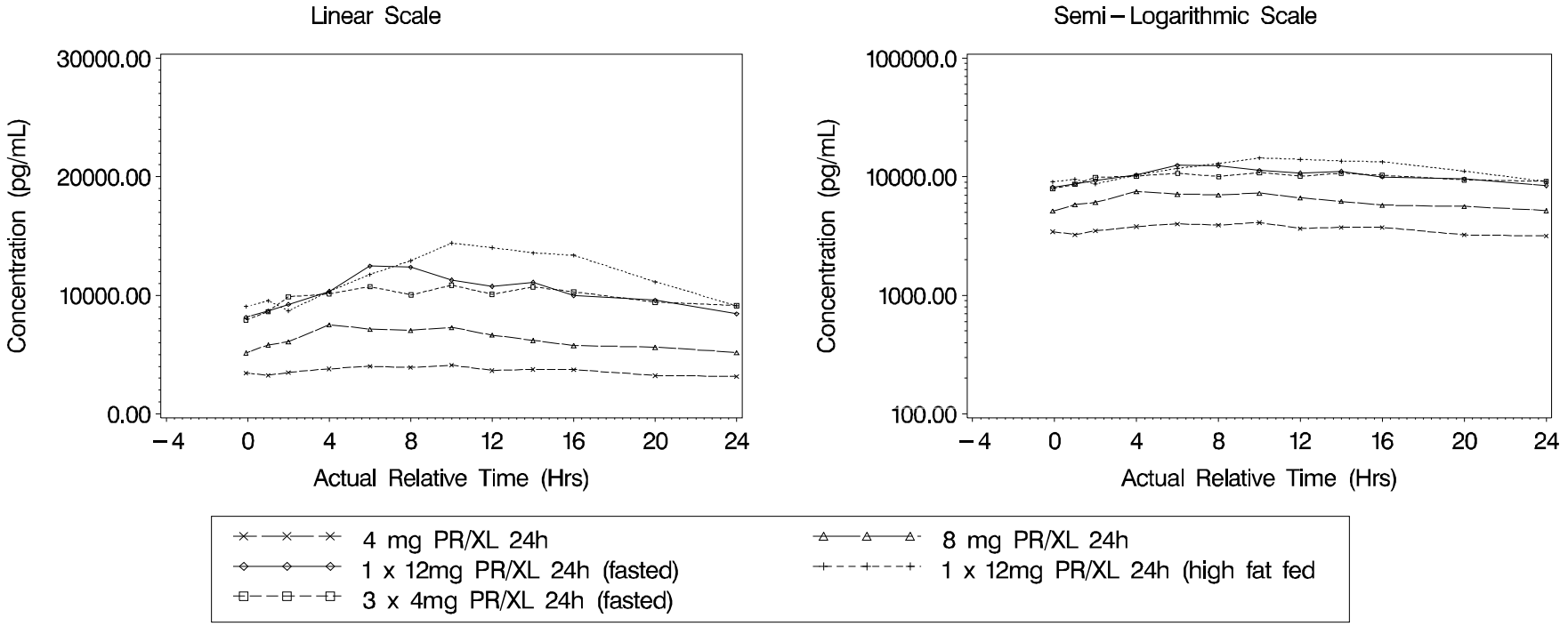
Figure 12.12
Individual plasma Metabolite (SKF−104557) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 50 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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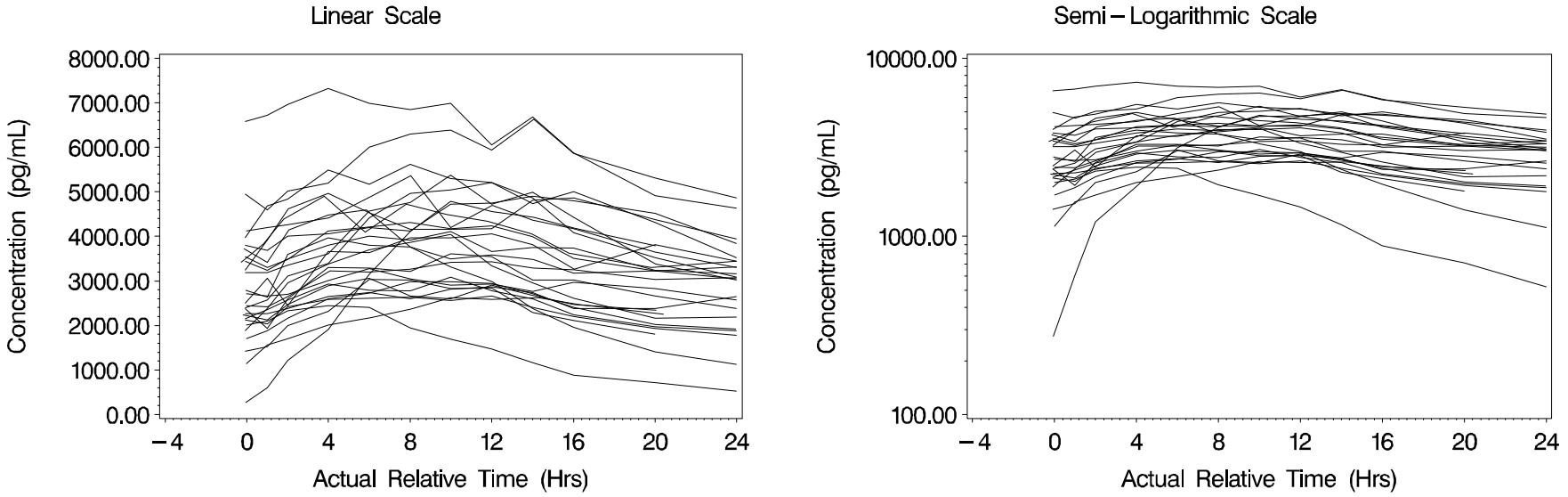
Figure 12.13
Individual Plasma Metabolite (SKF−104557) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=4 mg PR/XL 24h



NOTE: LLQ = 50 pg/mL

[redacted]

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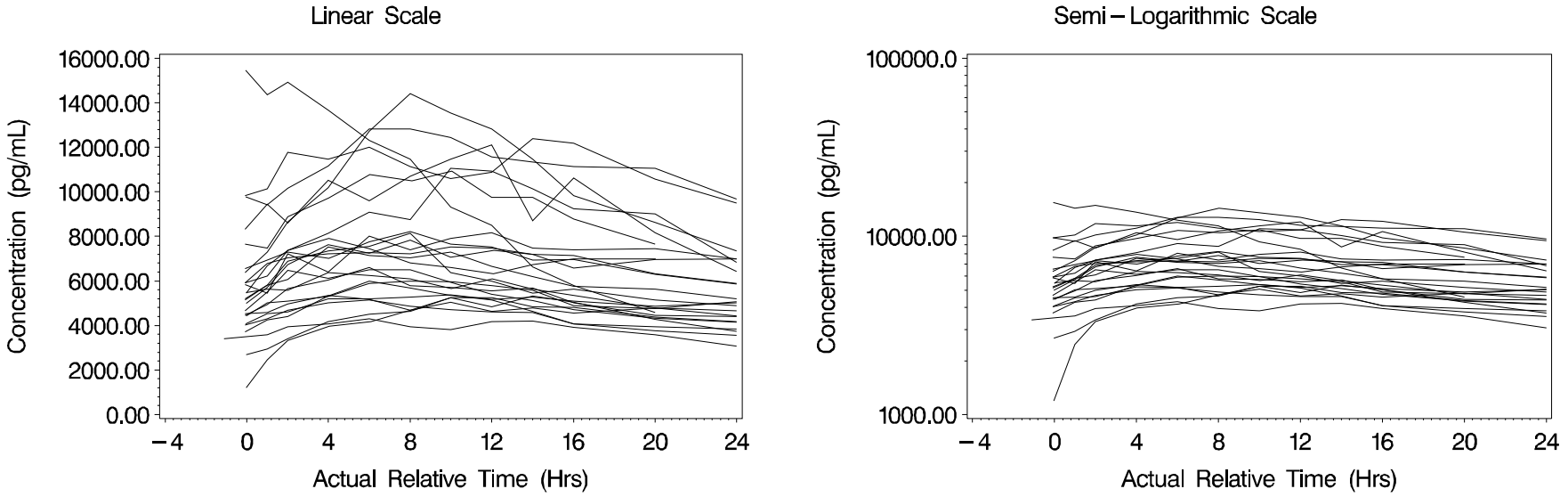
Figure 12.13
Individual Plasma Metabolite (SKF−104557) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=8 mg PR/XL 24h



NOTE: LLQ = 50 pg/mL

[redacted]

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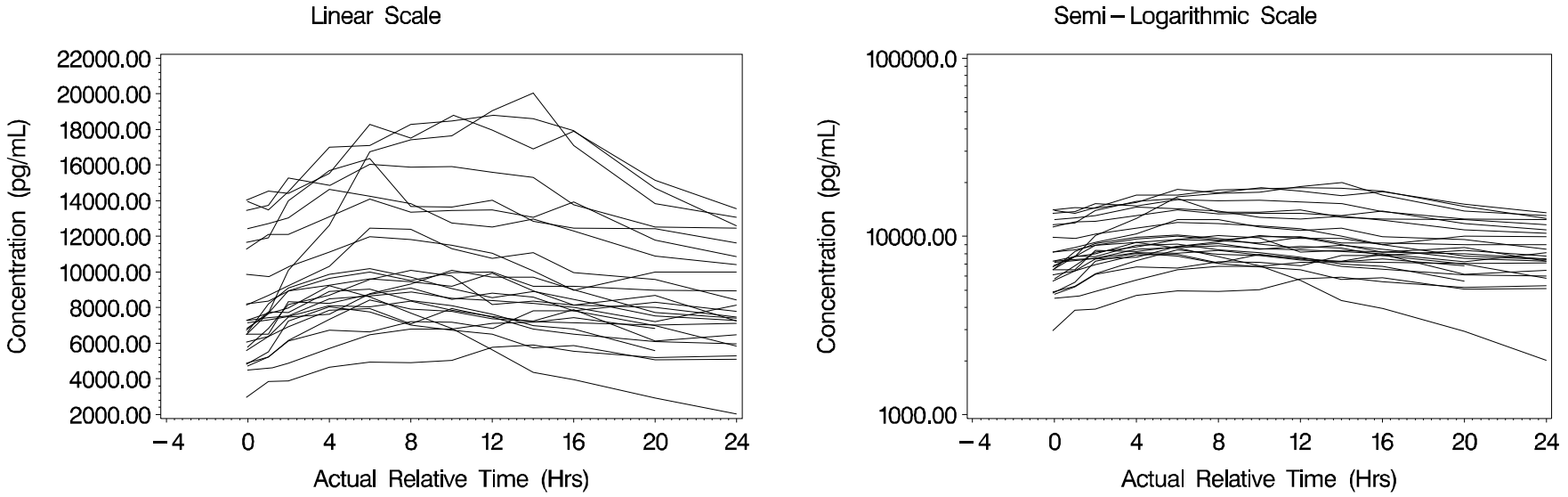
Figure 12.13
Individual Plasma Metabolite (SKF−104557) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=1 x 12mg PR/XL 24h (fasted)



NOTE: LLQ = 50 pg/mL

[redacted]

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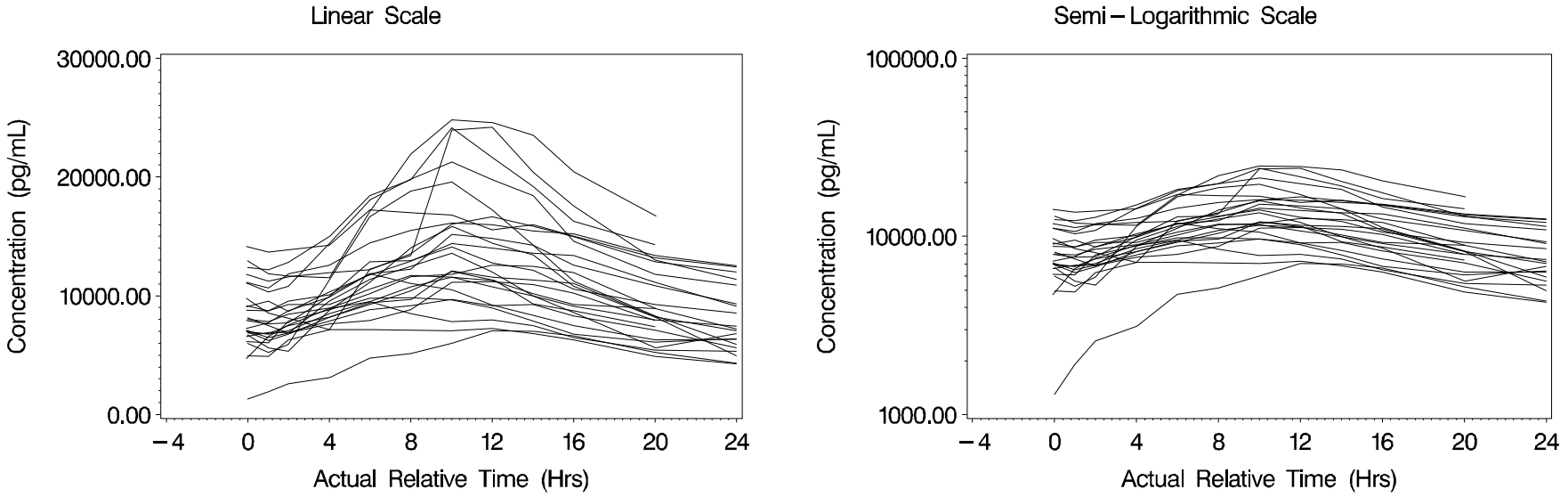
Figure 12.13
Individual Plasma Metabolite (SKF−104557) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=1 x 12mg PR/XL 24h (high fat fed)



NOTE: LLQ = 50 pg/mL

[redacted]

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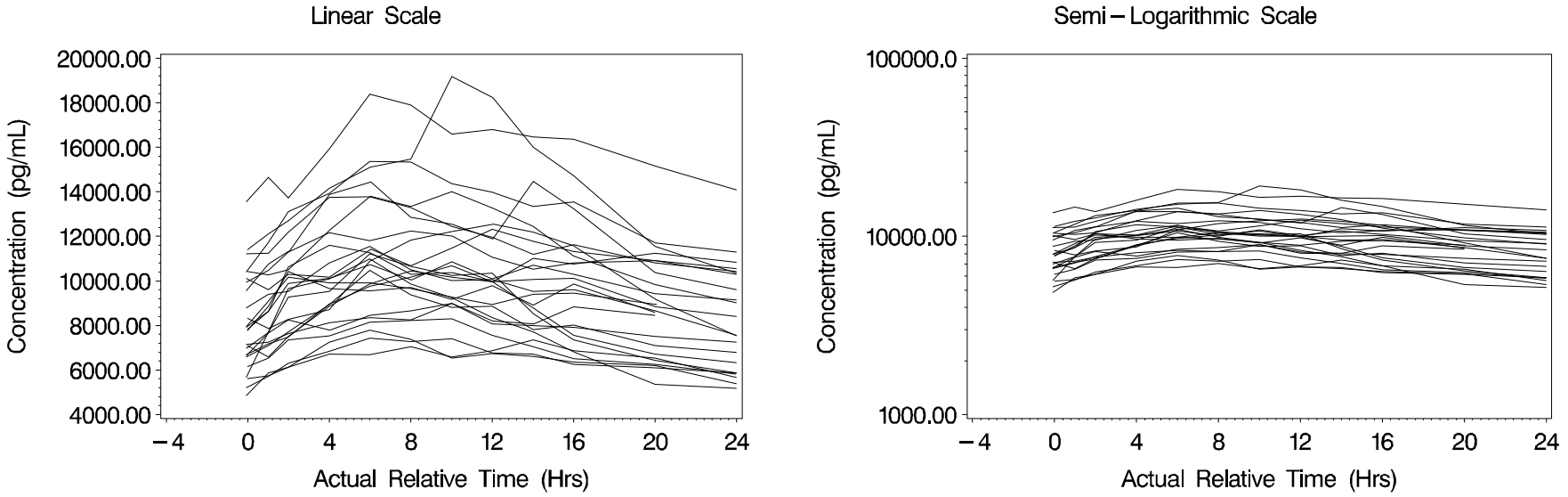
Figure 12.13
Individual Plasma Metabolite (SKF−104557) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=3 x 4mg PR/XL 24h (fasted)



NOTE: LLQ = 50 pg/mL

[redacted]

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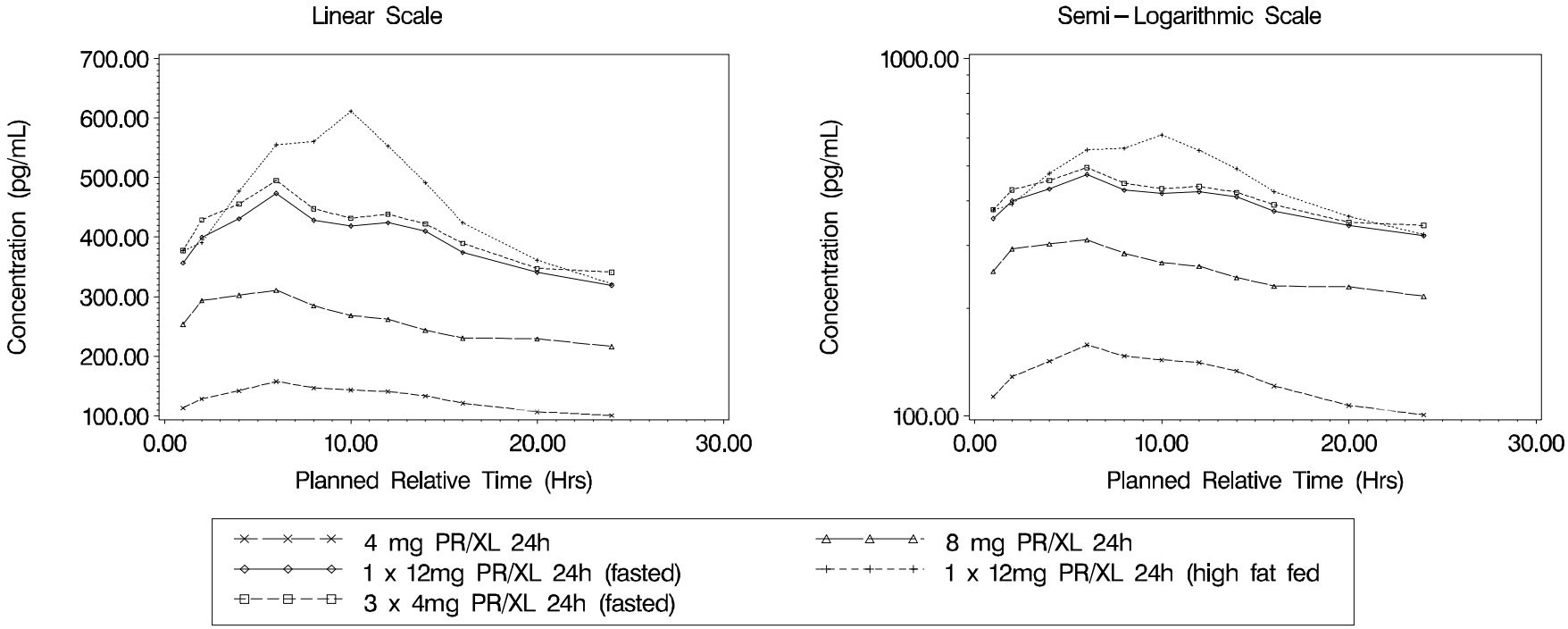
Figure 12.14
Mean Plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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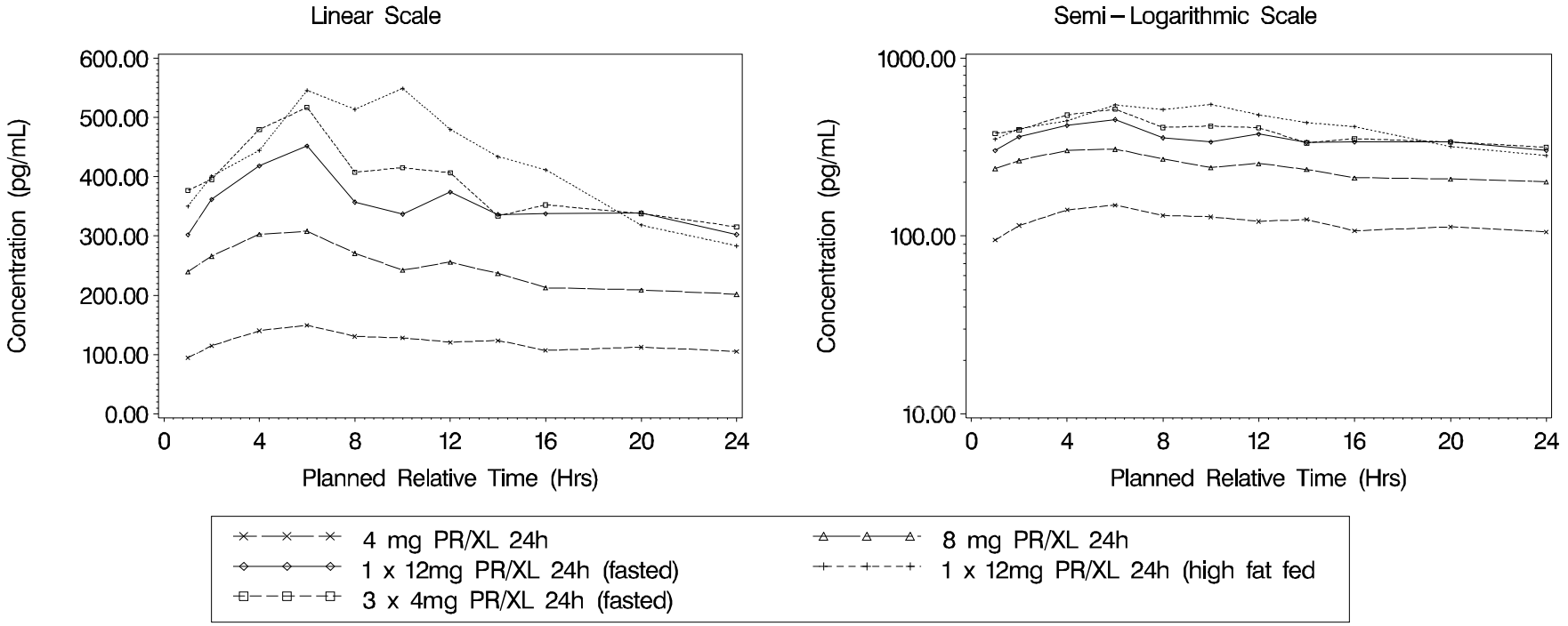
Figure 12.15
Median plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

[redacted]

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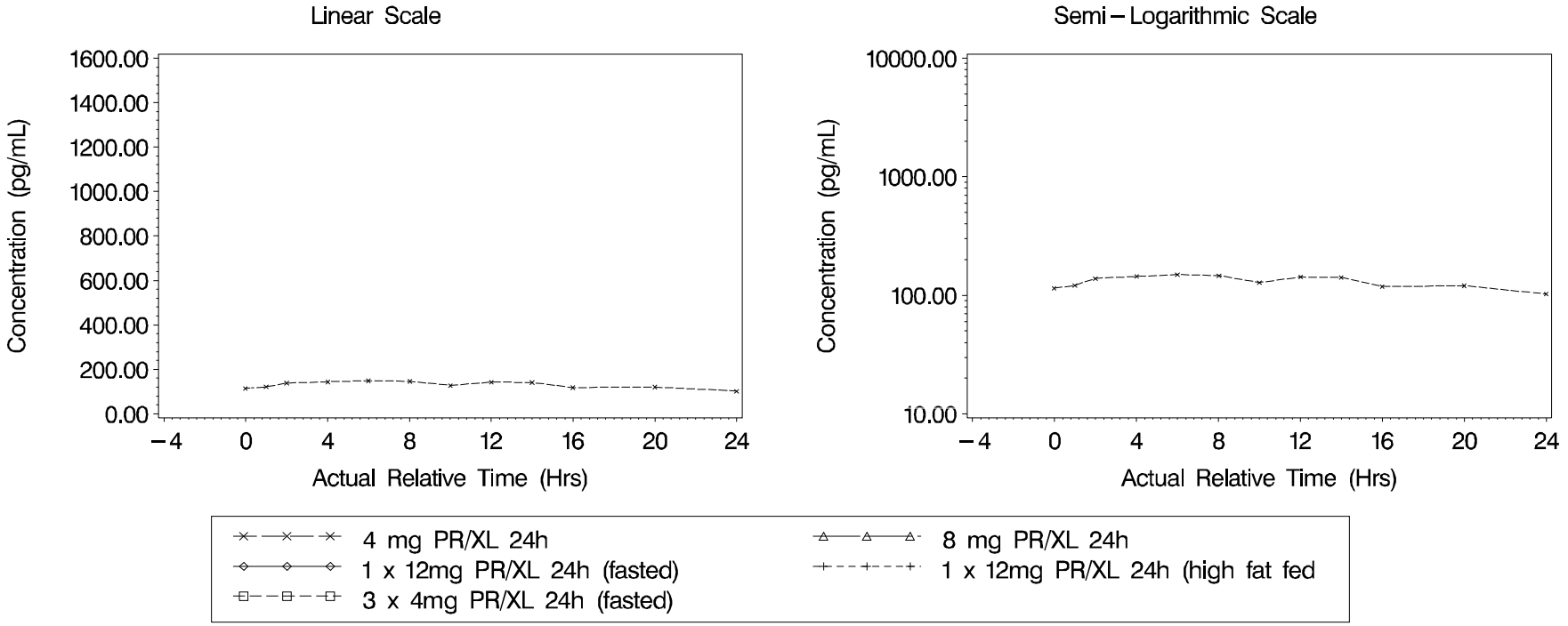
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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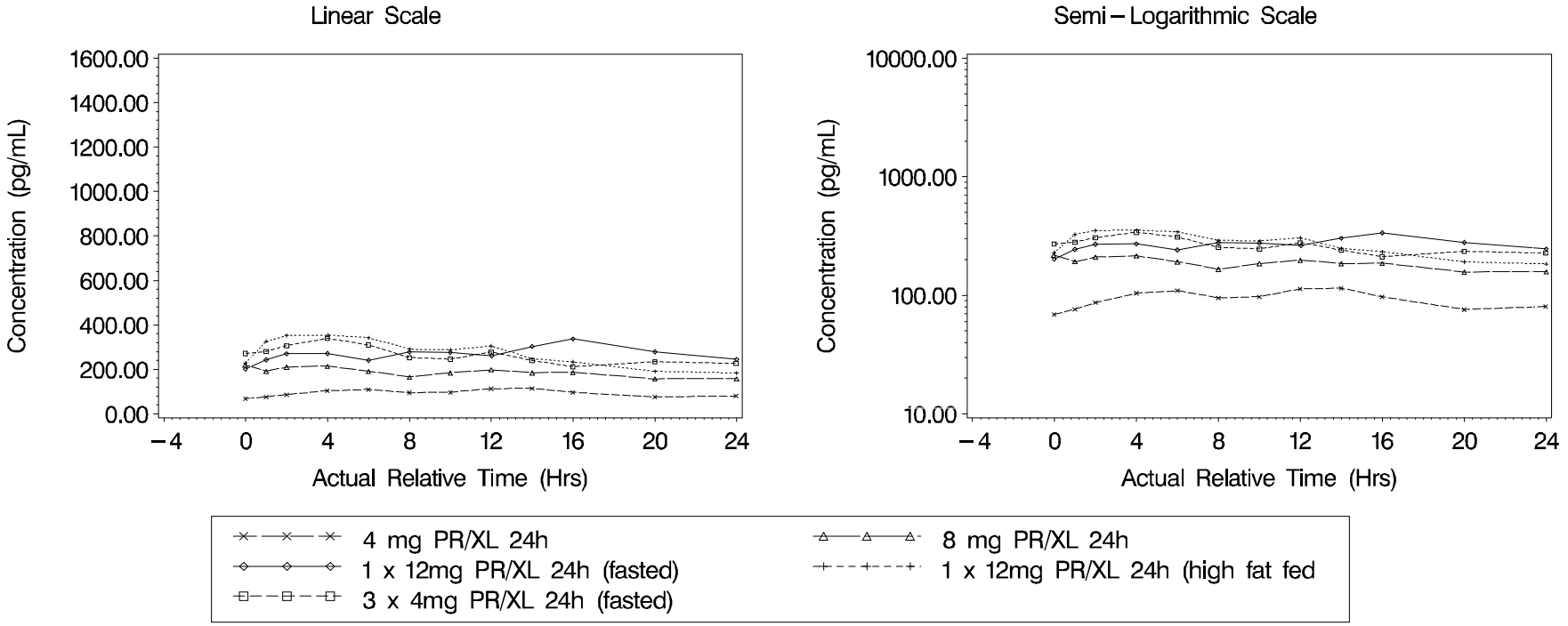
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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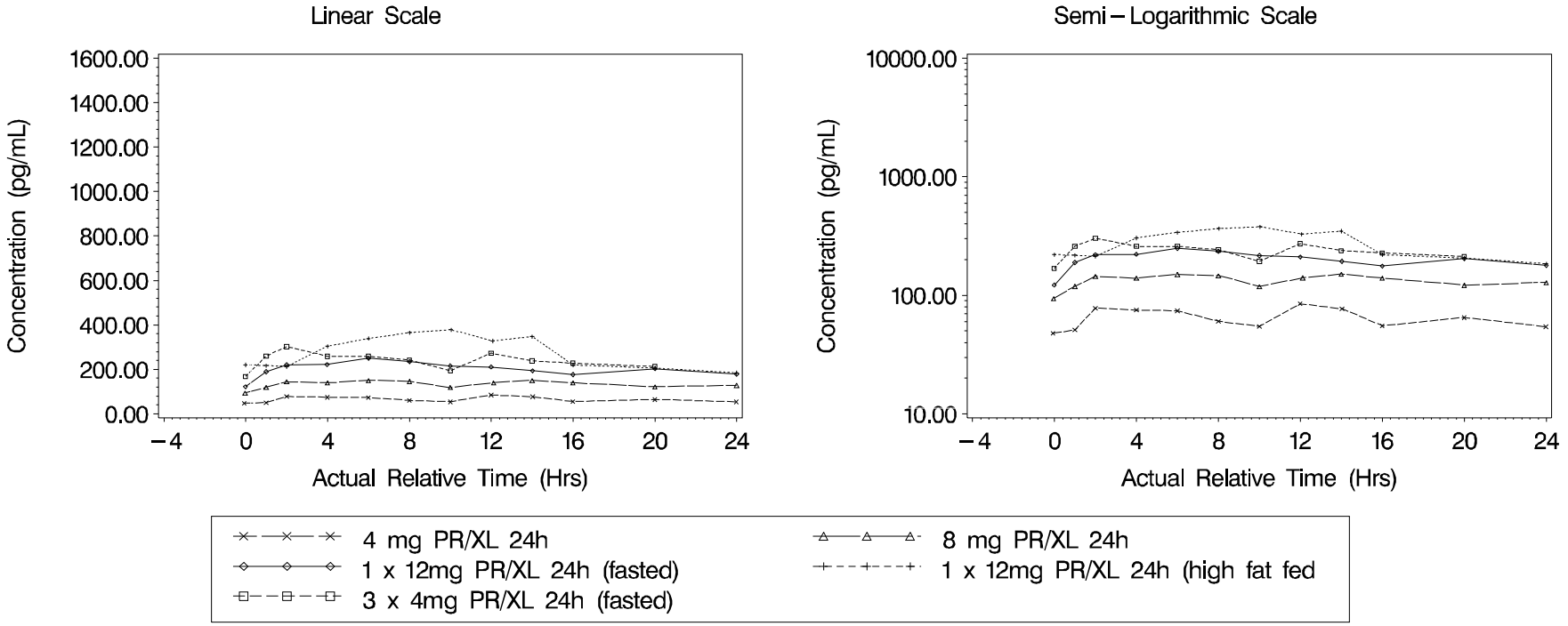
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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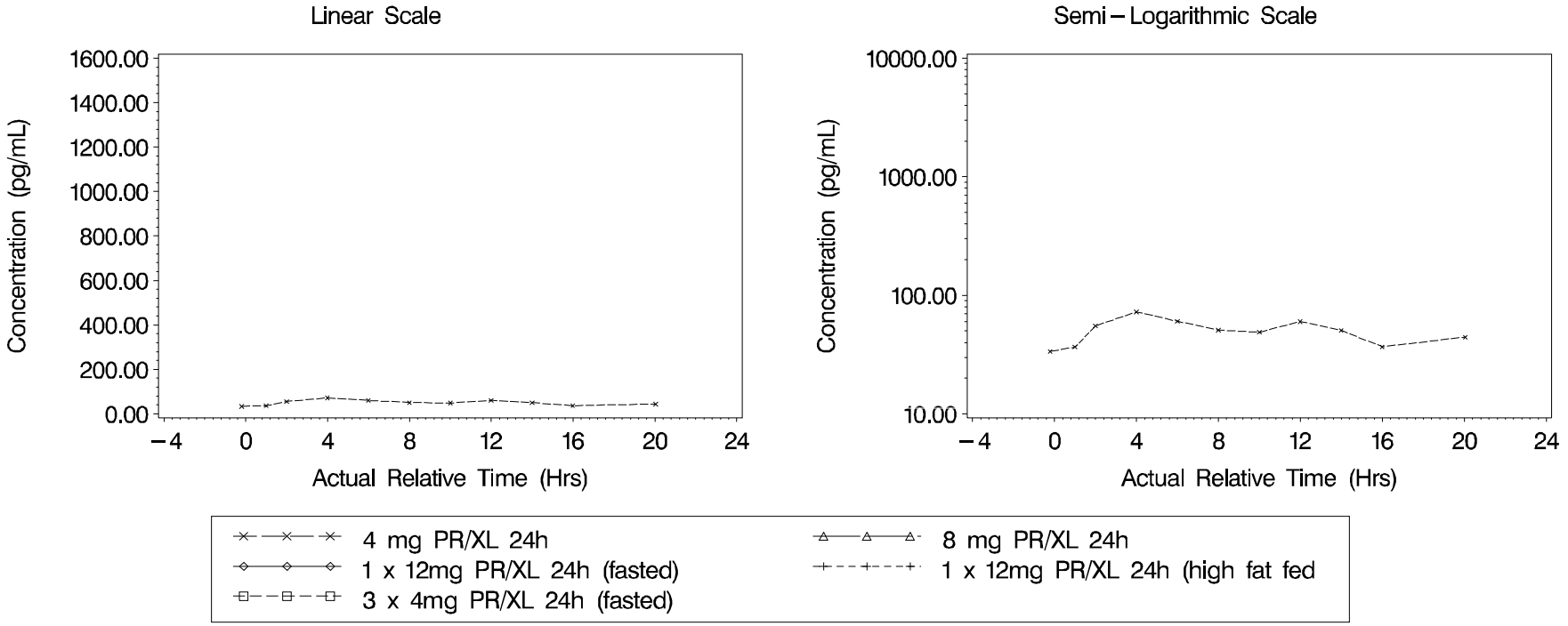
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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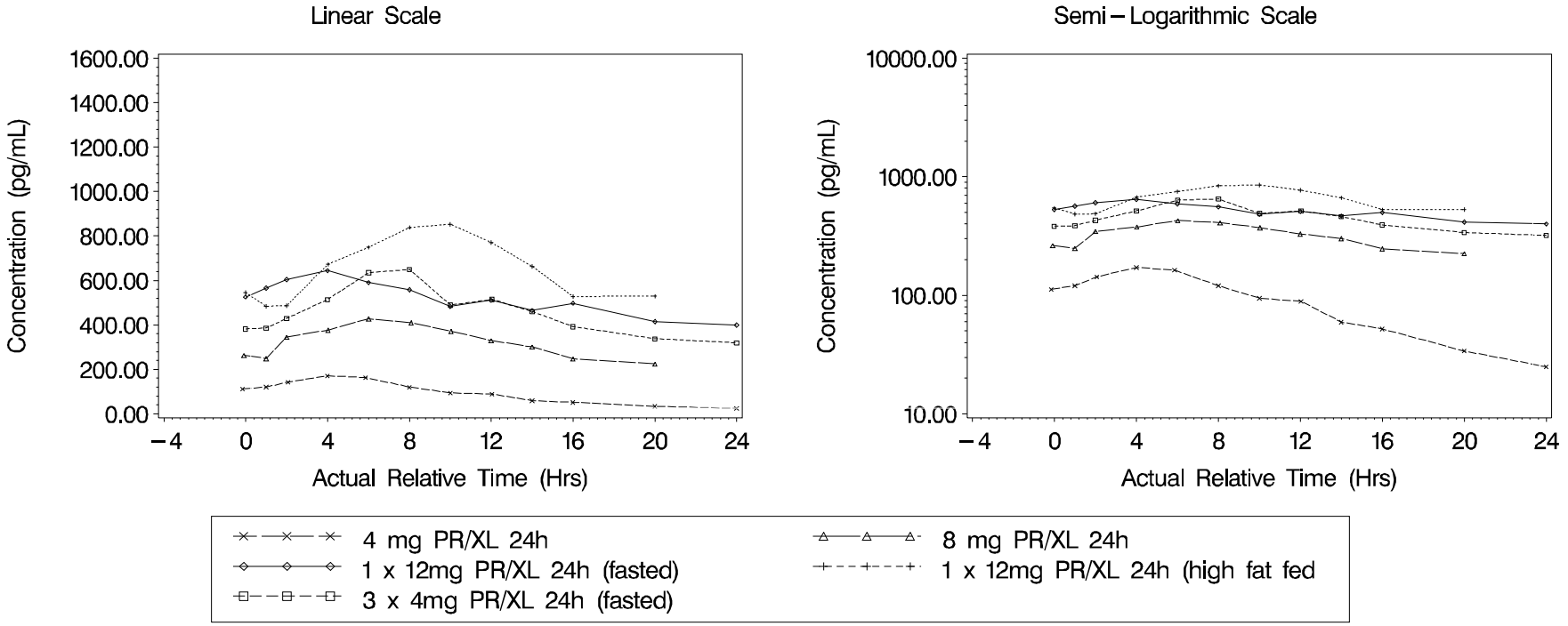
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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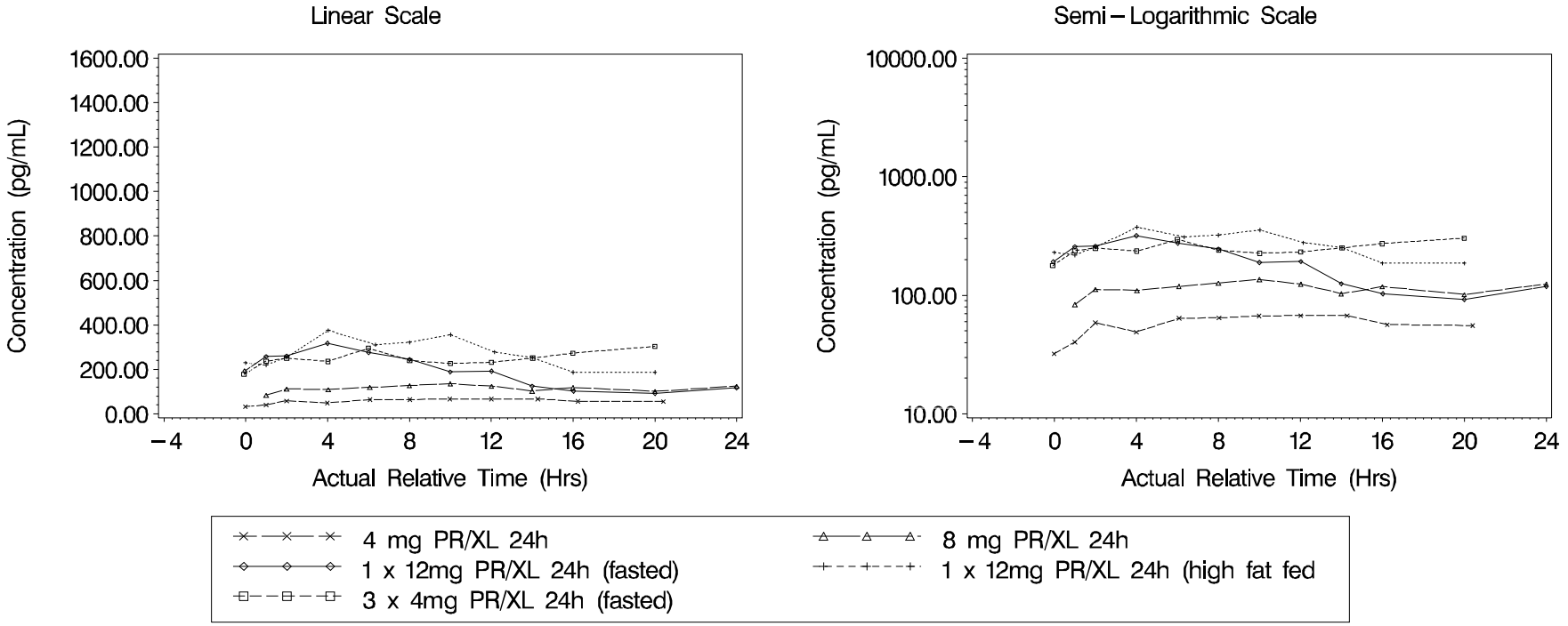
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
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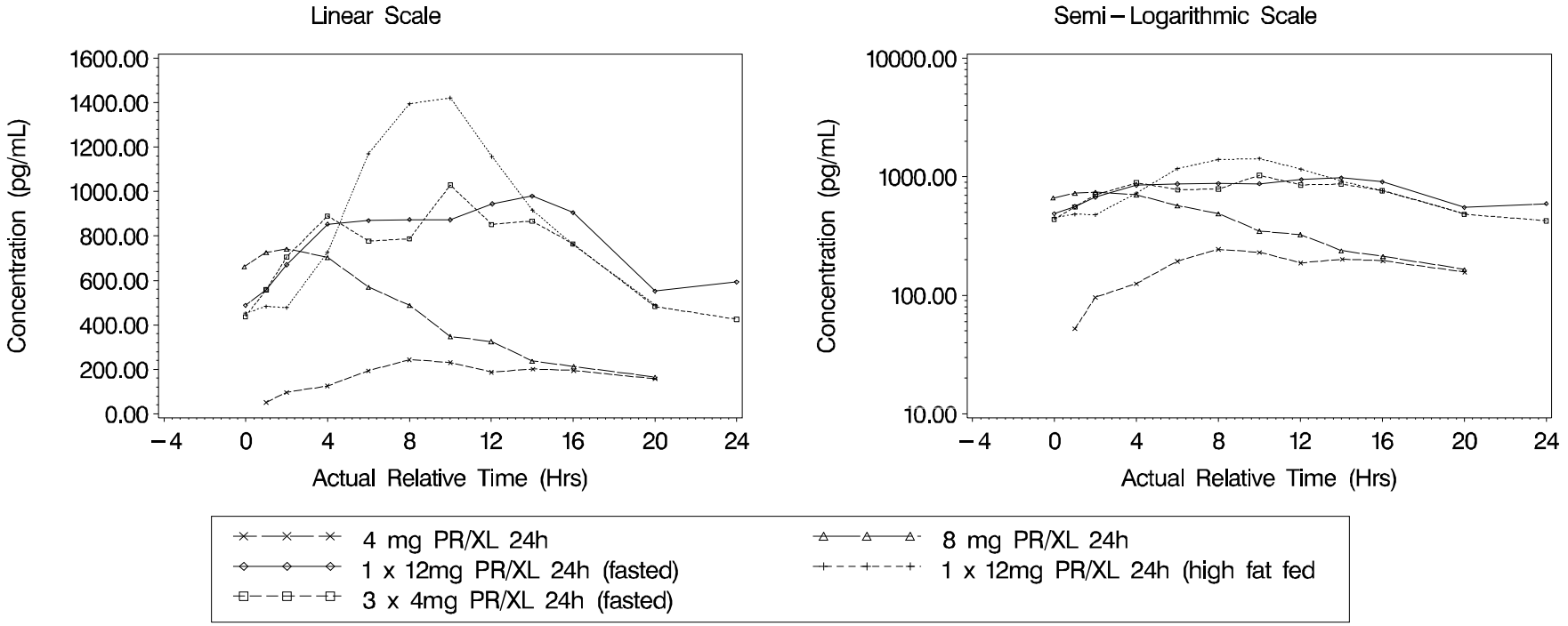
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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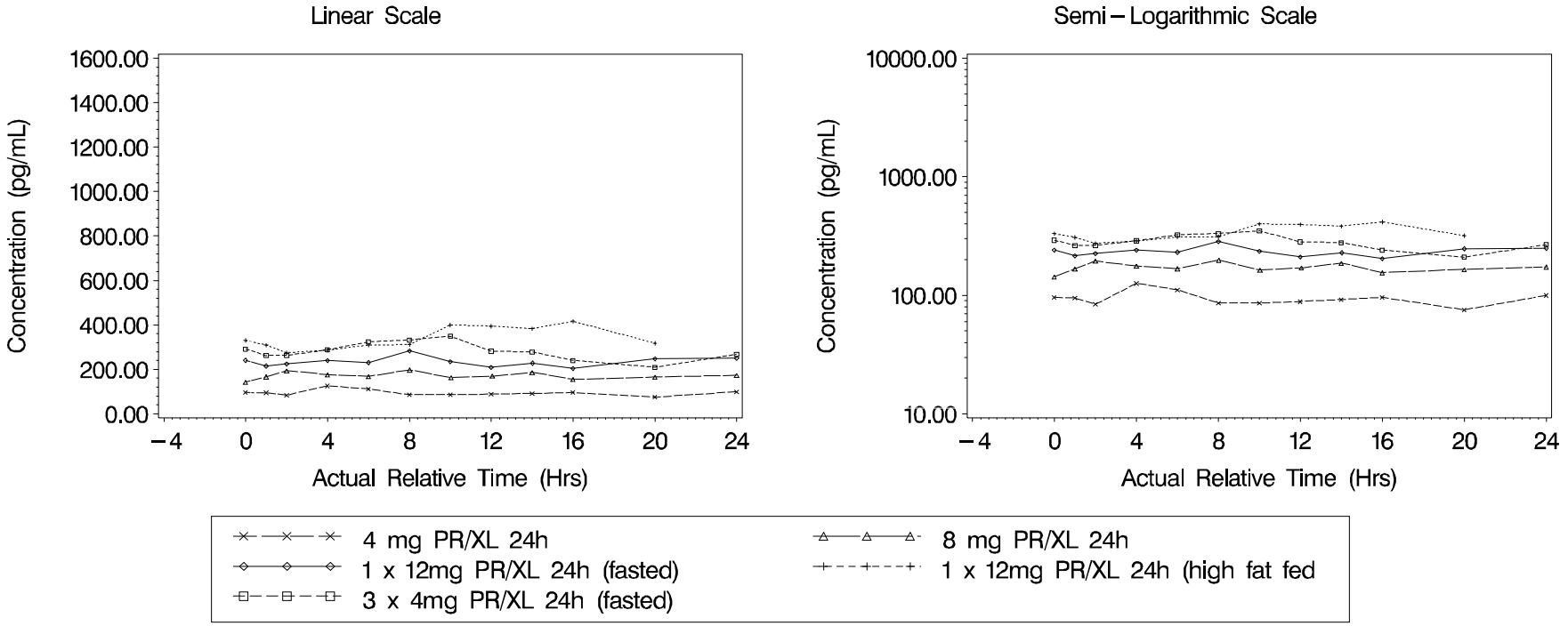
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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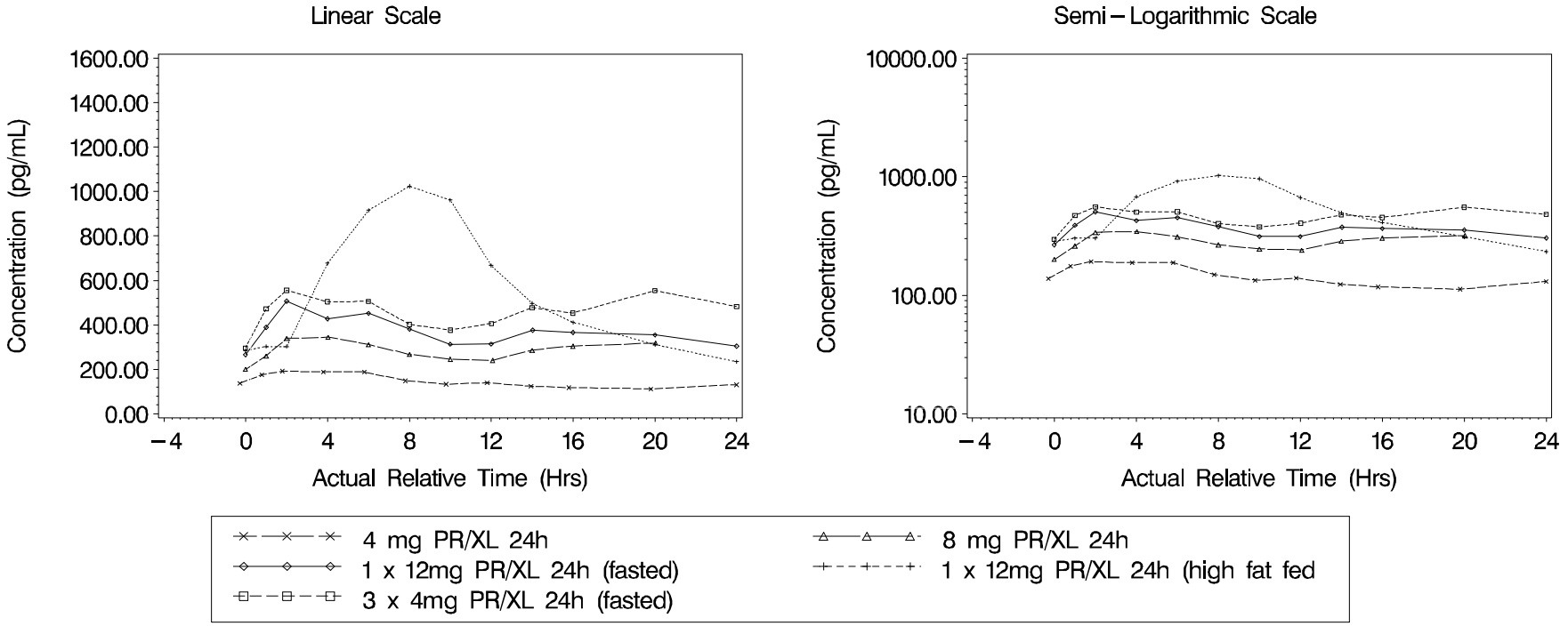
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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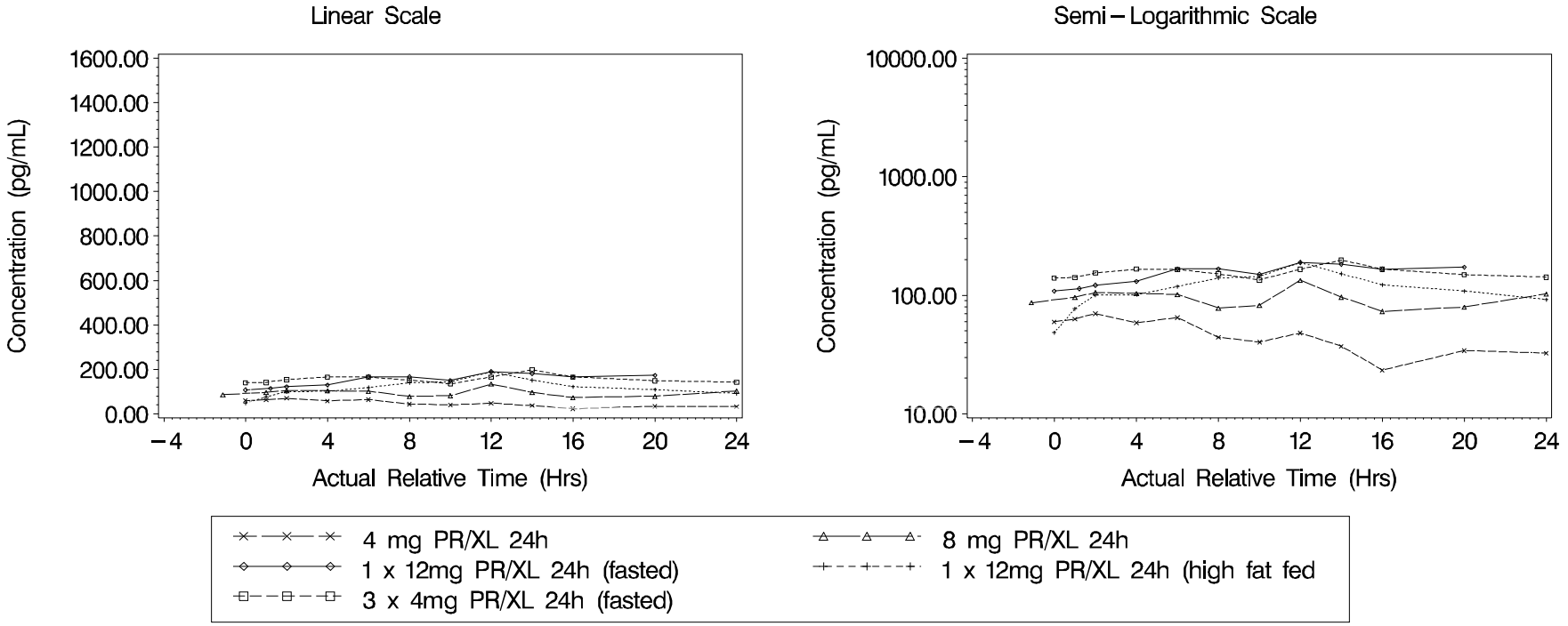
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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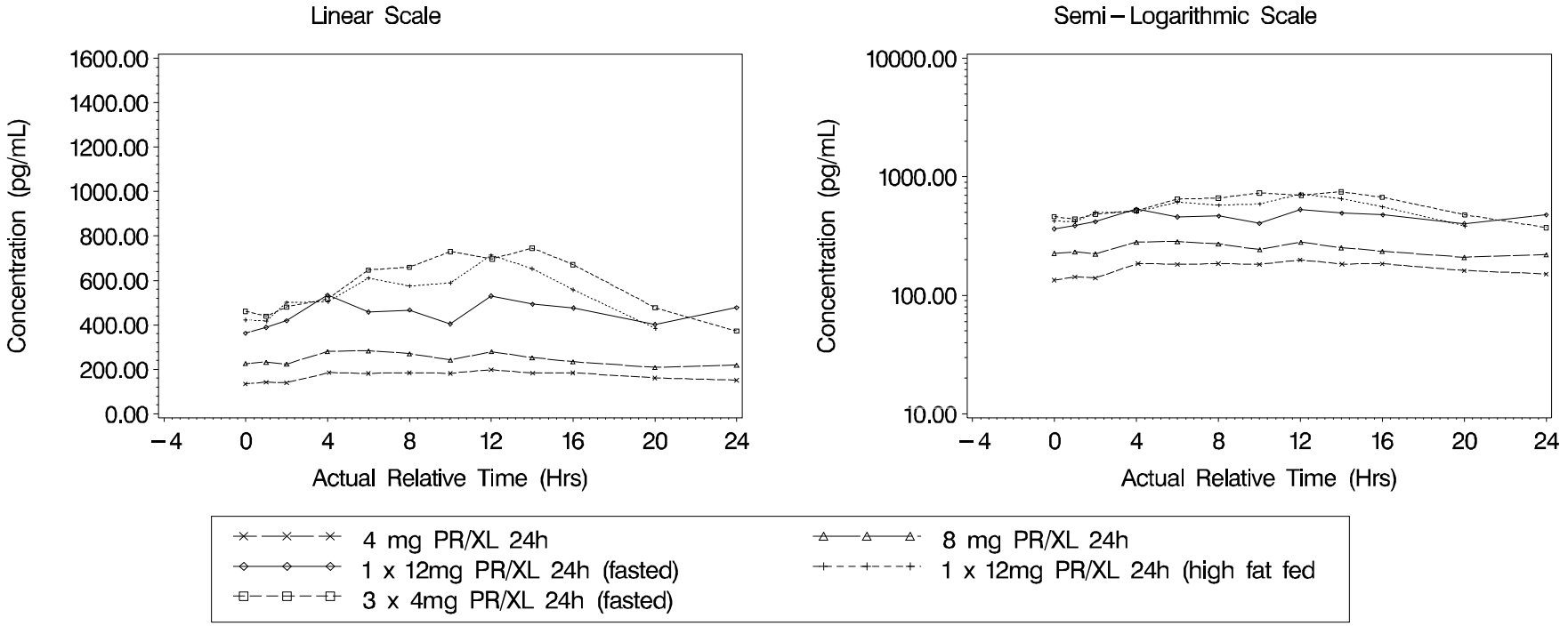
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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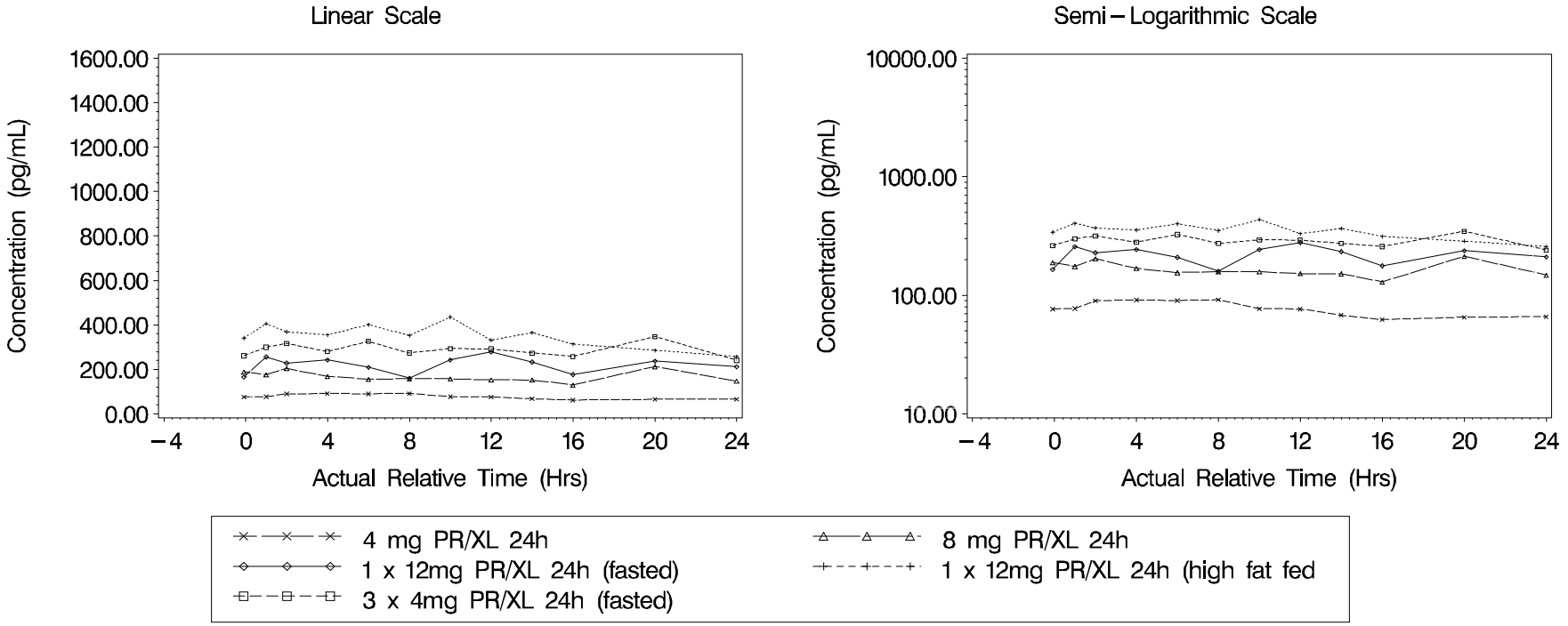
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
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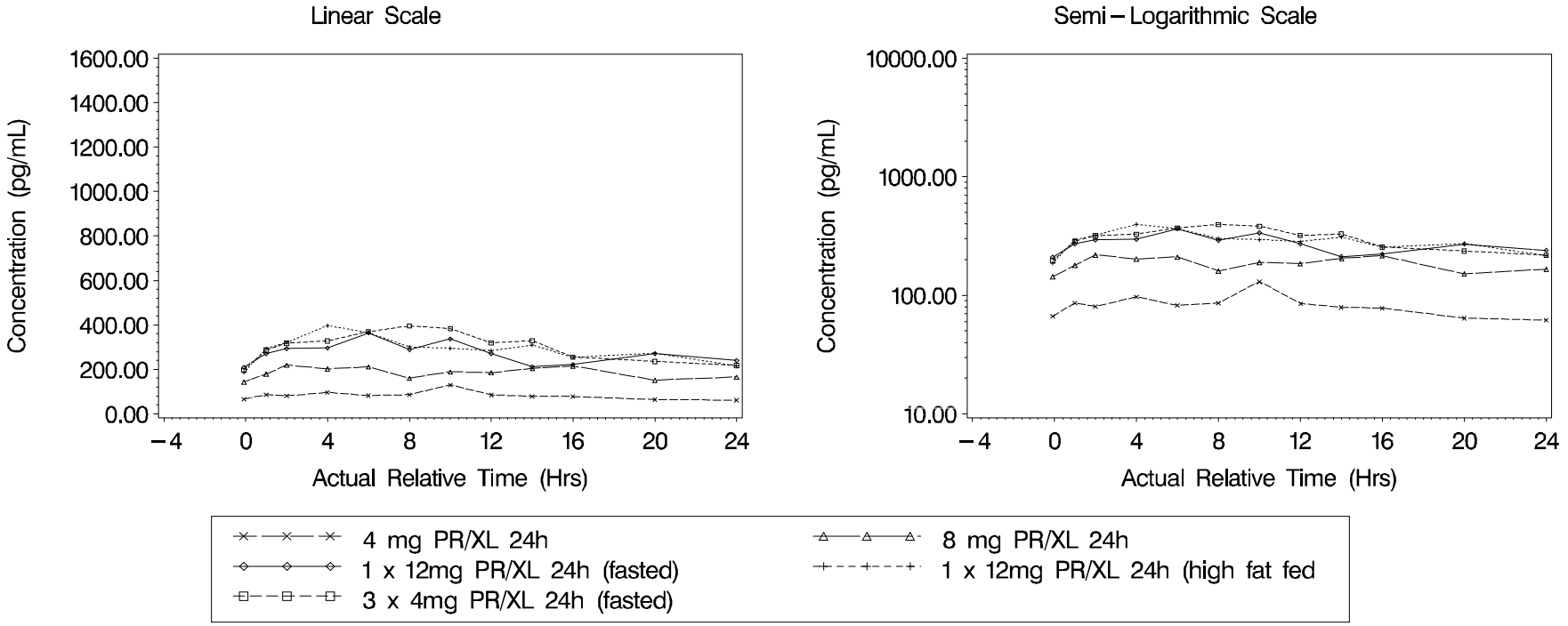
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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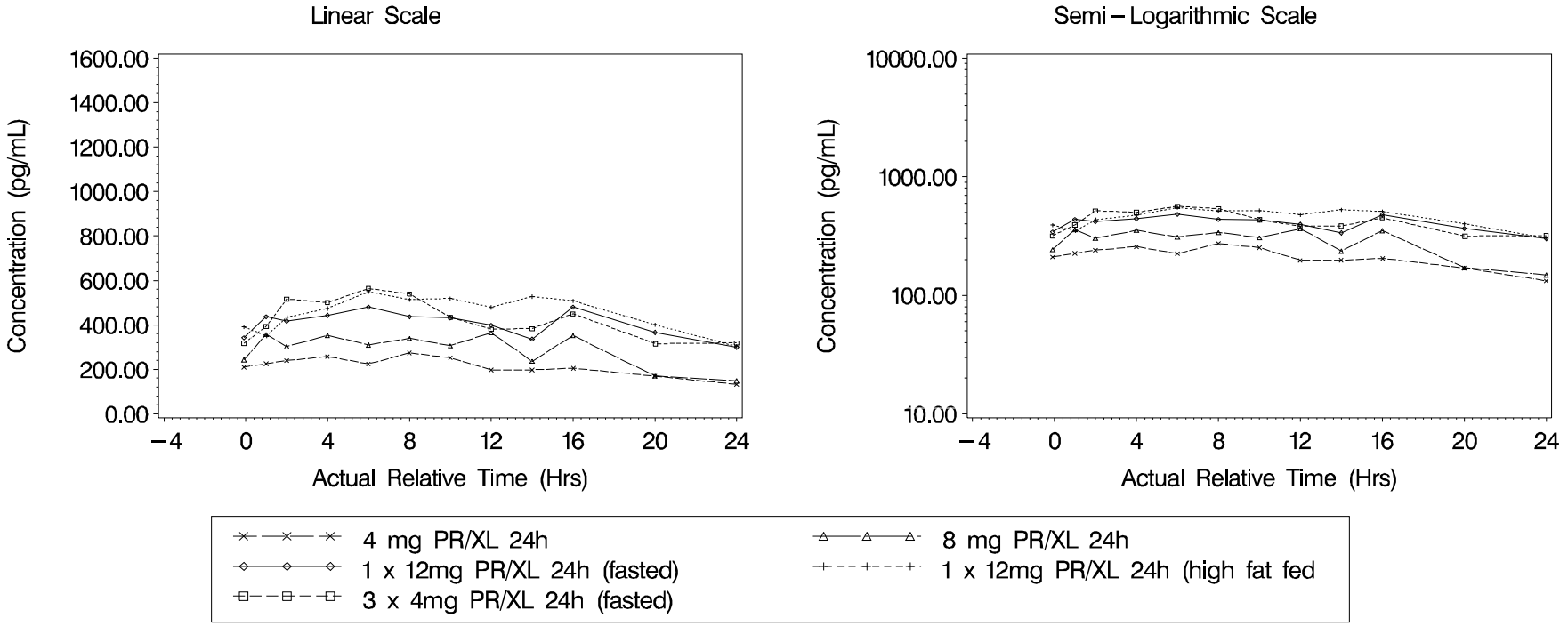
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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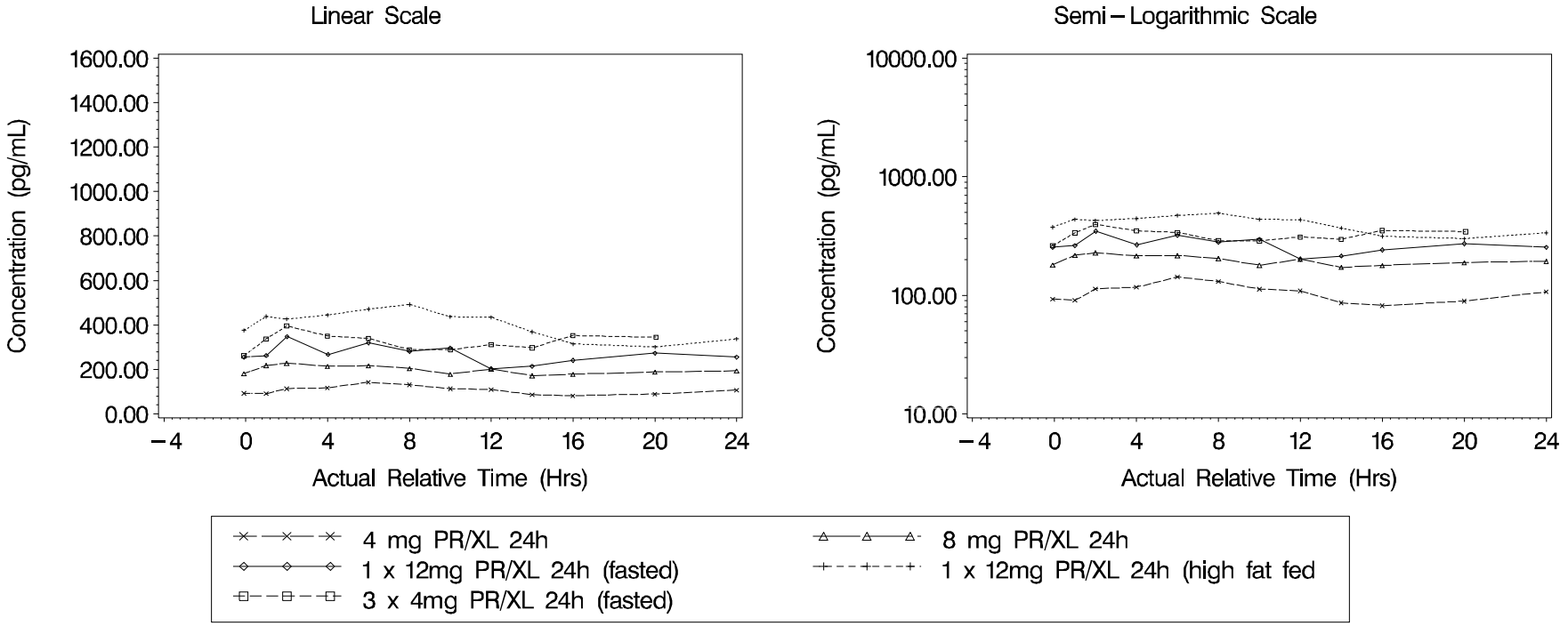
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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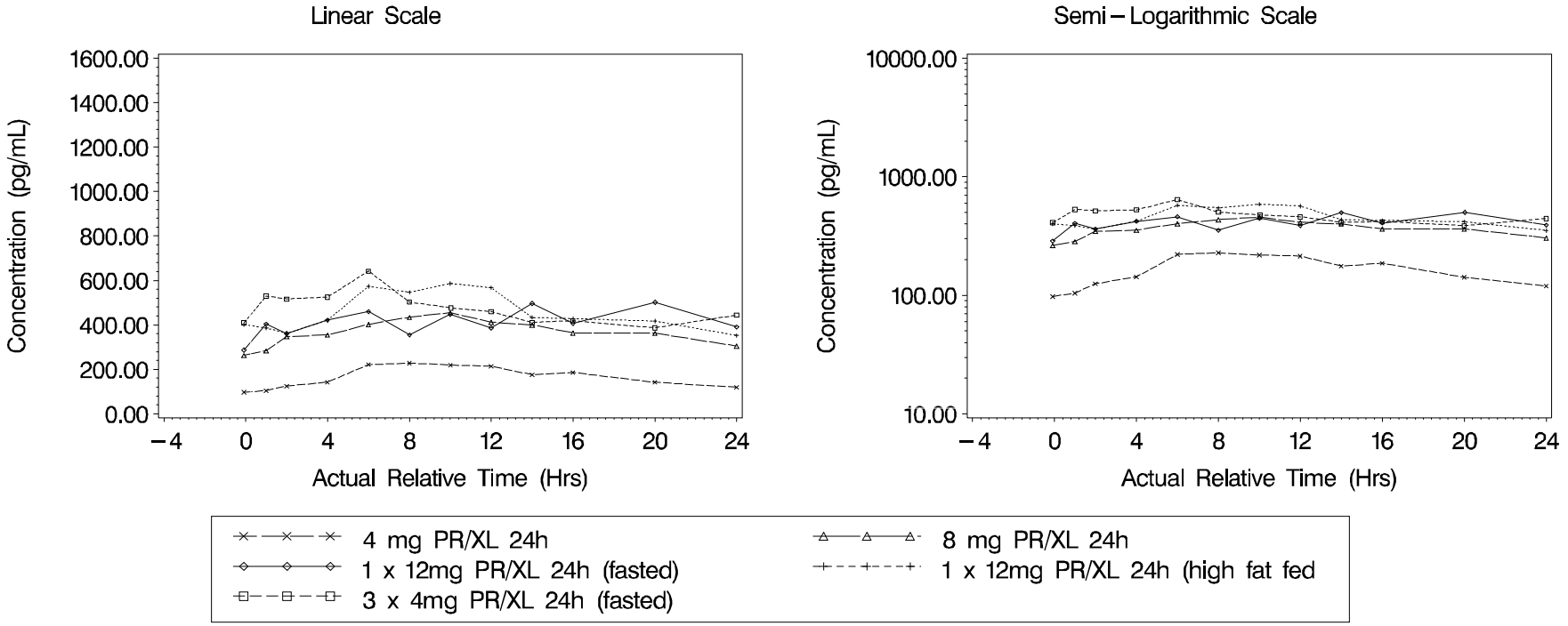
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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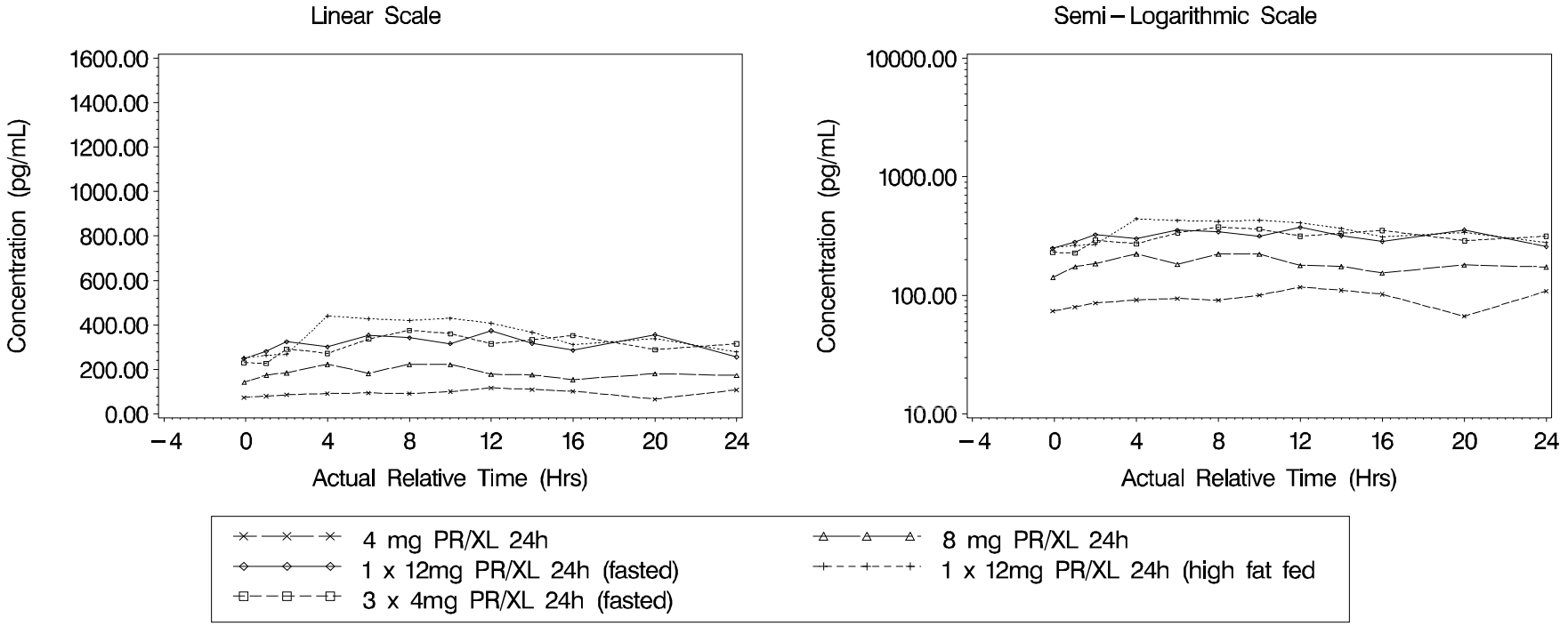
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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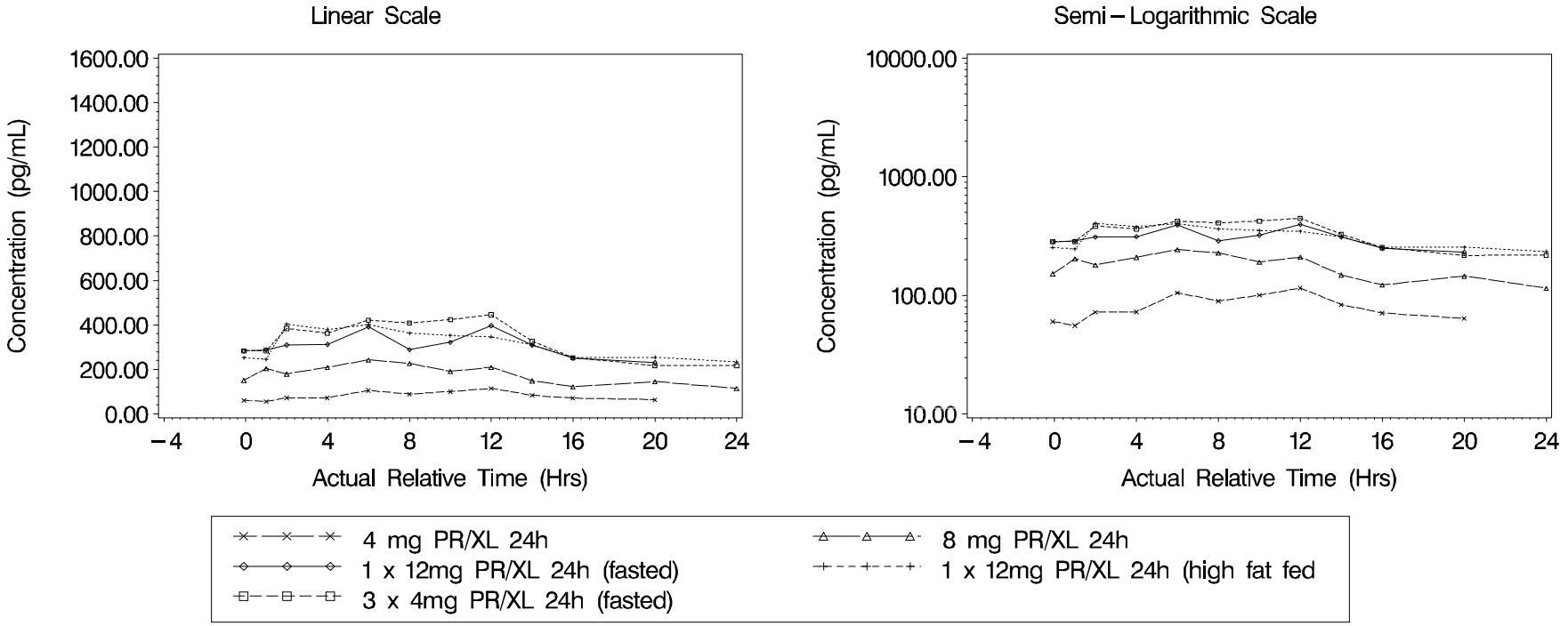
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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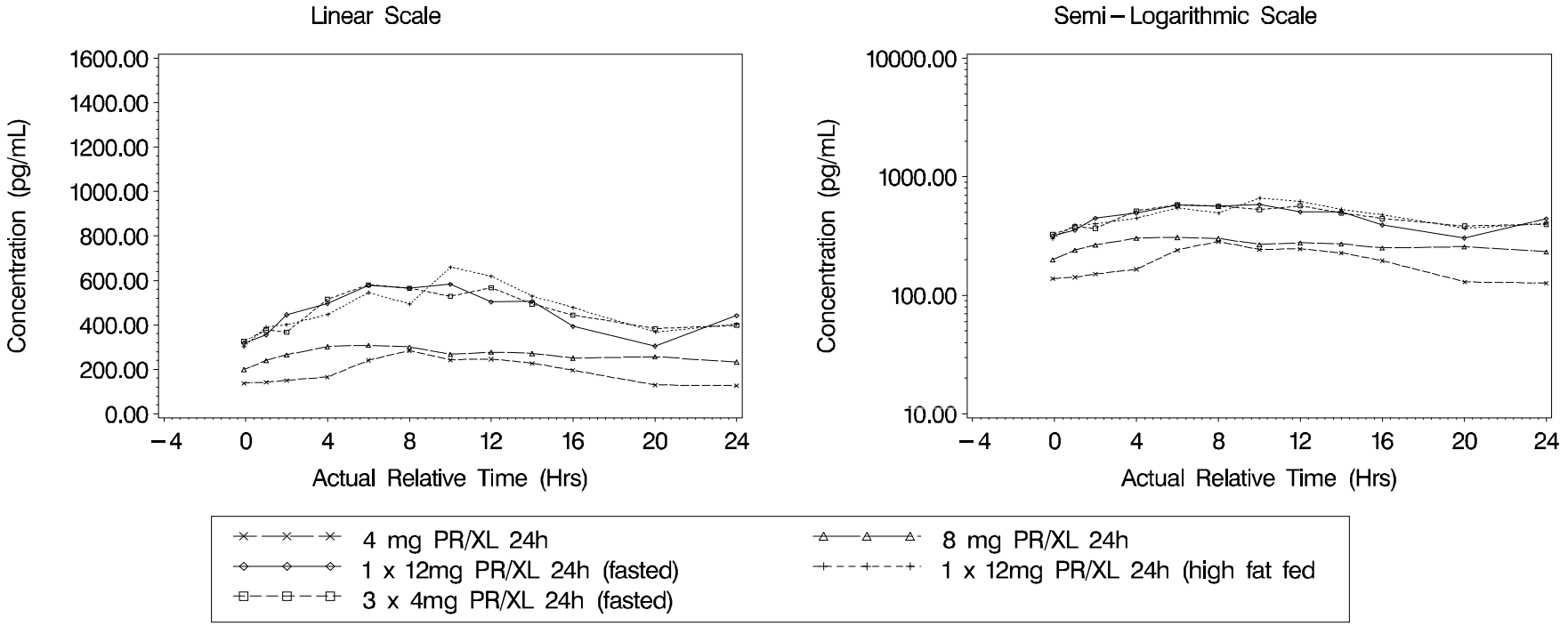
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
[redacted]

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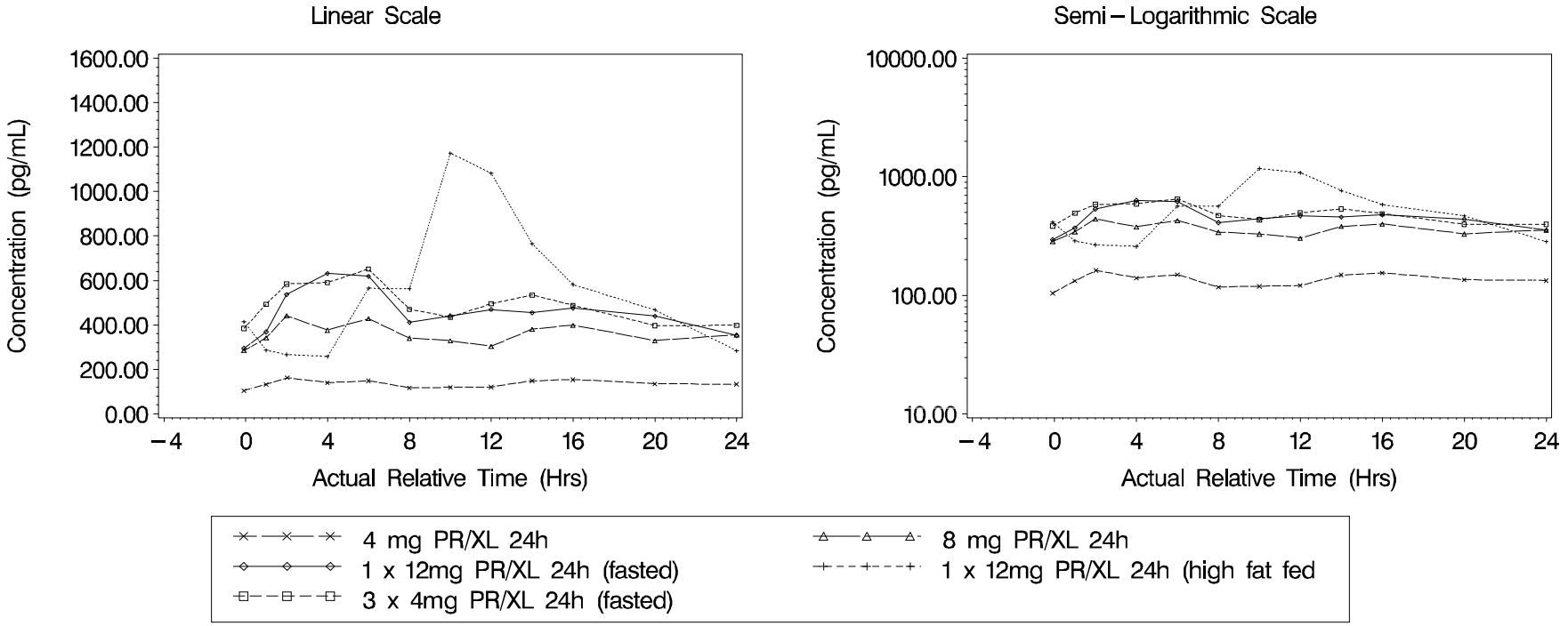
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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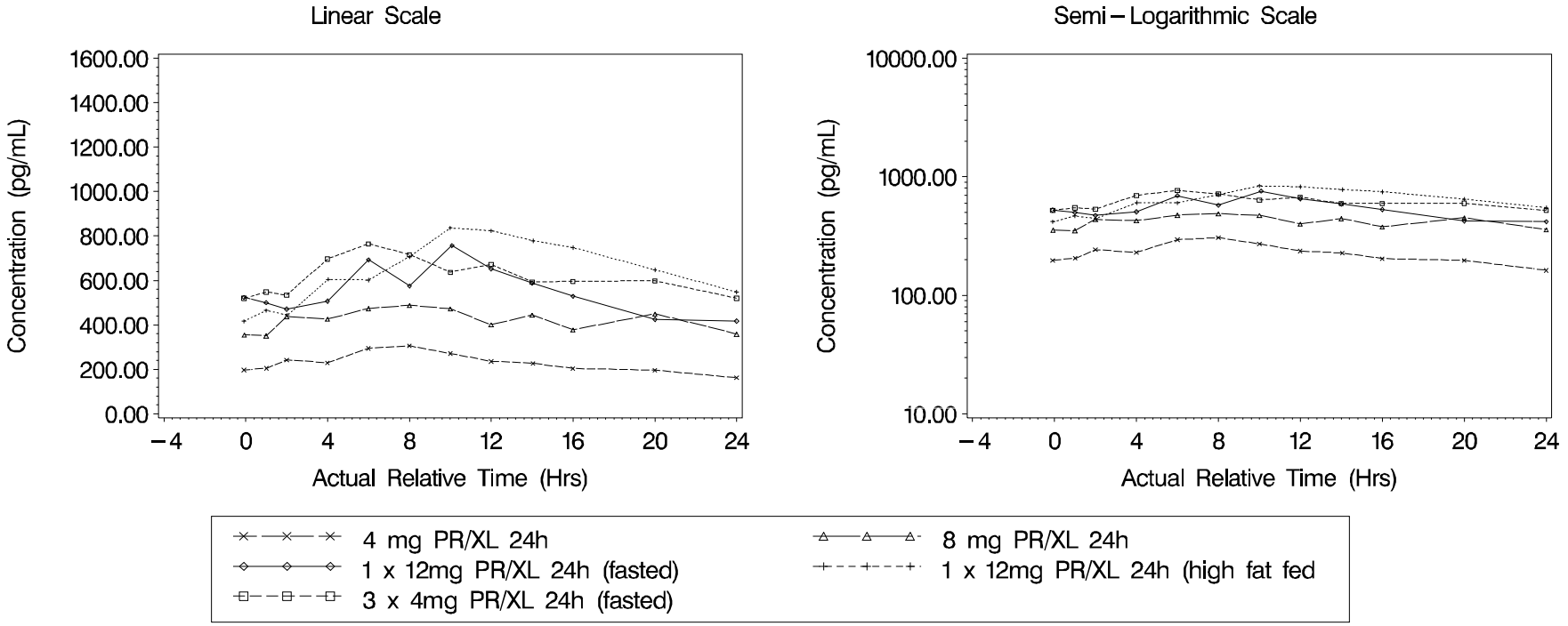
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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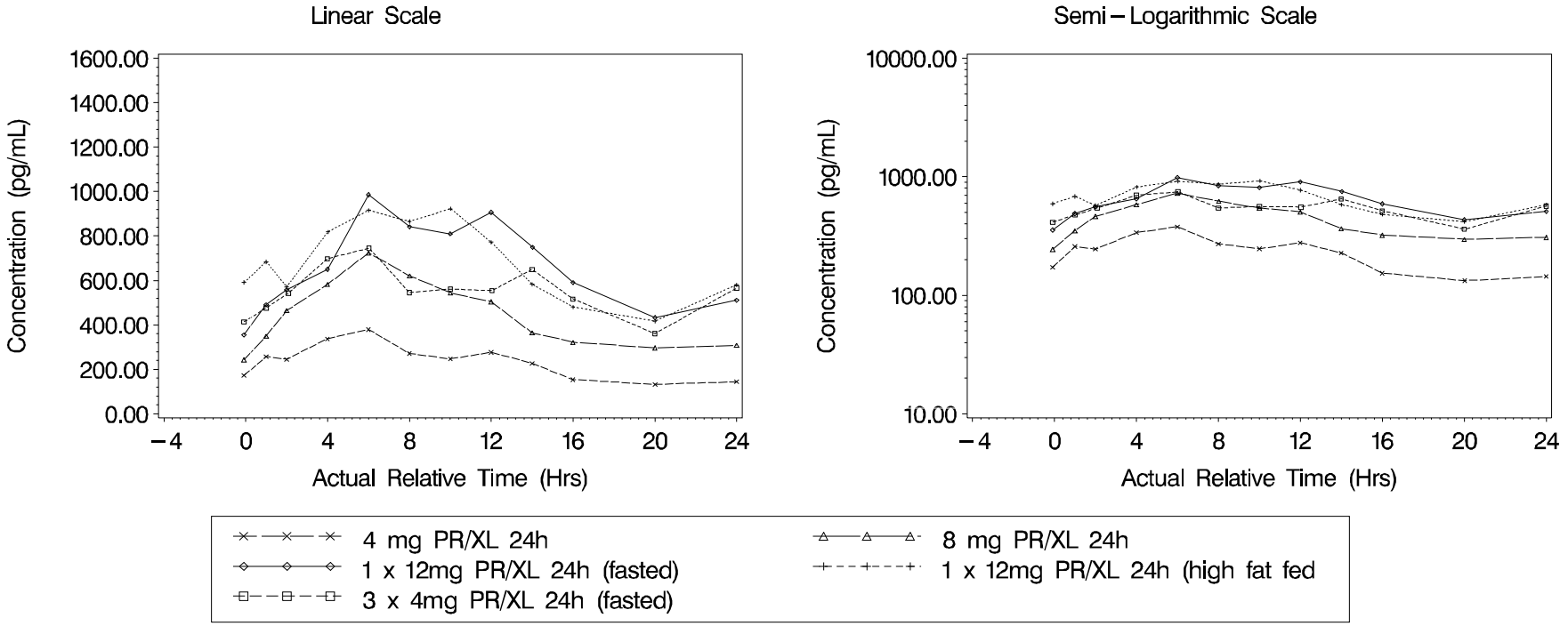
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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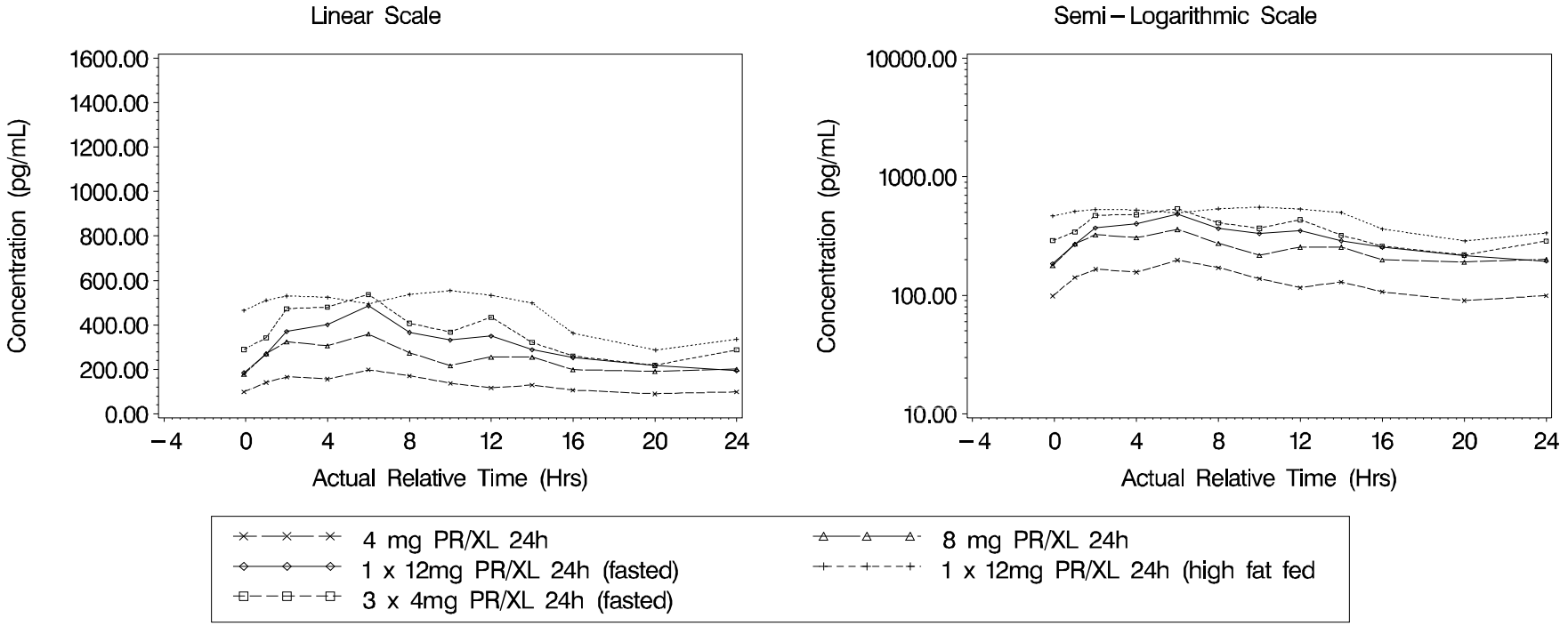
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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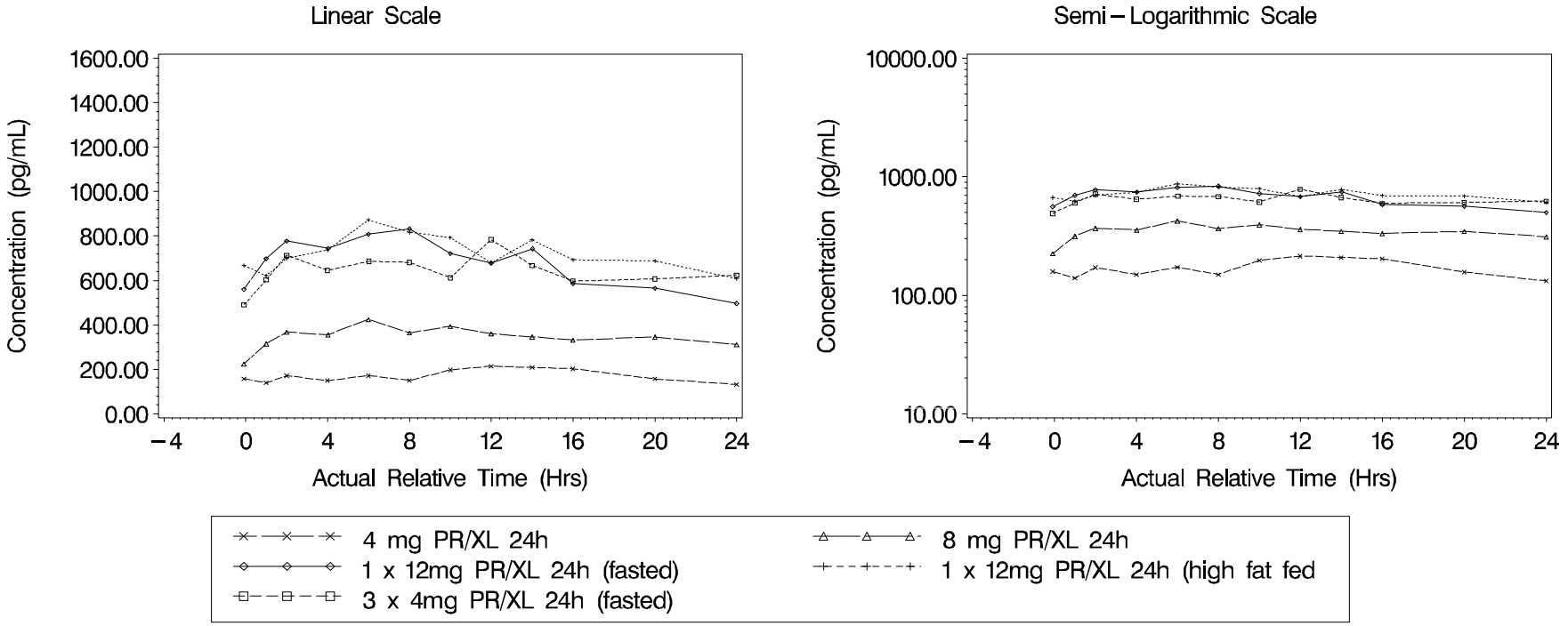
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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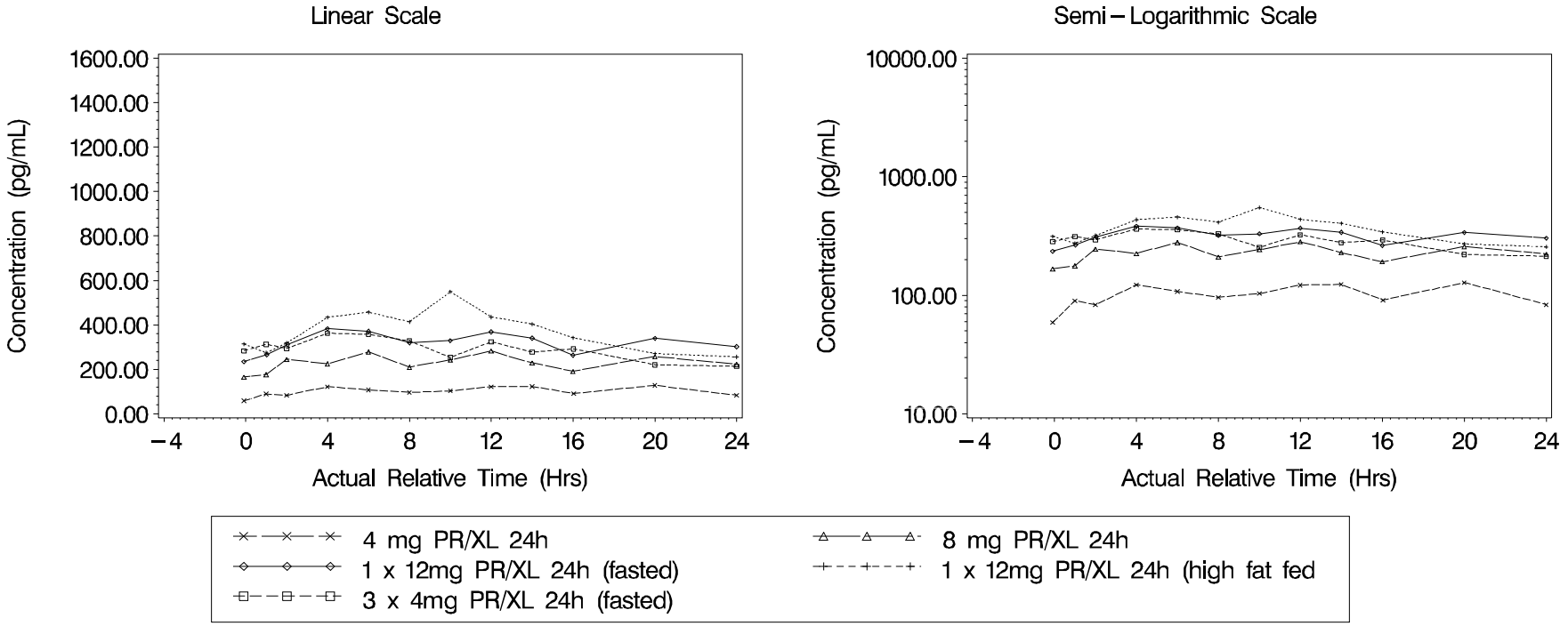
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G
[redacted]



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)
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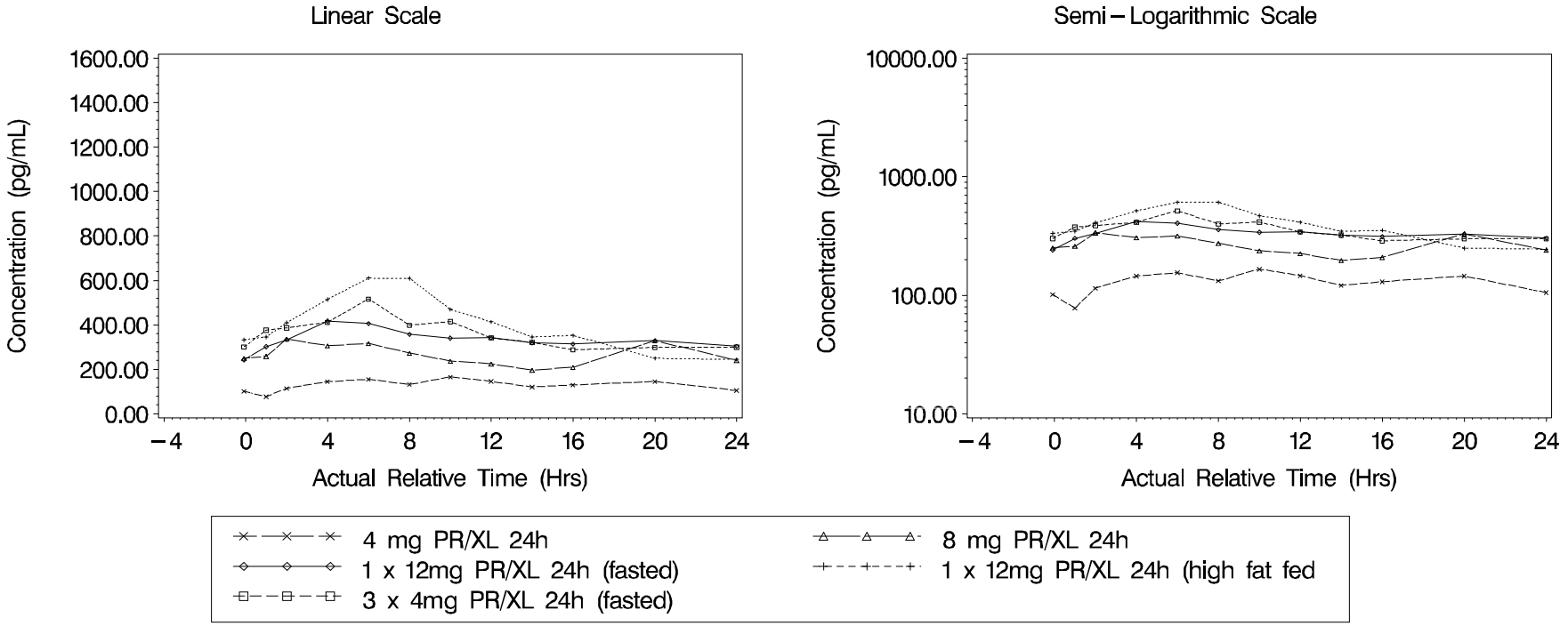
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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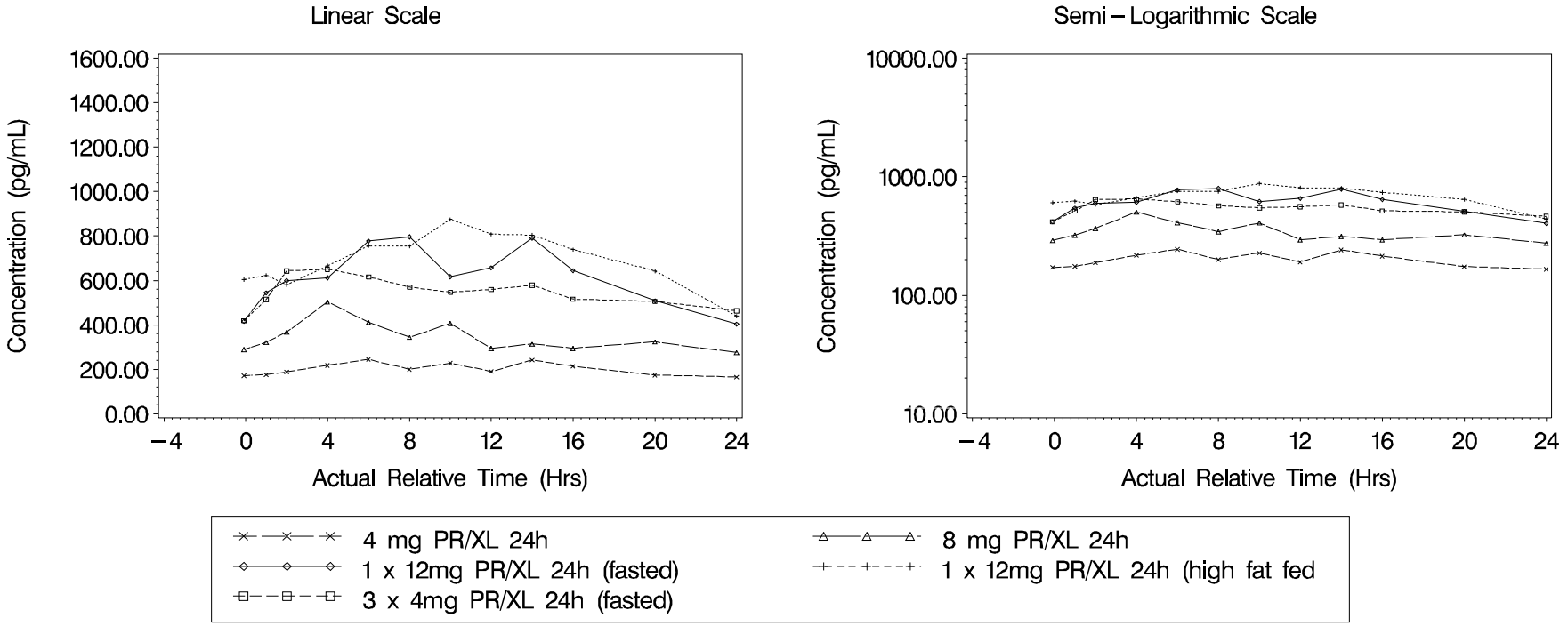
Figure 12.16
Individual plasma Metabolite (SKF−89124) Concentration−Time Plots (Linear and Semi−log) − B,D,E,F,G



NOTE: LLQ = 20 pg/mL
B=1 x 4 mg PR/XL, D=1 x 8 mg PR/XL, E=1 x 12 mg PR/XL 24h (fasted), F=1 x 12 mg PR/XL 24h (high fat fed), G=3 x 4 mg PR/XL 24h (fasted)

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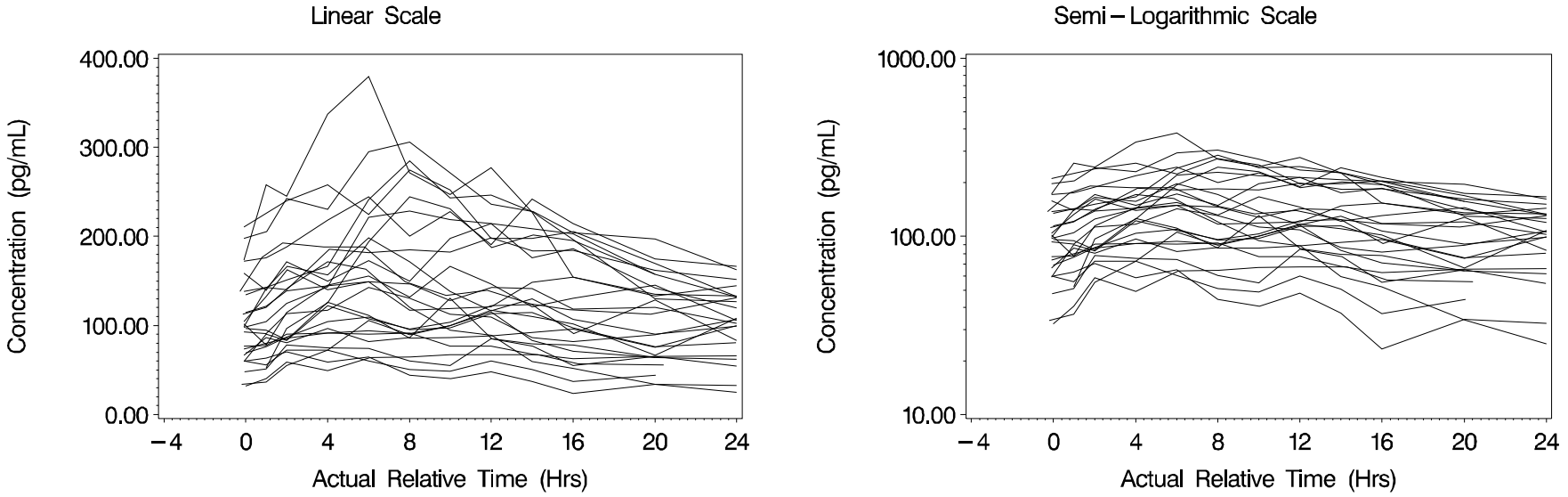
Figure 12.17
Individual Plasma Metabolite (SKF−89124) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=4 mg PR/XL 24h



NOTE: LLQ = 20 pg/mL

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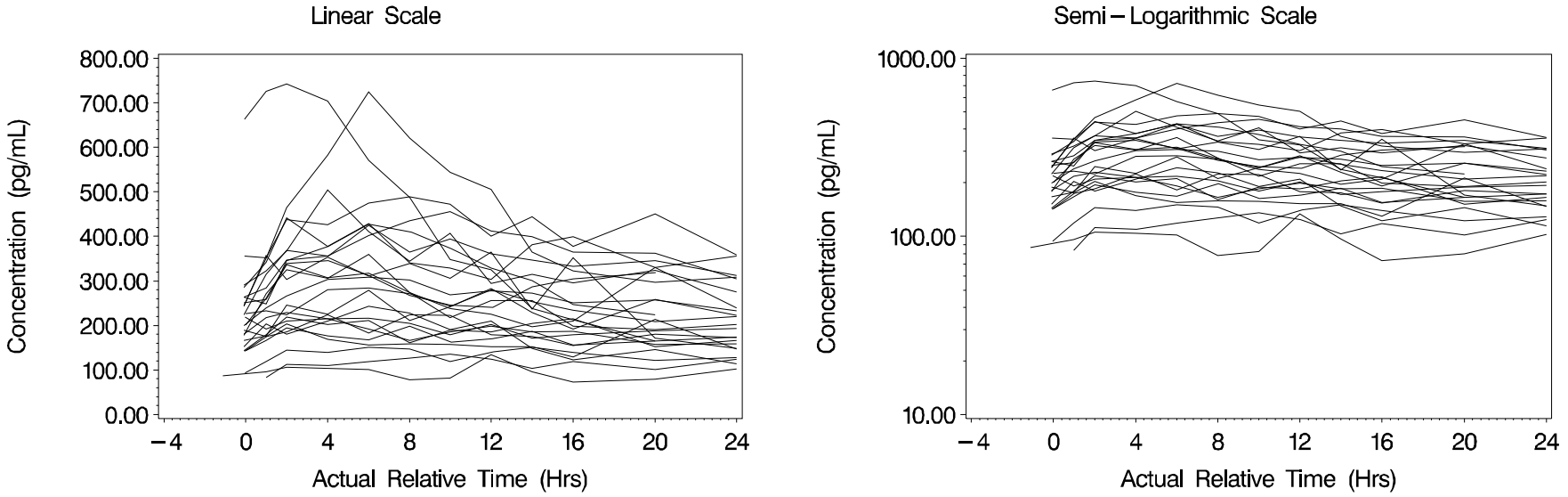
Figure 12.17
Individual Plasma Metabolite (SKF−89124) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=8 mg PR/XL 24h



NOTE: LLQ = 20 pg/mL

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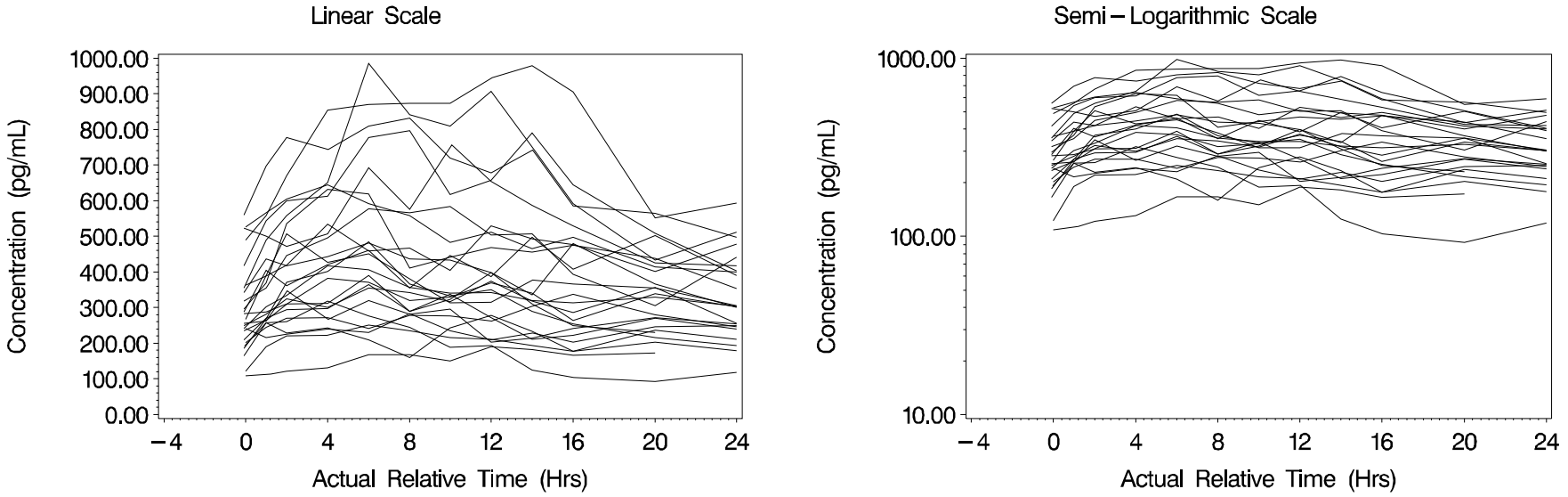
Figure 12.17
Individual Plasma Metabolite (SKF−89124) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=1 x 12mg PR/XL 24h (fasted)



NOTE: LLQ = 20 pg/mL

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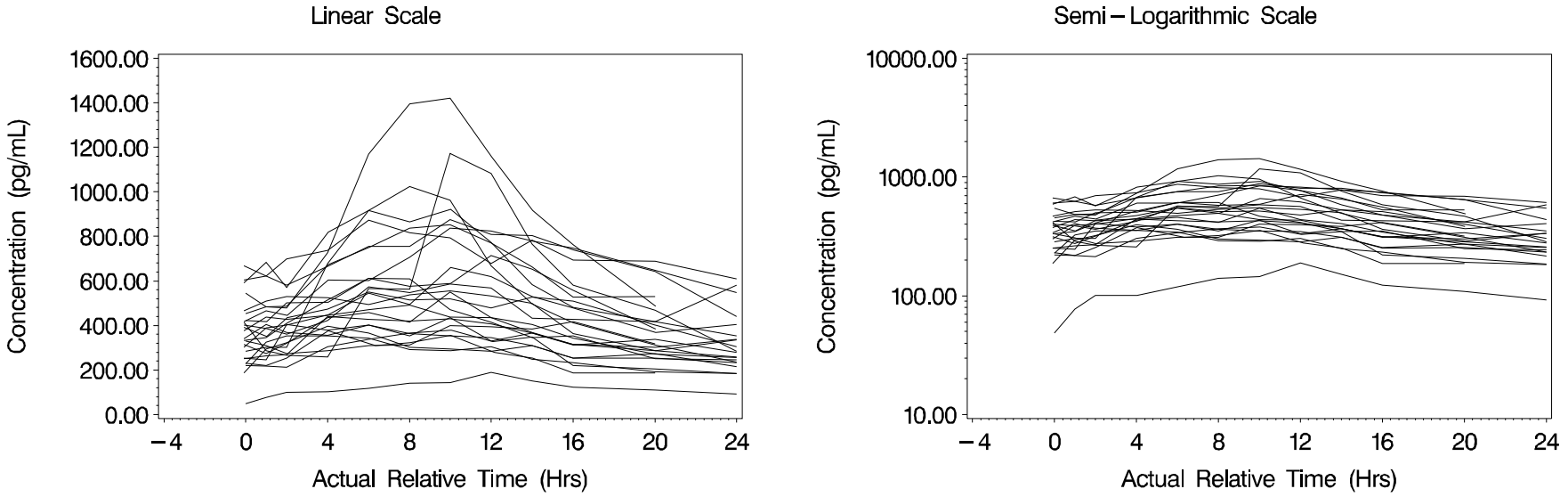
Figure 12.17
Individual Plasma Metabolite (SKF−89124) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=1 x 12mg PR/XL 24h (high fat fed)



NOTE: LLQ = 20 pg/mL

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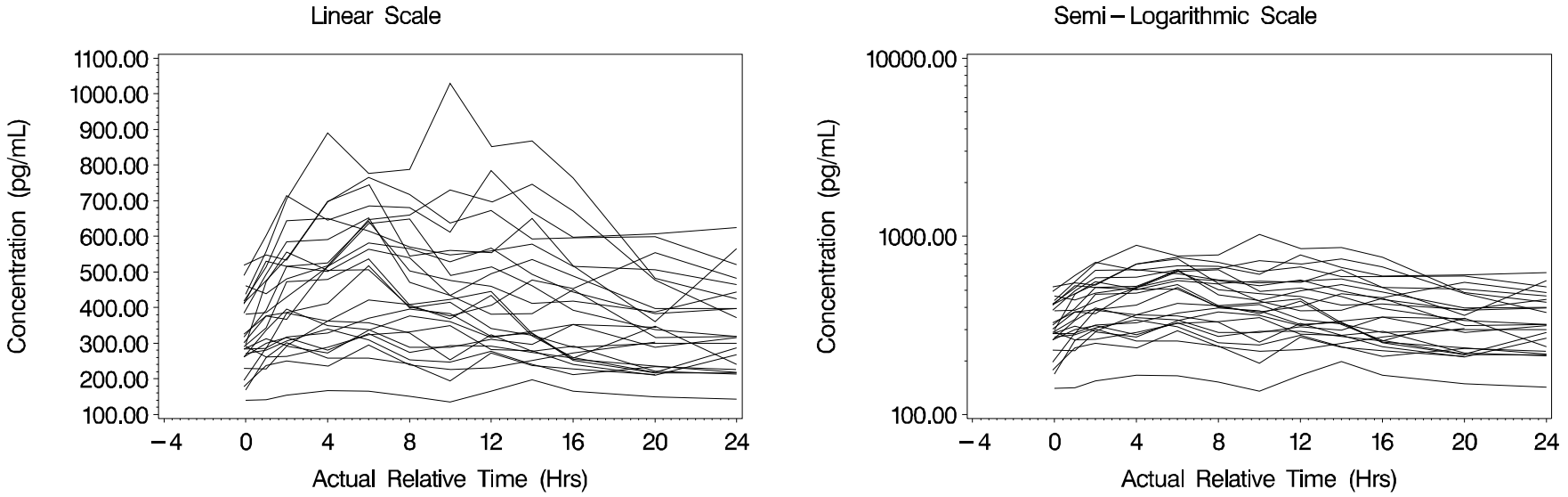
Figure 12.17
Individual Plasma Metabolite (SKF−89124) Concentration−Time Plot for each Treatment (Linear and Semi−Log)
Period Treatment Group=3 x 4mg PR/XL 24h (fasted)



NOTE: LLQ = 20 pg/mL

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Table 12.01
Summary of Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
4 mg PR/XL 24h	27	PRE-DOSE 1	27	0	2091.99	1373.100	1960.90	25.1	5053.5
		1H	27	0	2340.60	1310.663	2215.00	339.4	5318.5
		2H	27	0	2872.46	1436.105	2686.50	970.2	6434.7
		4H	27	0	3284.26	1491.455	3186.60	1261.5	6573.4
		6H	27	0	3387.45	1460.042	3237.40	1086.1	6528.5
		8H	27	0	3239.13	1496.063	3068.00	814.6	6227.1
		10H	27	0	3176.01	1590.315	3036.60	646.9	7440.9
		12H	27	0	2941.77	1580.279	2596.50	454.1	7399.7
		14H	27	0	2799.13	1758.368	2593.80	320.5	8966.6
		16H	27	0	2546.27	1717.911	2269.60	225.5	8402.6
		20H	27	0	2170.10	1510.365	1980.90	138.2	7139.0
		24H	27	0	1878.23	1225.832	1576.30	85.1	5610.2
8 mg PR/XL 24h	25	PRE-DOSE 1	25	0	4278.54	2613.548	3922.60	302.3	10527.9
		1H	25	0	5142.62	2715.323	4839.80	1993.0	12369.6
		2H	25	0	6106.04	2828.401	5649.80	2345.8	13454.4

NOTE: LLQ = 20.0 pg/mL

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Table 12.01
Summary of Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
8 mg PR/XL 24h	25	4H	25	0	6593.98	2744.350	6265.40	2335.9	13714.8
		6H	25	0	6678.84	2927.479	6336.40	2607.5	14111.2
		8H	25	0	6357.26	3110.144	6092.60	2043.5	14663.6
		10H	25	0	6050.27	3060.180	5842.30	1894.5	15336.5
		12H	25	0	5675.04	2842.125	5262.10	2481.8	14657.6
		14H	25	0	5301.23	2805.992	4460.60	2098.9	14045.2
		16H	25	0	5058.59	2924.444	4784.60	1870.7	13902.3
		20H	25	0	4410.06	2711.440	4016.40	1335.5	13155.8
		24H	25	0	3974.58	2654.928	3511.50	947.2	13053.8
1 x 12mg PR/XL 24h (fasted)	25	PRE-DOSE 1	25	0	5397.16	4136.526	4578.60	1630.4	20285.3
		1H	25	0	6511.42	4364.108	5117.00	1897.9	23011.4
		2H	25	0	8020.88	4680.752	6792.60	2397.6	25050.0
		4H	25	0	9153.60	4588.386	7960.80	3471.5	24487.9
		6H	25	0	9566.84	5106.959	8602.40	3616.7	27374.9
		8H	25	0	9008.48	4858.165	8179.00	3318.3	25894.0

NOTE: LLQ = 20.0 pg/mL

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Table 12.01
Summary of Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
1 x 12mg PR/XL 24h (fasted)	25	10H	25	0	8657.22	4755.991	7610.80	3188.2	24819.7
		12H	25	0	8027.32	4547.776	6718.20	2563.9	23823.4
		14H	25	0	7863.44	4373.875	7510.00	2008.4	22590.4
		16H	25	0	7333.47	4159.560	6513.90	1314.4	20478.3
		20H	25	0	6571.32	4064.304	6013.00	962.7	20326.8
		24H	25	0	5936.10	3843.204	4764.60	511.3	19154.1
1 x 12mg PR/XL 24h (high fat fed)	25	PRE-DOSE 1	25	0	5992.33	4150.341	4922.10	254.0	20057.2
		1H	25	0	6129.31	3927.530	5433.40	888.2	18865.0
		2H	25	0	6802.00	4078.809	6346.90	1088.6	19716.0
		4H	25	0	8983.16	4165.059	8584.10	2149.6	21942.9
		6H	25	0	11640.77	5134.213	11291.20	3280.5	30074.4
		8H	25	0	12477.88	5347.868	11299.80	3236.3	26943.7
		10H	25	0	13617.16	6204.662	12719.70	3576.7	26772.7
		12H	25	0	12054.55	5882.141	11119.60	3887.6	23770.7

NOTE: LLQ = 20.0 pg/mL

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Table 12.01
Summary of Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
1 x 12mg PR/XL 24h (high fat fed)	25	14H	25	0	10443.95	5215.078	9649.30	3234.8	21935.5
		16H	25	0	8648.33	4468.028	8213.60	2610.0	19185.6
		20H	25	0	6443.34	3683.337	5991.10	2025.9	17138.0
		24H	25	0	5317.62	3408.792	4518.00	814.3	15999.8
3 x 4mg PR/XL 24h (fasted)	25	PRE-DOSE 1	25	0	5840.18	4778.475	5125.00	1543.3	26205.6
		1H	25	0	7057.05	5039.470	6344.80	2658.9	28838.6
		2H	25	0	8394.26	5372.482	7153.40	2995.3	31134.3
		4H	25	0	9696.20	5713.272	8757.60	3273.9	32496.9
		6H	25	0	10083.70	6364.690	8766.40	3114.2	35636.0
		8H	25	0	9670.29	6329.394	8399.50	2878.8	34469.6
		10H	25	0	9282.40	6310.335	8144.40	2523.0	34298.8
		12H	25	0	8894.47	6598.924	7575.60	2898.1	36578.4
		14H	25	0	8461.96	5862.341	6902.70	2965.8	33350.6
		16H	25	0	7955.06	5814.951	6555.50	2627.4	33035.5

NOTE: LLQ = 20.0 pg/mL

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Table 12.01
Summary of Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
3 x 4mg PR/XL 24h (fasted)	25	20H	25	0	7040.40	5492.111	6183.90	2565.9	30922.6
		24H	25	0	6277.42	5120.185	5328.40	2110.5	28303.9

NOTE: LLQ = 20.0 pg/mL

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Table 12.02
Summary of Plasma Ropinirole (SKF-104557) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
4 mg PR/XL 24h	27	PRE-DOSE 1	27	0	2828.74	1259.800	2491.20	273.5	6577.6
		1H	27	0	2922.57	1237.996	2630.30	603.3	6721.7
		2H	27	0	3255.19	1237.477	2960.70	1209.3	6968.4
		4H	27	0	3652.74	1217.544	3394.00	1907.1	7326.6
		6H	27	0	3823.65	1117.233	3703.50	2173.5	6992.3
		8H	27	0	3891.19	1207.638	3869.10	1950.0	6844.7
		10H	27	0	3913.87	1222.704	3973.10	1692.5	6985.1
		12H	27	0	3794.66	1107.634	3581.70	1466.1	6053.5
		14H	27	0	3670.96	1311.294	3485.70	1164.4	6683.9
		16H	27	0	3391.28	1230.531	3255.80	886.0	5880.6
		20H	27	0	3038.94	1106.500	3218.90	711.5	5317.8
		24H	27	0	2817.26	997.235	3040.60	520.9	4865.9
8 mg PR/XL 24h	25	PRE-DOSE 1	25	0	5800.94	2825.255	5192.90	1191.2	15461.6
		1H	25	0	6210.32	2551.776	5718.90	2467.8	14365.0
		2H	25	0	6842.58	2665.210	6734.10	3322.1	14913.0

NOTE: LLQ = 50.0 pg/mL

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Table 12.02
Summary of Plasma Ropinirole (SKF-104557) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
8 mg PR/XL 24h	25	4H	25	0	7312.67	2549.041	7013.40	3978.3	13674.7
		6H	25	0	7656.33	2672.163	7232.10	4160.1	12813.6
		8H	25	0	7619.94	2797.528	7031.40	3938.3	14422.1
		10H	25	0	7515.18	2697.970	6606.70	3816.5	13540.2
		12H	25	0	7305.82	2607.392	6325.70	4181.7	12819.6
		14H	25	0	6928.20	2376.294	6200.10	4204.4	12396.3
		16H	25	0	6623.79	2381.021	5763.10	3926.0	12181.1
		20H	25	0	6094.68	2126.169	5152.70	3575.2	11070.2
		24H	25	0	5575.78	1761.080	5067.80	3063.0	9687.3
1 x 12mg PR/XL 24h (fasted)	25	PRE-DOSE 1	25	0	7887.98	3181.357	6839.80	2959.2	14043.2
		1H	25	0	8385.84	3030.784	7682.90	3854.8	14554.3
		2H	25	0	9198.32	3091.575	8338.80	3893.3	15275.1
		4H	25	0	10131.66	3338.244	9232.50	4651.0	17004.1
		6H	25	0	10830.17	3772.235	9597.20	4956.0	18292.2
		8H	25	0	10624.90	3725.185	9442.00	4895.6	18283.5

NOTE: LLQ = 50.0 pg/mL

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Table 12.02
Summary of Plasma Ropinirole (SKF-104557) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
1 x 12mg PR/XL 24h (fasted)	25	10H	25	0	10511.87	3873.078	9196.10	5023.1	18785.6
		12H	25	0	10346.64	4027.439	8807.30	5627.2	19039.6
		14H	25	0	10085.66	4096.719	8908.80	4355.0	20032.7
		16H	25	0	9684.51	3842.014	8149.50	3936.2	17923.3
		20H	25	0	8771.25	3203.992	8003.10	2923.8	15151.7
		24H	25	0	8257.53	2915.868	7464.80	2018.0	13549.2
1 x 12mg PR/XL 24h (high fat fed)	25	PRE-DOSE 1	25	0	8238.34	2896.450	7925.80	1294.7	14136.7
		1H	25	0	7989.90	2640.966	7641.70	1906.5	13691.9
		2H	25	0	8420.01	2566.175	7882.90	2591.7	13856.6
		4H	25	0	9738.85	2611.253	9275.10	3134.1	15000.5
		6H	25	0	11768.04	3522.394	11351.80	4742.2	18412.1
		8H	25	0	12726.52	4169.976	12225.80	5130.2	21925.2
		10H	25	0	14271.03	5221.459	13584.40	6012.0	24806.2
		12H	25	0	13673.91	4909.415	12582.50	7057.6	24573.4

NOTE: LLQ = 50.0 pg/mL

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Table 12.02
Summary of Plasma Ropinirole (SKF-104557) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
1 x 12mg PR/XL 24h (high fat fed)	25	14H	25	0	12698.03	4431.148	12156.00	6815.8	23501.6
		16H	25	0	11340.70	3796.750	10809.50	6298.8	20441.3
		20H	25	0	9316.49	3226.858	8305.80	4875.6	16693.4
		24H	25	0	8133.08	2821.538	7042.00	4266.3	13010.5
3 x 4mg PR/XL 24h (fasted)	25	PRE-DOSE 1	25	0	8148.65	2197.701	7805.90	4831.4	13560.4
		1H	25	0	8735.52	2235.883	8640.50	5709.1	14660.7
		2H	25	0	9500.33	2189.172	9650.60	6111.2	13730.5
		4H	25	0	10305.92	2552.110	9910.50	6722.3	15933.6
		6H	25	0	11089.74	2804.719	10896.80	6692.9	18392.9
		8H	25	0	10820.24	2705.400	10294.70	7043.0	17890.3
		10H	25	0	10818.58	2955.450	10247.40	6529.1	19172.0
		12H	25	0	10503.54	2914.804	9962.20	6739.2	18231.8
		14H	25	0	10184.57	2789.108	9539.50	6605.3	16469.2
		16H	25	0	9876.48	2720.023	9861.30	6240.6	16371.9

NOTE: LLQ = 50.0 pg/mL

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Table 12.02
Summary of Plasma Ropinirole (SKF-104557) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
3 x 4mg PR/XL 24h (fasted)	25	20H	25	0	8909.33	2338.954	8840.70	5366.5	15147.9
		24H	25	0	8314.99	2248.997	8158.60	5171.1	14086.7

NOTE: LLQ = 50.0 pg/mL

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Table 12.03
Summary of Plasma Ropinirole (SKF-89124) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
4 mg PR/XL 24h	27	PRE-DOSE 1	27	1	100.73	51.980	97.60	0.0	210.7
		1H	27	0	113.26	57.348	94.90	36.6	257.9
		2H	27	0	128.72	56.901	114.70	55.1	245.1
		4H	27	0	142.15	65.296	140.30	49.1	337.5
		6H	27	0	157.93	76.934	149.30	60.3	379.5
		8H	27	0	146.96	77.301	130.70	44.2	306.0
		10H	27	0	143.35	69.980	128.10	40.4	271.5
		12H	27	0	140.96	62.510	120.90	48.1	277.3
		14H	27	0	133.59	62.503	123.80	37.1	242.1
		16H	27	0	121.26	59.809	107.00	23.4	214.3
		20H	27	0	106.97	47.458	112.60	33.9	196.8
		24H	27	0	100.57	40.359	105.40	24.9	166.3
8 mg PR/XL 24h	25	PRE-DOSE 1	25	1	216.20	119.255	200.80	0.0	662.5
		1H	25	0	253.91	126.133	239.80	83.6	726.2
		2H	25	0	293.45	137.239	266.10	105.6	741.9

NOTE: LLQ = 20.0 pg/mL

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Table 12.03
Summary of Plasma Ropinirole (SKF-89124) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
8 mg PR/XL 24h	25	4H	25	0	302.69	144.363	303.00	104.0	703.9
		6H	25	0	310.98	149.006	308.30	101.6	724.4
		8H	25	0	284.82	130.661	270.90	78.0	620.6
		10H	25	0	268.40	119.514	242.50	82.3	544.5
		12H	25	0	262.20	97.703	255.90	124.4	505.1
		14H	25	0	243.87	93.047	236.70	96.5	444.3
		16H	25	0	230.74	91.084	212.70	73.3	399.3
		20H	25	0	229.60	93.508	209.10	79.7	450.6
		24H	25	0	216.20	76.417	201.90	102.9	358.7
1 x 12mg PR/XL 24h (fasted)	25	PRE-DOSE 1	25	0	297.42	124.721	266.90	108.5	559.5
		1H	25	0	356.75	140.092	302.20	114.0	698.3
		2H	25	0	399.65	159.270	361.70	121.8	777.9
		4H	25	0	430.95	181.156	418.20	130.6	853.6
		6H	25	0	473.80	219.471	451.80	167.4	986.2
		8H	25	0	428.39	212.063	357.30	160.0	874.1

NOTE: LLQ = 20.0 pg/mL

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Table 12.03
Summary of Plasma Ropinirole (SKF-89124) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
1 x 12mg PR/XL 24h (fasted)	25	10H	25	0	418.79	200.188	337.20	150.2	873.3
		12H	25	0	424.35	209.680	374.40	189.6	945.6
		14H	25	0	410.12	217.986	336.40	125.1	979.7
		16H	25	0	374.06	187.101	337.40	103.3	906.2
		20H	25	0	340.74	121.651	339.30	92.4	565.2
		24H	25	0	319.06	124.945	302.50	118.5	593.3
1 x 12mg PR/XL 24h (high fat fed)	25	PRE-DOSE 1	25	0	363.01	143.237	341.20	48.3	667.5
		1H	25	0	376.97	141.410	350.30	77.2	684.4
		2H	25	0	390.87	131.963	400.90	100.8	699.4
		4H	25	0	477.04	170.980	444.50	101.2	818.9
		6H	25	0	555.11	237.054	545.70	118.8	1170.9
		8H	25	0	560.57	275.217	513.80	139.8	1394.9
		10H	25	0	611.22	302.013	549.10	144.3	1421.5
		12H	25	0	552.99	251.874	479.70	188.9	1157.7

NOTE: LLQ = 20.0 pg/mL

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Table 12.03
Summary of Plasma Ropinirole (SKF-89124) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
1 x 12mg PR/XL 24h (high fat fed)	25	14H	25	0	491.44	203.602	433.70	151.9	915.8
		16H	25	0	424.07	181.759	411.80	122.4	761.7
		20H	25	0	361.42	149.815	318.20	108.8	688.1
		24H	25	0	321.59	128.768	283.40	92.1	607.9
3 x 4mg PR/XL 24h (fasted)	25	PRE-DOSE 1	25	0	320.76	102.285	296.90	140.2	519.9
		1H	25	0	377.79	121.688	376.80	141.4	602.9
		2H	25	0	429.14	147.796	395.70	154.2	713.9
		4H	25	0	455.64	175.868	479.90	166.4	890.7
		6H	25	0	495.07	177.477	516.90	165.1	777.3
		8H	25	0	447.56	169.219	407.80	151.7	787.4
		10H	25	0	431.96	191.433	415.30	134.8	1029.2
		12H	25	0	438.40	177.356	406.70	166.0	852.3
		14H	25	0	422.19	178.445	333.70	198.2	867.2
		16H	25	0	389.73	157.577	352.60	166.2	764.5

NOTE: LLQ = 20.0 pg/mL

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Table 12.03
Summary of Plasma Ropinirole (SKF-89124) Pharmacokinetic Concentration-Time Data (pg/mL)

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
3 x 4mg PR/XL 24h (fasted)	25	20H	25	0	347.71	128.984	338.00	149.1	607.1
		24H	25	0	341.14	124.236	315.40	142.5	624.1

NOTE: LLQ = 20.0 pg/mL

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Table 12.04
Summary Statistics by Regimen for Ropinirole (SFK-101468) Pharmacokinetic Parameters

Parameter	Treatment	N	n	Mean	95% CI (Lower,Upper)	SD	Median	Min.	Max.
AUC(0-24)-ss (ng*hr/mL)	4 mg PR/XL 24h	27	27	65.331	(51.579,79.083)	34.7637	58.542	13.57	167.02
	8 mg PR/XL 24h	25	25	130.366	(103.708,157.023)	64.5797	119.152	48.86	328.62
	1 x 12mg PR/XL 24h (fasted)	25	25	185.748	(142.831,228.665)	103.9707	161.051	74.80	549.66
	1 x 12mg PR/XL 24h (high fat fed)	25	25	219.536	(177.398,261.674)	102.0834	206.692	65.22	510.11
	3 x 4mg PR/XL 24h (fasted)	25	25	199.150	(142.425,255.874)	137.4210	169.319	69.72	781.50
Cmax-ss (ng/mL)	4 mg PR/XL 24h	27	27	3.717	(3.033,4.401)	1.7291	3.390	1.26	8.97
	8 mg PR/XL 24h	25	25	7.222	(5.933,8.510)	3.1214	6.747	2.61	15.34
	1 x 12mg PR/XL 24h (fasted)	25	25	10.045	(7.969,12.120)	5.0275	8.602	3.83	27.37
	1 x 12mg PR/XL 24h (high fat fed)	25	25	14.465	(11.772,17.158)	6.5241	13.389	4.49	30.07
	3 x 4mg PR/XL 24h (fasted)	25	25	10.837	(8.161,13.513)	6.4827	10.024	3.87	36.58
Cmin-ss (ng/mL)	4 mg PR/XL 24h	27	27	1.985	(1.490,2.480)	1.2514	1.747	0.46	5.29
	8 mg PR/XL 24h	25	25	4.127	(3.140,5.113)	2.3906	3.642	1.30	11.60
	1 x 12mg PR/XL 24h (fasted)	25	25	5.667	(4.042,7.291)	3.9359	4.620	1.77	19.72
	1 x 12mg PR/XL 24h (high fat fed)	25	25	5.655	(4.114,7.196)	3.7321	4.756	0.84	18.03
	3 x 4mg PR/XL 24h (fasted)	25	25	6.059	(4.030,8.088)	4.9158	5.166	1.83	27.25
tmax-ss (hr)	4 mg PR/XL 24h	27	27	6.516	(5.364,7.667)	2.9107	6.000	2.03	14.00
	8 mg PR/XL 24h	25	25	5.284	(4.276,6.291)	2.4414	4.030	2.00	10.00
	1 x 12mg PR/XL 24h (fasted)	25	25	5.921	(4.482,7.360)	3.4867	4.020	2.00	16.00
	1 x 12mg PR/XL 24h (high fat fed)	25	25	8.963	(8.036,9.890)	2.2458	10.000	4.00	12.00
	3 x 4mg PR/XL 24h (fasted)	25	25	5.921	(4.649,7.193)	3.0812	6.000	2.00	14.00

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Table 12.05

Summary Statistics by Regimen for Log-Transformed Ropinirole (SFK-101468) Pharmacokinetic Parameters

Parameter	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD Logs	%CVb
AUC(0-24)-ss (ng*hr/mL)	4 mg PR/XL 24h	27	27	57.056	(45.918,70.896)	0.5490	59.31
	8 mg PR/XL 24h	25	25	118.107	(98.272,141.946)	0.4454	46.84
	1 x 12mg PR/XL 24h (fasted)	25	25	164.408	(134.189,201.432)	0.4920	52.34
	1 x 12mg PR/XL 24h (high fat fed)	25	25	197.324	(161.494,241.104)	0.4854	51.55
	3 x 4mg PR/XL 24h (fasted)	25	25	173.170	(140.653,213.205)	0.5038	53.76
Cmax-ss (ng/mL)	4 mg PR/XL 24h	27	27	3.362	(2.800,4.038)	0.4630	48.89
	8 mg PR/XL 24h	25	25	6.628	(5.559,7.903)	0.4262	44.63
	1 x 12mg PR/XL 24h (fasted)	25	25	9.056	(7.492,10.947)	0.4593	48.46
	1 x 12mg PR/XL 24h (high fat fed)	25	25	13.080	(10.775,15.878)	0.4697	49.68
	3 x 4mg PR/XL 24h (fasted)	25	25	9.571	(7.811,11.729)	0.4924	52.39
Cmin-ss (ng/mL)	4 mg PR/XL 24h	27	27	1.642	(1.273,2.117)	0.6426	71.50
	8 mg PR/XL 24h	25	25	3.584	(2.869,4.479)	0.5395	58.12
	1 x 12mg PR/XL 24h (fasted)	25	25	4.744	(3.719,6.052)	0.5897	64.48
	1 x 12mg PR/XL 24h (high fat fed)	25	25	4.565	(3.403,6.125)	0.7119	81.23
	3 x 4mg PR/XL 24h (fasted)	25	25	5.069	(4.021,6.391)	0.5614	60.87

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Table 12.06
Listing of Derived Ropinirole (SKF-101468) Pharmacokinetic Parameters

Subject	Treatment	Period	AUC(0-24)-ss (ng*hr/mL)	Cmax-ss (ng/mL)	Cmin-ss (ng/mL)	tmax-ss (hr)

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.

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Table 12.07
Summary Statistics by Regimen for Metabolite (SKF-104557) Pharmacokinetic Parameters

Parameter	Treatment	N	n	Mean	95% CI (Lower,Upper)	SD	Median	Min.	Max.
AUC(0-24)-ss (ng*hr/mL)	4 mg PR/XL 24h	27	27	82.632	(72.352,92.912)	25.9869	82.052	35.31	148.68
	8 mg PR/XL 24h	25	25	163.358	(141.140,185.577)	53.8263	151.266	92.37	270.84
	1 x 12mg PR/XL 24h (fasted)	25	25	231.732	(197.841,265.623)	82.1044	204.945	121.58	396.25
	1 x 12mg PR/XL 24h (high fat fed)	25	25	261.752	(228.380,295.125)	80.8493	244.689	121.86	435.63
	3 x 4mg PR/XL 24h (fasted)	25	25	236.302	(211.977,260.627)	58.9298	223.356	156.63	384.01
Cmax-ss (ng/mL)	4 mg PR/XL 24h	27	27	4.193	(3.699,4.686)	1.2484	4.056	2.44	7.33
	8 mg PR/XL 24h	25	25	8.267	(6.965,9.569)	3.1540	7.535	4.29	15.46
	1 x 12mg PR/XL 24h (fasted)	25	25	11.347	(9.705,12.989)	3.9776	9.998	5.91	20.03
	1 x 12mg PR/XL 24h (high fat fed)	25	25	14.540	(12.459,16.621)	5.0416	13.584	7.06	24.81
	3 x 4mg PR/XL 24h (fasted)	25	25	11.585	(10.334,12.837)	3.0320	10.999	7.36	19.17
Cmin-ss (ng/mL)	4 mg PR/XL 24h	27	27	2.823	(2.423,3.223)	1.0103	2.758	1.26	5.60
	8 mg PR/XL 24h	25	25	5.688	(4.873,6.503)	1.9743	5.161	2.69	9.73
	1 x 12mg PR/XL 24h (fasted)	25	25	8.073	(6.881,9.264)	2.8862	7.140	4.12	13.80
	1 x 12mg PR/XL 24h (high fat fed)	25	25	8.186	(7.027,9.344)	2.8062	7.402	2.81	13.28
	3 x 4mg PR/XL 24h (fasted)	25	25	8.232	(7.340,9.123)	2.1598	7.957	5.11	13.82
tmax-ss (hr)	4 mg PR/XL 24h	27	27	8.657	(7.389,9.924)	3.2049	9.980	3.80	14.05
	8 mg PR/XL 24h	25	25	7.844	(6.456,9.232)	3.3625	8.000	0.00	14.00
	1 x 12mg PR/XL 24h (fasted)	25	25	8.487	(6.972,10.001)	3.6688	8.000	4.00	16.00
	1 x 12mg PR/XL 24h (high fat fed)	25	25	9.844	(9.093,10.594)	1.8188	10.000	6.00	12.00
	3 x 4mg PR/XL 24h (fasted)	25	25	8.004	(6.654,9.353)	3.2696	8.000	2.00	14.00

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Table 12.08

Summary Statistics by Regimen for Log-Transformed Metabolite (SFK-104557) Pharmacokinetic Parameters

Param.	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD Logs	%CVb
AUC(0-24)-ss (ng*hr/mL)	4 mg PR/XL 24h	27	27	78.783	(69.462,89.355)	0.3183	32.65
	8 mg PR/XL 24h	25	25	155.406	(136.190,177.335)	0.3198	32.81
	1 x 12mg PR/XL 24h (fasted)	25	25	218.974	(190.353,251.897)	0.3393	34.93
	1 x 12mg PR/XL 24h (high fat fed)	25	25	249.859	(219.416,284.526)	0.3148	32.27
	3 x 4mg PR/XL 24h (fasted)	25	25	229.631	(207.739,253.830)	0.2427	24.63
Cmax-ss (ng/mL)	4 mg PR/XL 24h	27	27	4.022	(3.581,4.517)	0.2937	30.01
	8 mg PR/XL 24h	25	25	7.752	(6.683,8.993)	0.3596	37.15
	1 x 12mg PR/XL 24h (fasted)	25	25	10.753	(9.392,12.312)	0.3279	33.70
	1 x 12mg PR/XL 24h (high fat fed)	25	25	13.742	(11.925,15.836)	0.3436	35.40
	3 x 4mg PR/XL 24h (fasted)	25	25	11.232	(10.125,12.460)	0.2513	25.54
Cmin-ss (ng/mL)	4 mg PR/XL 24h	27	27	2.658	(2.309,3.060)	0.3555	36.70
	8 mg PR/XL 24h	25	25	5.375	(4.662,6.197)	0.3448	35.54
	1 x 12mg PR/XL 24h (fasted)	25	25	7.604	(6.576,8.794)	0.3520	36.31
	1 x 12mg PR/XL 24h (high fat fed)	25	25	7.704	(6.620,8.965)	0.3672	38.00
	3 x 4mg PR/XL 24h (fasted)	25	25	7.969	(7.159,8.871)	0.2598	26.42

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Table 12.09
Listing of Derived Metabolite (SKF-104557) Pharmacokinetic Parameters

Subject	Treatment	Period	AUC(0-24)-ss (ng*hr/mL)	Cmax-ss (ng/mL)	Cmin-ss (ng/mL)	tmax-ss (hr)

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.

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Table 12.10
Summary Statistics by Regimen for Metabolite (SKF-89124) Pharmacokinetic Parameters

Parameter	Treatment	N	n	Mean	95% CI (Lower,Upper)	SD	Median	Min.	Max.
AUC(0-24)-ss (ng*hr/mL)	4 mg PR/XL 24h	27	27	3.074	(2.548,3.601)	1.3310	3.131	1.05	5.52
	8 mg PR/XL 24h	25	25	6.182	(5.211,7.154)	2.3536	5.941	2.23	10.61
	1 x 12mg PR/XL 24h (fasted)	25	25	9.387	(7.735,11.039)	4.0019	8.159	3.83	18.65
	1 x 12mg PR/XL 24h (high fat fed)	25	25	10.985	(9.252,12.718)	4.1978	10.718	2.92	20.05
	3 x 4mg PR/XL 24h (fasted)	25	25	9.793	(8.345,11.241)	3.5075	8.575	3.79	17.27
Cmax-ss (ng/mL)	4 mg PR/XL 24h	27	27	0.173	(0.142,0.205)	0.0793	0.162	0.07	0.38
	8 mg PR/XL 24h	25	25	0.338	(0.272,0.405)	0.1615	0.308	0.13	0.74
	1 x 12mg PR/XL 24h (fasted)	25	25	0.507	(0.415,0.598)	0.2216	0.481	0.19	0.99
	1 x 12mg PR/XL 24h (high fat fed)	25	25	0.643	(0.523,0.764)	0.2915	0.554	0.19	1.42
	3 x 4mg PR/XL 24h (fasted)	25	25	0.529	(0.448,0.611)	0.1972	0.537	0.20	1.03
Cmin-ss (ng/mL)	4 mg PR/XL 24h	27	27	0.101	(0.084,0.117)	0.0422	0.099	0.04	0.18
	8 mg PR/XL 24h	25	25	0.216	(0.182,0.250)	0.0828	0.196	0.06	0.42
	1 x 12mg PR/XL 24h (fasted)	25	25	0.308	(0.259,0.357)	0.1190	0.273	0.13	0.54
	1 x 12mg PR/XL 24h (high fat fed)	25	25	0.342	(0.288,0.397)	0.1315	0.347	0.07	0.64
	3 x 4mg PR/XL 24h (fasted)	25	25	0.331	(0.286,0.376)	0.1085	0.301	0.14	0.56
tmax-ss (hr)	4 mg PR/XL 24h	27	27	8.217	(6.551,9.882)	4.2107	8.000	1.80	20.00
	8 mg PR/XL 24h	25	25	6.802	(4.881,8.724)	4.6543	6.000	0.00	20.00
	1 x 12mg PR/XL 24h (fasted)	25	25	8.005	(6.112,9.897)	4.5852	6.000	2.00	20.02
	1 x 12mg PR/XL 24h (high fat fed)	25	25	8.485	(7.153,9.817)	3.2275	10.000	2.00	16.00
	3 x 4mg PR/XL 24h (fasted)	25	25	8.081	(6.039,10.124)	4.9486	6.000	2.00	20.00

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Table 12.11

Summary Statistics by Regimen for Log-Transformed Metabolite (SFK-89124) Pharmacokinetic Parameters

Param.	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD Logs	%CVb
AUC(0-24)-ss (ng*hr/mL)	4 mg PR/XL 24h	27	27	2.784	(2.314,3.351)	0.4684	49.53
	8 mg PR/XL 24h	25	25	5.724	(4.824,6.793)	0.4146	43.31
	1 x 12mg PR/XL 24h (fasted)	25	25	8.610	(7.218,10.270)	0.4271	44.73
	1 x 12mg PR/XL 24h (high fat fed)	25	25	10.154	(8.518,12.104)	0.4256	44.56
	3 x 4mg PR/XL 24h (fasted)	25	25	9.186	(7.879,10.710)	0.3718	38.51
Cmax-ss (ng/mL)	4 mg PR/XL 24h	27	27	0.156	(0.130,0.188)	0.4692	49.62
	8 mg PR/XL 24h	25	25	0.305	(0.251,0.370)	0.4661	49.26
	1 x 12mg PR/XL 24h (fasted)	25	25	0.463	(0.388,0.554)	0.4320	45.30
	1 x 12mg PR/XL 24h (high fat fed)	25	25	0.584	(0.484,0.705)	0.4549	47.95
	3 x 4mg PR/XL 24h (fasted)	25	25	0.494	(0.421,0.580)	0.3884	40.35
Cmin-ss (ng/mL)	4 mg PR/XL 24h	27	27	0.092	(0.077,0.110)	0.4488	47.23
	8 mg PR/XL 24h	25	25	0.200	(0.168,0.238)	0.4269	44.71
	1 x 12mg PR/XL 24h (fasted)	25	25	0.286	(0.243,0.337)	0.3981	41.45
	1 x 12mg PR/XL 24h (high fat fed)	25	25	0.315	(0.261,0.379)	0.4508	47.47
	3 x 4mg PR/XL 24h (fasted)	25	25	0.314	(0.273,0.361)	0.3400	35.01

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Table 12.12
Listing of Derived Metabolite (SKF-89124) Pharmacokinetic Parameters

Subj.	Treatment	Period	AUC(0-24)-ss (ng*hr/mL)	Cmax-ss (ng/mL)	Cmin-ss (ng/mL)	tmax-ss (hr)
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.						

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Population: Pk parameter

Table 12.13
Dose Proportionality (B, D, E): Summary of Statistical Analysis Ropinirole (SKF-101468)

Parameter	Slope Log(Parameter) vs Log(Dose)	Standard Error	90% Confidence Interval	CVw%
AUC (0-24)-ss (ng*hr/mL)	0.970	0.0455	(0.893,1.046)	18.06
Cmax-ss (ng/mL)	0.905	0.0415	(0.835,0.974)	16.45
Cmin-ss (ng/mL)	0.986	0.0639	(0.878,1.093)	25.61

Key:
B = 4 mg PR/XL 24h
D = 8 mg PR/XL 24h
E = 1 x 12 mg PR/XL 24h (fasted)

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Table 12.14
Food Effect (F:E): Summary of Statistical Analysis Ropinirole (SKF-101468)

Parameter	Geometric LS Mean Test	Geometric LS Mean Ref	LS Means Ratio	90% CI (Lower,Upper)	CVw%
AUC (0-24)-ss (ng*hr/mL)	196.59	163.85	1.20	(1.12,1.28)	14.08
Cmax-ss (ng/mL)	13.03	9.02	1.44	(1.34,1.56)	15.85
Cmin-ss (ng/mL)	4.54	4.72	0.96	(0.86,1.08)	24.51

Key:
E = 1 x 12 mg PR/XL 24hr (fasted)
F = 1 x 12 mg PR/XL 24hr (high fat fed)

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Table 12.15
Dosage Strength Equivalence (E:G) : Summary of Statistical Analysis Ropinirole (SKF-101468)

Parameter	Geometric LS Mean Test	Geometric LS Mean Ref	LS Means Ratio	90% CI (Lower,Upper)	CVw%
AUC (0-24)-ss (ng*hr/mL)	163.85	173.18	0.95	(0.89,1.01)	14.08
Cmax-ss (ng/mL)	9.02	9.56	0.94	(0.88,1.02)	15.85
Cmin-ss (ng/mL)	4.72	5.07	0.93	(0.83,1.04)	24.51

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x4 mg PR/XL 24h (fasted)

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Table 12.16
Summary of Analysis of tmax Ropinirole (SKF-101468) (E vs G and F vs E)

Comparison (Test vs Ref)	Median Test Treatment (hrs)	Median Ref. Treatment (hrs)	Estimate of median Difference (hrs)	90% CI
F vs E	10.00	4.02	3.01	(2.00, 4.01)
E vs G	4.02	6.00	0.00	(-1.00, 1.00)

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
F = 1 x 12 mg PR/XL 24h (high fat fed)
G = 3 x 4 mg PR/XL 24h (fasted)

[redacted]

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Table 12.17
Dose Proportionality (B, D, E): Power Model ANOVA for AUC(0-24ss) Ropinirole (SKF-101468)

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.

Key:
B = 4 mg PR/XL 24h
D = 8 mg PR/XL 24h
E = 1 x 12 mg PR/XL 24h (fasted)

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Table 12.18
Dose Proportionality (B, D, E): Power Model ANOVA for Cmaxss Ropinirole (SKF-101468)

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.

Key:
B = 4 mg PR/XL 24hr
D = 8 mg PR/XL 24hr
E = 1 x 12 mg PR/XL 24hr (fasted)

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Table 12.19
Dose Proportionality (B, D, E): Power Model ANOVA for Cminss Ropinirole (SKF-101468)

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.

Key:
B = 4 mg PR/XL 24hr
D = 8 mg PR/XL 24hr
E = 1 x 12 mg PR/XL 24hr (fasted)

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Table 12.20
Food Effect (F:E): ANOVA for AUC(0-24ss) Ropinirole (SKF-101468)

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.

Key:
E = 1 x 12 mg PR/XL 24h (fatsed)
F = 1 x 12 mg PR/XL 24h (high fat fed)

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Table 12.21
Food Effect (F:E): ANOVA for Cmaxss Ropinirole (SKF-101468)

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.

Key:
E = 1 x 12 mg PR/XL 24h (fatsed)
F = 1 x 12 mg PR/XL 24h (high fat fed)

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Table 12.22
Food Effect (F:E): ANOVA for Cminss Ropinirole (SKF-101468)

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.

Key:
E = 1 x 12 mg PR/XL 24h (fatsed)
F = 1 x 12 mg PR/XL 24h (high fat fed)

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Table 12.23
Dosage Strength Equivalence (E:G): ANOVA for AUC(0-24ss) Ropinirole (SKF-101468)

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.

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x 4 mg PR/XL 24h (fasted)

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Table 12.24
Dosage Strength Equivalence (E:G): ANOVA for Cmaxss Ropinirole (SKF-101468)

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.

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x 4 mg PR/XL 24h (fasted)

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Table 12.25
Dosage Strength Equivalence (E:G): ANOVA for Cminss Ropinirole (SKF-101468)

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.

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x 4 mg PR/XL 24h (fasted)

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Table 12.26
Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (F vs E)

The UNIVARIATE Procedure
Variable: avdiff

Moments

N	325	Sum Weights	325
Mean	3.0424	Sum Observations	988.78
Std Deviation	2.34998695	Variance	5.52243867
Skewness	-0.568265	Kurtosis	-0.2324401
Uncorrected SS	4797.5344	Corrected SS	1789.27013
Coeff Variation	77.2412224	Std Error Mean	0.13035382

Basic Statistical Measures

Location		Variability	
Mean	3.042400	Std Deviation	2.34999
Median	3.010000	Variance	5.52244
Mode	6.000000	Range	10.02000
		Interquartile Range	3.99000

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	23.33955	Pr > |t|	<.0001
Sign	M	128.5	Pr >= |M|	<.0001
Signed Rank	S	22708	Pr >= |S|	<.0001

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
F = 1 x 12 mg PR/XL 24h (high fat fed)

[redacted]

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Table 12.26
Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (F vs E)

The UNIVARIATE Procedure
Variable: avdiff

Quantiles (Definition 5)

Quantile	Estimate
100% Max	6.02
99%	6.01
95%	6.01
90%	6.00
75% Q3	5.00
50% Median	3.01
25% Q1	1.01
10%	0.00
5%	-1.00
1%	-3.00
0% Min	-4.00

Extreme Observations

----Lowest----		----Highest---	
Value	Obs	Value	Obs
-4	3	6.01	321
-4	2	6.01	322
-4	1	6.02	323
-3	5	6.02	324
-3	4	6.02	325

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
F = 1 x 12 mg PR/XL 24h (high fat fed)

[redacted]

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Table 12.26
Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (F vs E)

Obs	Comparison (Test vs Ref)	Parameter	Number of Subjects	Median (Test)	Median (Ref)	Lower CL	Median of average differences	Upper CL
1	F vs E	Tmax (hr)	25	10.00	4.02	2	3.01	4.01

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
F = 1 x 12 mg PR/XL 24h (high fat fed)

[redacted]

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Table 12.27
Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (E vs G)

The UNIVARIATE Procedure
Variable: avdiff

Moments

N	325	Sum Weights	325
Mean	-0.0004	Sum Observations	-0.13
Std Deviation	1.87128129	Variance	3.50169367
Skewness	0.49555087	Kurtosis	1.5293681
Uncorrected SS	1134.5488	Corrected SS	1134.54875
Coeff Variation	-467820.32	Std Error Mean	0.10380001

Basic Statistical Measures

Location		Variability	
Mean	-0.00040	Std Deviation	1.87128
Median	0.00000	Variance	3.50169
Mode	0.00000	Range	14.00000
		Interquartile Range	2.00000

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	-0.00385	Pr > |t|	0.9969
Sign	M	-11.5	Pr >= |M|	0.1580
Signed Rank	S	-543.5	Pr >= |S|	0.6180

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x 4 mg PR/XL 24h (fasted)

[redacted]

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Table 12.27
Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (E vs G)

The UNIVARIATE Procedure
Variable: avdiff

Quantiles (Definition 5)

Quantile	Estimate
100% Max	8
99%	5
95%	4
90%	2
75% Q3	1
50% Median	0
25% Q1	-1
10%	-2
5%	-3
1%	-4
0% Min	-6

Extreme Observations

----Lowest----		----Highest---	
Value	Obs	Value	Obs
-6	1	5.00	321
-5	2	5.00	322
-4	8	5.01	323
-4	7	6.00	324
-4	6	8.00	325

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x 4 mg PR/XL 24h (fasted)

[redacted]

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Table 12.27
Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (E vs G)

Obs	Comparison (Test vs Ref)	Parameter	Number of Subjects	Median (Test)	Median (Ref)	Lower CL	Median of average differences	Upper CL
1	E vs G	Tmax (hr)	25	4.02	6.00	-1	0	1

Key:
E = 1 x 12 mg PR/XL 24h (fasted)
G = 3 x 4 mg PR/XL 24h (fasted)

[redacted]

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ATTACHMENT 1: STUDY ADMINISTRATION

Germany	Name and Address	Role/Responsibilities
Ethics Committee/ Institutional Review Board (IRB)	[redacted] Germany	
Contract Research Organization	[redacted] Germany	Study management in Germany
Activities Outsourced to Other CROs/Companies	St. Hubertus Apotheke OHG Bernd Drevenstedt Martin-Luther-Str. 20a 10777 Berlin Germany	Pharmacy IMP dose preparation from the bulk supplies
Monitor	[redacted] An den Deichwiesen 21a 30659 Hannover Germany	
Central Laboratory (ies) List each laboratory	W&T GmbH Dr. [redacted] Haus M Turmstr. 21 10559 Berlin Germany Quest Diagnostics Clinical Trials Unit B1 Parkway West Industrial Estate Cranford Lane Heston, Middlesex TW5 9QA United Kingdom	Safety analysis Clinical Chemistry Clinical Haematology Serology / Endocrinology Pharmacogenetics

South Africa	Name and Address	Role/Responsibilities
Ethics Committee/ Institutional Review Board (IRB)	Dr [redacted] South Africa	
Contract Research Organization	[redacted] South Africa	Study management in South Africa
Activities Outsourced to Other CROs/Companies		
Monitor	[redacted] CLINDEV Limited, Corporate Park, 5 Regency Drive, Irene 0062, South Africa	
Central Laboratory (ies) List each laboratory	[redacted] South Africa Quest Diagnostics Clinical Trials Unit B1 Parkway West Industrial Estate Cranford Lane Heston, Middlesex TW5 9QA United Kingdom	Safety analysis Clinical Chemistry Clinical Haematology Serology / Endocrinology Pharmacogenetics

ATTACHMENT 2: TIME AND EVENTS TABLE

TIME AND EVENTS TABLE FOR STUDY ROP109087

Study Activity	Screening	Study Day																			Down-titration	Follow-Up
		1	2-7	8	9-11	12-14[a]	15	16-21	22	23-25	26-28[a]	29	30	31	32	33	34	35	36	37	38-44	
Dosing at clinic		X		X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Dosing at home			X		X			X		X												
AE recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PK blood samples[b]						X					X			X			X			X		
Blood pressure, pulse rate[e]	X	X[c]		X		X[d]	X		X		X[d]	X		X[d]	X		X[d]	X		X[d]		X
ABPM[g]		X		X			X		X			X										
12-lead ECG[h]	X	X		X		X	X		X		X	X		X	X		X	X		X		X
Laboratory safety/Urinalysis	X																					X
Alcohol test	X	X																				
Urine screen for undeclared drugs	X	X					X															
HIV/Hepatitis serology	X																					
Pregnancy test[f]	X	X					X															X
Epworth Sleepiness Scale (ESS) assessment	X																					
Physical examination	X																					X
Smoking History	X																					
Medical History (including PD History)	X																					
Con Med History	X																					
PGx sample collection[i]	←----------																					

a. PK assessment days conducted on any day between Days 12-14 and Days 26-28 respectively
b. Serial PK samples were drawn pre-dose and at the following times post-dose: 1h, 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 20h and 24h
c. Vital sign measurements (supine and standing) – minimum of 3 sets required (maximum of 6 sets) to establish stable baseline at pre-dose Day 1 only
d. Vital sign measurements (supine and standing) were taken at 4h, 6h, 12h and 24h post-dose on PK assessment days
e. Vital sign measurements conducted in supine and standing position at all time-points
f. Pregnancy test performed in WCBP only
g. Subjects were provided with ABPM device to record hourly measurements up to 12h post-dose
h. ECG measurements were performed in triplicate (10 minutes apart) at baseline and in singleton at all other time-points
i. A pharmacogenetic sample could be taken at any time during the study after informed consent for PGx sampling was taken and Ethics Committee approval received

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

Title:	Reporting and Analysis Plan for ROP109087. An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12 mg tablets.

Compound Number: SK&F-101468

Effective Date: [30-OCT-2007]

Description:

This study consists of an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and is conducted in PD patients. The study is designed to demonstrate dose proportionality for an extended release (PR/XL 24h) formulation of ropinirole over the dose range 4 - 12 mg, to determine the effect of food on the absorption of ropinirole PR/XL 24h at 12 mg (highest tablet strength) and to determine dosage strength equivalence for PR/XL 24h administered as 1x12 mg tablet compared with 3 x 4 mg tablets. Patients will receive ropinirole PR/XL 24h *od* starting at a dose of 2 mg/day with weekly dose escalation of 2 - 4 mg (2, 4, 6, 8 and 12 mg dose levels). The 12 mg dose level will incorporate three dosing regimens; 1 x 12 mg tablet for three days including steady state PK profile (fasted), 1 x 12 mg tablet for three days including steady state PK profile (high fat fed) and 3 x 4 mg for three days including steady state PK profile (fasted).

The study will be conducted at two clinical pharmacology units. Patients will be resident in the clinical pharmacology units for PK days and will dose as outpatients for the remainder of the study with the exception of the 12 mg dose level when patients will be resident in-house.

Identifier/Version Number: HM2007/00088/01

Subject: SK&F101468, prolonged release for PD, pharmacokinetic, food effect, PD

Author's Name, Title and Functional Area: [redacted] Statistician
Discovery Biometrics

The GlaxoSmithKline group of companies

Approved by:

[redacted]

30th October 2007
Date

Manager, Discovery Statistics, Neurology/GI

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ABBREVIATIONS

ABPM	Ambulatory blood pressure monitor
AE	Adverse Event
ALT	S-alanine aminotransferase
AST	S-aspartate aminotransferase
AUC(0-24ss)	Steady-state area under the plasma concentration-time profile over the dosing interval 0 to 24 hours
BMI	Body Mass Index
CPDS	Clinical Pharmacology Data Sciences
CR	Controlled Release
CRF	Case report form
Cmaxss	Maximum observed plasma concentration at steady state
Cminss	Minimum concentration at steady state
CPK/M&S	Clinical Pharmacokinetics Modelling and Simulation
DB	Discovery Biometrics
ECG	Electrocardiogram
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
h, hrs	Hour(s)
ICH	International Conference for Harmonization
IR	Immediate release
kg	Kilogram
L	Litre
mcg	Microgram
mg	Milligram
min	Minute
mL	Millilitre
PD	Parkinson's Disease
PGx	Pharmacogenetics
PK	Pharmacokinetic
PR	Prolonged release
SRM	Study Reference Manual
tmax	Time to achieve maximum plasma concentration
WBC	White blood cells

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Pharmacology Study Report for study ROP109087. The contents of this RAP was based on the Original Protocol [GlaxoSmithKline Document Number HM2006/00649/00] effective 6th December 2006, Protocol Amendment #1 [GlaxoSmithKline Document Number HM2006/00649/01] effective 5th January 2007 and Protocol Amendment #2 [GlaxoSmithKline Document Number HM2006/00649/02] effective 2nd July 2007.

The RAP is based on standard operating procedure SOP-WWD-4000 regarding the Development, Review, and Approval of Reporting and Analysis Plans. In addition, the RAP is developed per the document standard, DS-WWD-4000, for Reporting and Analysis Plans.

All analyses, quality control procedures, and data displays will follow the GlaxoSmithKline (GSK) "Standard Methods for the Non-compartmental Analysis of Pharmacokinetic Data" (SOP-CPK-0001), "Standard Statistical Methods for the Analysis of Pharmacokinetic Data " (SOP-BMD-4002), "Review/Quality Control of BDS Phase I-IV Results for Statistics and Programming" (SOP-BMD-1001), and the GSK Integrated Data Standards Library (IDSL) Reporting Agreements effective at the time of RAP completion.

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

2.1. Study Objective(s)

Primary

- To demonstrate dose proportionality for ropinirole using an extended release (PR/XL 24h) formulation of ropinirole over the dose range 4 - 12 mg when administered to patients with a diagnosis of idiopathic Parkinson's Disease.
- To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PR/XL 24h at 12 mg (highest tablet strength).
- To determine dosage strength equivalence for ropinirole PR/XL 24h administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets.

Secondary

- To further confirm the safety and tolerability of ropinirole PR/XL 24h over a dose range of 2 - 12 mg when administered to patients with a diagnosis of idiopathic Parkinson's Disease.

2.2. Study Endpoint(s)

Primary

- Ropinirole AUC (0-24ss), the area under the steady-state plasma concentration-time curve over the dosing interval
- Ropinirole Cmaxss: the maximum observed steady-state plasma concentration

Secondary

- Ropinirole Tmax, the time to attain ropinirole Cmax
- Ropinirole Cminss, miniumum concentration at steady state
- Cmaxss and AUC(0-24ss) for the metabolites of ropinirole, SKF-104557 and
- SKF-89124
- Incidence of Adverse events
- Vital signs, ECG and clinical laboratory data

2.3. Statistical Hypotheses

For the assessment of dose proportionality of ropinirole PR/XL 24h over the dose range of 4 - 12 mg, dose proportionality will be demonstrated if the 90% confidence interval of the estimated mean slope based on the power model of ropinirole AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.797 to 1.203.

For the assessment of the effect of food on absorption of ropinirole PR/XL 24h 12 mg, an estimation approach will be adopted. Point estimates and corresponding 90% confidence intervals will be estimated for AUC(0-24ss), Cmaxss and Cminss.

For the assessment of dosage strength equivalence of ropinirole PR/XL 24h tablet formulations (1 x 12 mg vs 3 x 4 mg), dose strength equivalence will be demonstrated if the 90% confidence interval for the ratios of AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.80 to 1.25.

There are no other formal statistical hypotheses to be tested with regard to safety, tolerability and pharmacokinetics. Data for the metabolites will be summarised only.

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

Not applicable.

3. STUDY DESIGN

This study consists of an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and will be conducted in PD patients. Patients will receive ropinirole PR/XL 24h *od* starting at a dose of 2 mg/day with weekly dose escalation of 2 - 4 mg (2, 4, 6, 8 and 12 mg). Patients will generally take their study medication at home and complete diary cards apart from on PK Study Days and during the 12 mg dosing session (when patients will remain resident in the clinic for logistical reasons).

For the 2 mg dose level patients will attend the unit for dosing and safety assessments only.

For the 4 and 8 mg dose levels, patients will attend the clinic after they have received at least 5 sequential days of dosing at these dose levels, for 24-hour pharmacokinetic (PK) and safety evaluations. At these PK clinic visits, ropinirole PR/XL 24h will be administered in the fasted state.

For the 6 mg dose level, patients will continue taking their medication at home and will attend the clinic for safety evaluations; however pharmacokinetic assessments will not be taken.

Once patients have titrated to 12 mg, they will remain at this dose for the remainder of the study. At the 12 mg dose, patients will be randomised to one of three treatments according to six possible treatment sequences (EFG, EGF, FEG, FGE, GEF, GFE) according to the treatments defined in Table 1

Table 1 Study Design for ROP109087

Dose Level	Dosing Days	PR/XL 24h Dose (mg)	PK Assessments
1	1 - 7	2	-
2	8 - 14	4	Any day between Days 12-14, 4 mg steady state (fasted) (Treatment B)
3	15 - 21	6	-
4	22 - 28	8	Any day between Days 26-28, 8 mg steady state (fasted) (Treatment D)
5	29 - 37	12	Assessments on Days 31, 34 and 37. Randomised, 12 mg steady state: (I) Ropinirole PR/XL 24h 1 x 12 mg tablet (fasted) (E) (ii) Ropinirole PR/XL 24h 1 x 12 mg tablet (fed : standard high fat FDA breakfast) (F) (III) Ropinirole PR/XL 24h 3 x 4 mg tablets (fasted) (G)
	38-44	Down titration	-

On all PK assessment days, ropinirole PR/XL 24h will be administered in the fasted state except for treatment sequence F, where dosing will occur after a standardised high fat FDA breakfast. Patients will be down-titrated according to the down titration schedule in Table 2.

Table 2 Down-Titration Schedule for study ROP109087

PR/XL 24h Daily Dose (mg) at the end of the treatment phase	Down Titration Schedule	
	4 Days @	3 Days @
2.0	Not applicable	Not applicable
4.0	2.0	Not applicable
6.0	4.0	2.0
8.0	6.0	4.0
12.0	8.0	4.0

Lastly, patients will attend the clinic for a follow up visit 7-14 days after completion of last administration of study drug.

4. PLANNED ANALYSES

The final analysis will be conducted after database freeze (DBF).

The pharmacokinetic parameter Cminss was not included as an endpoint in the protocol but will be required for the assessment of dose proportionality, food effect and dosage strength equivalence.

4.1. Interim Analyses

An interim analysis is not planned.

4.2. Final Analysis

Dose proportionality of ropinirole will be assessed by fitting the loge-transformed parameters AUC(0-24ss), Cmaxss and Cminss for ropinirole 4 to 12 mg PR/XL (B, D, E) to the Power Model [$parameter = e^{a} (dose)^{b}$, i.e., $\log(parameter) = a + (b * \log(dose))$], where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality. Dose proportionality will be demonstrated if the 90% confidence interval of the estimated mean slope of AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.797 to 1.203.

The effect of food (F-E) will be assessed separately by fitting the loge-transformed parameters AUC(0-24ss), Cmaxss and Cminss to a mixed model analysis of variance (ANOVA). Back-transformed point estimates and 90% confidence intervals will be derived for the ratio of fed:fasted (F:E).

The effect of dosage strength equivalence (E-G) of ropinirole will be assessed by fitting the loge-transformed parameters AUC(0-24ss), Cmaxss and Cminss to a mixed model analysis of variance (ANOVA). Back-transformed point estimates and 90% confidence intervals for the ratio E:G will be presented. Dosage strength equivalence will be demonstrated if the 90% confidence intervals for the ratios of AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.80 to 1.25.

The parameter tmax will be analysed using the Wilcoxon Signed Rank Test, for the comparisons of dosage strength equivalence and food effect. Point estimates and confidence intervals for the median difference between treatment groups will be presented.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

Approximately thirty-six patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

Based on the results of study SK101468/165, estimates of the within-subject variability for loge-transformed ropinirole AUC(0-24) and Cmax from an analysis of dose proportionality and an analysis of dosage strength equivalence, ranged between 18% and 25%.

Using a within-subject variability of 23.5%, close to the high end of the ranges observed; it is estimated that 23 evaluable patients will be required to demonstrate dose proportionality. Sample size calculations for the assessment of dose proportionality have been based on the power model, such that the 90% confidence interval of the estimated mean slope of AUC(0-24) and Cmax are completely contained within the range 0.797-1.203. The calculation was based on a two-tailed procedure on loge-transformed data with a power of at least 90% and a type I error of 5%. No adjustments for multiple comparisons were made.

Using a within-subject variability of 23.5%, it is estimated that 25 evaluable subjects should provide at least 90% power to demonstrate dosage strength equivalence (based on two one-sided tests). Equivalence will be demonstrated if the 90% confidence interval for the ratios of both ropinirole AUC(0-24) and Cmax are completely contained within the range 0.80 and 1.25.

Using the estimate of within subject variability of 23.5% and assuming a sample size of 25 subjects, it is estimated that the lower and upper bounds of the 90% confidence intervals for the ratio of the 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 11.7% of the point estimates for AUC(0-24) and Cmax. This calculation is based on a two-tailed type 1 error rate of 10%, with no adjustment for multiple comparisons.

5.2. Sample Size Sensitivity

To account for the sampling error of the within-subject variability estimates used in the sample size calculations observed in study SK101468/165, a sensitivity analysis was undertaken.

The 95th percentile of the within-subject variability estimate was 31.7%. Based on variability of 31.7%, it is estimated that 25 evaluable patients should provide at least 65% power to demonstrate dose proportionality and 59% power to demonstrate dosage strength equivalence (based on two one-sided tests). Assuming a sample size of 25 patients and variability of 31.7%, the lower and upper bounds of the 90% confidence intervals for the ratio 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 16.0% of the point estimates for AUC(0-24) and Cmax.

If the within subject variability is 23.5% and assuming a ratio of 1.05 (i.e., a deviation of 5% from unity), there would be 81% power to demonstrate dose strength equivalence with 25 evaluable subjects.

5.3. Sample Size Re-estimation

No sample size re-estimation will be conducted for this study.

6. ANALYSIS POPULATIONS

Safety Population:

All patients who receive at least one dose of study medication.

PK Concentration Population:

PK concentrations may be excluded from the pharmacokinetic analysis and/or generation of mean and/or median concentration time profiles if there is insufficient concentration data, major protocol violations, incorrect dose, emesis after dosing or patients missing days of dosing.

PK Parameter Population:

All patients with evaluable pharmacokinetic data from at least one session will be included in the pharmacokinetic listings. For the assessments of dosage strength equivalence (E vs G), food effect (F vs E) and dose proportionality, all patients with evaluable pharmacokinetic data from at least one of the sessions of interest will be included in the statistical analysis.

7. TREATMENT COMPARISONS

There is no intention to conduct specific analyses investigating the relationship between patient gender and the effect of repeat doses of ropinirole (SKF-101468) on pharmacokinetics. Recruitment of approximately equal numbers of male and female patients is intended to ensure inclusion of reasonable numbers of both sexes and is not for the purposes of comparative gender analysis.

Primary Comparisons of Interest

- To demonstrate dose proportionality of ropinirole PR/XL 24h over the dose range of 4 mg to 12 mg (treatments B, D, E). The estimated mean slope and 90% confidence interval will be based on the power model and will be constructed for ropinirole AUC(0-24ss), Cmaxss and Cminss. Dose proportionality of ropinirole PR/XL 24h will be demonstrated if the 90% confidence interval of the estimated mean slope of AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.797 to 1.203.
- To estimate the effect of food on absorption of ropinirole PR/XL 24h at 12 mg. The point estimates and 90% confidence intervals will be derived for the ratio of "fed to fasted" (F:E) for ropinirole AUC(0-24ss), Cmaxss and Cminss.
- To demonstrate dose strength equivalence of ropinirole PR/XL 24h 1 x 12 mg tablet compared to ropinirole PR/XL 24h 3 x 4 mg tablets. Point estimates and 90% confidence intervals will be derived for the ratio of "ropinirole 1 x 12 mg PR/XL 24h : ropinirole 3 x 4 mg PR/XL 24h" (E:G). Dose strength equivalence will be demonstrated if the 90% confidence interval for the ratios of ropinirole AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.80 to 1.25.

Other Comparisons of Interest

Analysis of the pharmacokinetic parameter tmax will be carried out to estimate the median difference in tmax between 1 x 12 mg fed and 1 x 12 mg fasted treatments (F vsE), and between the 1 x 12 mg tablet and 3 x 4 mg tablets (E vs G).

There are no other comparisons of interest.

7.1. Data Display Treatment and Other Sub-group Descriptors

Treatment Group	Descriptor	Description used in All Output	Short Description for Graphics (if required)
A	2 mg PR/XL 24h	2 mg PR/XL 24h	2 mg
B	4 mg PR/XL 24h	4 mg PR/XL 24h	4 mg
C	6 mg PR/XL 24h (1 x 4 mg PR/XL 24h + 1 x 2 mg PR/XL 24h)	6 mg PR/XL 24h	6 mg
D	8 mg PR/XL 24h	8 mg PR/XL 24h	8 mg
E	1 x 12 mg PR/XL 24h (fasted)	1 x 12 mg PR/XL 24h (fasted)	1 x 12 mg (fasted)
F	1 x 12 mg PR/XL 24h (high fat fed)	1 x 12 mg PR/XL 24h (high fat fed)	1 x 12 mg (high fat fed)
G	3 x 4 mg PR/XL 24h (fasted)	3 x 4 mg PR/XL 24h (fasted)	3 x 4 mg (fasted)

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8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The final statistical analysis will be carried out using SAS v8.2 or higher on a UNIX platform, and the final outputs will be generated using the HARP system.

8.1. Multicentre Studies

The study is being conducted at two centres. It is not anticipated that centre will have any effect on the statistical analysis; however this will be investigated if necessary.

8.2. Other Strata and Covariates

An examination of other strata or covariates is not planned.

8.3. Examination of Subgroups

An examination of subgroups is not planned.

8.4. Multiple Comparisons and Multiplicity

There will be no adjustments for multiple comparisons.

9. DATA HANDLING CONVENTIONS

All listings, tables and figures documented in this RAP will be produced by or under the direct auspices of Discovery Statistics, APT, CPK/ M&S, GSK.

Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

All data displays will be presented according to the IDSL statistical display principles and all approved IDSL TST standards, where applicable.

Unless otherwise stated, all statistical analyses and reporting will be performed using SAS version 8.2 or higher on a UNIX platform, and the final outputs will be generated using the HARP system. The actual version of SAS used will be documented in the study report.

The following conventions will be applied to the analyses/figures/tables/listings described in this RAP:

- In summary tables by time and mean/median concentration-time profiles, data will be grouped by planned relative time.
- In all tables/listings (except where otherwise stated), planned and actual relative times will be relative to the last study drug dosing time within the relevant period.

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- In all listings (except where otherwise stated) the data will be sorted by subject number, treatment period (chronologically i.e. in order of treatment start date) and then, where applicable, day and planned relative time.
- The between subject coefficient of variation (%CVb) will be calculated as 100x[SD/mean] in the summary tables for non-log-transformed data. If a log-transformation of the data is considered appropriate the %CVb will be calculated as in the bullet below instead.
- The between subject coefficient of variation (%CVb) for log-transformed data will be calculated as 100 x √(eSD**2 -1) and will be included with the summary statistics for log-transformed data.
- Any changes from the planned analyses described in this RAP will be documented in the clinical study report along with the reason for the changes.

9.1. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study will be documented and the reason for their withdrawal will be recorded in the final study report.

If a subject completes a session but has missing data these data will be highlighted in subject listings. Any unscheduled or unplanned readings will be presented within the subject's listings but only the first (i.e., scheduled readings) will be used in any analyses. No data imputation techniques will be employed.

All analyses will be based on the actual treatment each subject received. Any departures from the planned treatment according to the randomization schedule will be documented in the report.

9.2. Derived and Transformed Data

9.2.1. Change from Baseline

The change from baseline will be obtained by subtracting the baseline values from the individual post-randomisation values. If either the baseline or post-randomisation value is missing, the change from baseline value will also be set to missing.

The following table indicates the corresponding day to be used to calculate the change from baseline:

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Parameter	Baseline (Predose) Days Collected												Baseline (Predose) Day Used in Calculation
	Day 1	Day 8	Day 12-14	Day 15	Day 22	Day 26-28	Day 29	Day 31	Day 32	Day 34	Day 35	Day 37	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	Mean of Day 1 pre-dose triplicate
ECG	x	x	x	x	x	x	x	x	x	x	x	x	Mean of Day 1 pre-dose triplicate
ABPM	x	x	-	x	x	-	x	-	-	-	-	-	Last pre-dose measurement at each dose

The mean of replicate assessments at any given time point (e.g., ECGs, vital signs) will be used as the value for that time point in all summaries and figures.

9.2.2. Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived in accordance with "Standard Methods for the Non-Compartmental Analysis of Pharmacokinetic Data" (SOP-CPK-0001) and "Standard Methods for the Non-Compartmental Analysis of Absolute Bioavailability Studies" (SOP-CPK-0002). The derivation of pharmacokinetic parameters will be under the management of CPK/M&S, CPDM.

All PK parameters, with the exception of tmax, will be log-transformed prior to statistical analysis.

9.2.3. Ambulatory Blood Pressure Monitoring (ABPM) Data

For all patients, ambulatory blood pressure will be monitored on the Days 1, 8, 15, 22 and 29.

Readings from the ambulatory blood pressure monitoring devices will only be included for days at which the patient attended a scheduled visit and was given a dose increase by the investigator when calculating summary statistics for blood pressure absolute values and pre- to post-dose changes, i.e., if the date of reading does not match a date of dose, the data will be listed only. For values of potential clinical concern, all data will be assessed and listed.

If the ambulatory blood pressure monitoring device could not take a valid reading, the values for blood pressure parameters (ABSYSBP, ABDIABP, ABHEART), are recorded by the device as 0, with ABSTATCD also recorded as a 2 digit faulty code. For the purposes of reporting this data, these will be displayed as missing values in patient listings and the description of the faulty code displayed.

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9.2.3.1. Time Intervals

Readings from the ambulatory blood pressure monitoring device will be allocated to hourly timepoints using the following time intervals:

Time Interval	Time elapsed from time of dose to time of device reading
Pre-dose	≤ 0 mins
<30 minutes post-dose	> 0 mins AND < 30 mins
1 hour post-dose	≥ 30 mins AND < 1 hr 30 mins
2 hours post-dose	≥ 1 hr 30 mins AND < 2 hr 30 mins
3 hours post-dose	≥ 2 hr 30 mins AND < 3 hrs 30 mins
4 hours post-dose	≥ 3 hr 30 mins AND < 4 hrs 30 mins
5 hours post-dose	≥ 4 hr 30 mins AND < 5 hrs 30 mins
6 hours post-dose	≥ 5 hr 30 mins AND < 6 hrs 30 mins
7 hours post-dose	≥ 6 hr 30 mins AND < 7 hrs 30 mins
8 hours post-dose	≥ 7 hr 30 mins AND < 8 hrs 30 mins
9 hours post-dose	≥ 8 hr 30 mins AND < 9 hrs 30 mins
10 hours post-dose	≥ 9 hr 30 mins AND < 10 hrs 30 mins
11 hours post-dose	≥ 10 hr 30 mins AND < 11 hrs 30 mins
12 hours post-dose	≥ 11 hr 30 mins AND < 12 hrs 30 mins
> 12 hours post-dose	≥ 12 hr 30 mins

Notes:

i. If more than one reading falls within a time interval, the latest reading only will be used in the calculation of summary statistics. In the patient listing, all readings will be presented.

ii. If the time of dose is missing for a scheduled up-titration visit, device readings cannot be slotted using these time intervals – readings will be presented only in the patient listing using only the time of reading (as downloaded from the device).

iii. If a pre-dose measurement for a particular dose level is unavailable and the maximum (across all dose levels) occurs at that particular dose level, then the next highest max will be used in any summaries/figures where both maximum and pre-dose ABPM at a particular dose level are taken into account.

A dataset specification for an ABPM A&R dataset is included in Section 19.3. Please refer to studies SKF101468/ROR106470 and SKF101468/RRL103628 for programming examples.

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9.3. Adverse Events of Special Interest

In addition to the standard summaries of adverse events, a summary and listing of adverse events of special interest will need to be created. AEs of special interest will be identified via a list of pre-selected preferred terms categorised into 'topics'. Upon review by a medic with the help of some of the subject's supplementary safety data (Vital Signs) the AEs of special interest will be identified. For this review to take place, a spreadsheet of AEs and Vital Signs information will need to be created (with treatments omitted). An example of the AE spreadsheet is provided in Section 19.4.

After review by a medic, the spreadsheet will be returned to Discovery Biometrics with a flag added to identify the AEs of special interest ('1' identifies an AE of special interest). Comments may also be added for any AEs that need explanation as to why they were not flagged as AEs of special interest. Following this, an A&R dataset for AEs of special interest will be generated and a summary table and listing produced. Examples are provided in section 19.2. For the summary table, 'Topic' will be used in place of 'System Organ Class'. In the listing, the comment field will be added only if any comments are added to AEs not identified as AEs of special interest – these AEs will be included in the listing and highlighted.

9.4. Assessment Windows

No formal assessment windows will be defined.

For each treatment period, the start time of dosing will be designated to Time 0 and all other times will be relative to this time. Actual times of all assessments will be recorded in the CRF.

During the treatment phase, time deviations of up to 3 minutes on measurements scheduled (eg PK sampling, ECG assessment, vitals assessment) up to 1 hour after dosing will not be regarded as protocol violations. Deviations of up to 5 minutes on measurements scheduled from 1 hour to 4 hour after dosing will not be regarded as protocol violations. Deviations of up to 30 minutes on measurements scheduled from 4 hour to 24 hour after dosing will not be regarded as protocol violations. However, the actual time should be recorded and the investigator should make every effort to perform procedures at the scheduled times.

Where multiple assessments are due to be performed simultaneously, pharmacokinetic sampling should take priority and be performed first, followed by vital signs, ECGs and then any remaining assessments.

9.5. Values of Clinical Concern

Vital signs (supine and standing), ECG and safety laboratory data will be flagged against normal ranges and ranges of potential clinical concern. Any values that fall outside the potential clinical concern ranges will be summarised and listed by regimen and timepoint.

9.5.1. Laboratory Values of Potential Clinical Importance

Lab Parameter (units)	**Clinical Concern Range**	
	FDA	**Europe**
Sodium (mmol/L)	≤ 127, ≥ 151	≤ 130, ≥ 150
Potassium (mmol/L)	≤ 3.0, ≥ 6.0	≤ 3, ≥ 5.5
Chloride (mmol/L)	≤ 90, ≥ 112	≤ 80% NRL, ≥ 120% NRH
Glucose (mmol/L)	≤ 2.8, ≥ 11.1	≤ 2.8, ≥ 9.7
Phosphate (mmol/L)	≤ 0.6, ≥ 1.9	≤ 0.5, ≥ 1.7
Calcium (mmol/L)	≤ 1.9, ≥ 2.7	≤ 1.8, ≥ 3.0
Albumin (G/L)	≤ 26	-
Cholesterol (mmol/L)	≥ 6.5	-
Serum Creatinine (umol/L)	≥ 177	≤ 50% NRL, > 125% NRH
GGT (U/L)	≥ 3.0 x NRH: for males ≤ 64 years for females ≤ 64 years & for all ≥ 65 years	≥ 250% NRH
Alkaline Phosphatase (U/L)	≥ 3.0 x NRH	-
AST (U/L)	≥ 3.0 x NRH for ≤ 64 years, & for ≥ 65 years	≥ 250% NRH
ALT (U/L)	≥ 3.0 x NRH	≥ 250% NRH
Total Bilirubin (umol/L)	≥ 2.0 x NRH	≥ 150% NRH
Red Blood Cell Count (TI/L)	-	≤ 80% NRL, ≥ 120% NRH
Haemoglobin (G/L)	≤ 85 % NRL ≥ 115% NRH: for males ≤ 64 years, for females ≤ 64 years, for males ≥ 65 years, & for females ≥ 65 years	≤ 75% NRL, ≥ 115% NRH
Haematocrit (%)	≤ 85 % NRL ≥ 115% NRH: for males ≤ 64 years, for females ≤ 64 years, for males ≥ 65 years, & for females ≥ 65 years	≤ 80% NRL, ≥ 120% NRH

Continued…

9.5.1. Laboratory Values of Potential Clinical Importance(Continued)

Lab Parameter (units)	**Clinical Concern Range**	
	FDA	**Europe**
White Blood Cell Count (10^9/L)	≤ 3, ≥ 16	≤ 3, ≥ 15
Neutrophils (%)	-	≤ 75% NRL, ≥ 150% NRH
Neurophils (Seg) Absolute (10^9 / L)	≤ 1.5	-
Lymphocytes (%)		≤ 75% NRL, ≥ 150% NRH (%)
Lymphocytes Absolute (10^9 / L)	≤ 0.6, ≥ 5.0	-
Eosinophils (%)	≥ 10 %	≥ 200% NRH
Eosinophils Absolute (10^9 / L)	≥ 1.0	-
Platelets (10^9 / L)	≤ 100, ≥ 600	≤ 100, ≥ 500
Basophils (%)	≥ 5.0	≥ 200% NRH
Basophils Absolute (10^9 / L)	≥ 0.4	-
Monocytes (%)	≥ 20.0	≥ 200% NRH
Monocytes Absolute (10^9 / L)	≥ 2.0	-
Serum Protein (G/L)	-	≤ 80% NRL, ≥ 110% NRH

Note: NRL = Normal Range Low, NRH = Normal Range High

9.5.2. ECG Values of Potential Clinical Concern

ECG Parameter	**Values of Potential Clinical Concern**	
	FDA	**Europe**
PR Interval	> 300 msec OR Increase from baseline of > 25% **when Baseline PR > 0.2 sec OR** **Increase of > 50% when Baseline PR ≤ 0.2 sec**	> 300 msec OR Increase from baseline of >25% **when baseline PR > 0.2 sec OR** **Increase of >50% when baseline PR ≤ 0.2 sec**

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9.5.2. ECG Values of Potential Clinical Concern(Continued..)

ECG Parameter	**Values of Potential Clinical Concern**	
	FDA	**Europe**
QRS Interval	> 200 msec OR Increase from baseline of > 25% **when Baseline QRS > 100 msec OR** **Increase from baseline of > 50% when Baseline QRS ≤ 100 msec**	> 200 msec OR Increase from baseline of > 25% **when Baseline QRS > 100 msec OR** **Increase from baseline of > 50% when Baseline QRS ≤ 100 msec**
QT Interval (QT, QTcB and QTcF)	> 500 msec OR > 60 msec increase from Baseline	> 0.5 sec OR Increase from baseline of > 15% **when Baseline QTc > 440 msec OR** **Increase from baseline of > 30% when Baseline QTc ≤ 440 msec**

Please note: additional details in **bold underlined black** will be flagged by the programmer

9.5.3. Vital Sign Values of Potential Clinical Concern

Vital Sign	**Reference Range**	**Increase from Original Baseline**	**Decrease from original Baseline**	**Units**
Europe				
Systolic Blood Pressure	90-180	>30	>30	mmHg
Diastolic Blood Pressure	50-115	>20	>20	mmHg
Pulse	50-120	-	-	bpm
FDA				
Systolic Blood Pressure	-	≥20	≥20	mmHg
Diastolic Blood Pressure	-	≥10	≥10	mmHg
Pulse	-	≥15	≥15	bpm

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9.5.4. ABPM Values of Potential Clinical Concern

Ambulatory reading	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<80 and >190	mmHg
Diastolic Blood Pressure	<50 and >120	mmHg

10. STUDY POPULATION

Approximately 36 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. If practical, no further patients will be recruited to the study once 25 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

10.1. Disposition of Subjects

The End of Study Record (Study Conclusion) will be listed and summarized for the safety population. Subjects who withdraw due to an AE will be summarised.

10.2. Protocol Deviations

No protocol deviations that will impact on the statistical analysis are expected. Should any deviations occur then a decision will be made as to the inclusion within the relevant populations. Any inclusion/exclusion violations will be summarised and listed.

10.3. Demographic and Baseline Characteristics

Demographic, race and baseline characteristics for the Safety Population will be summarized by treatment and listed.

10.4. Treatment Compliance

The planned and actual treatment received for each subject will be listed.

11. EFFICACY ANALYSES

Not applicable.

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12. SAFETY ANALYSES

Safety data will be listed and summarised by regimen and time-point where appropriate. No formal statistical comparisons will be made for safety data. All safety outputs will be produced by Discovery Biometrics - Analysis and Programming Team (APT), with the exception of ABPM data, which will be the responsibility of Discovery Biometrics – statistics.

Summaries of safety data will be for scheduled treatment period visits. In addition, Screening, Follow-up and any unscheduled visits/timepoints will be included in the listings.

12.1. Extent of Exposure

Exposure data will be summarised by treatment and listed by subject.

12.2. Adverse Events

Adverse event (AE) verbatim text will be coded and classified by System Organ Class (body system), high level term and preferred term using the standardized GSK coding system: MedDRA.

All AEs will be listed and summarized by treatment. A listing of subject numbers for individual adverse events will also be produced. The relationship of AE systems organ class, high level term, preferred terms, and verbatim text will be listed. Drug-related AEs, SAEs and AEs by maximum intensity (mild/moderate/severe) will be summarised. Adverse events of special interest will also be summarised and listed.

12.3. Deaths and Serious Adverse Events

Deaths and other serious adverse events will be summarised should they occur and listed within the listing of all adverse events.

12.4. Device Incidents and Near Incidents

Not applicable.

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

Adverse events leading to withdrawal will be summarised by treatment group and listed.

12.6. Pregnancies (as applicable)

Any pregnancies will be listed with adverse events if applicable.

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12.7. Clinical Laboratory Evaluations

As Chemistry and haematology parameters are collected at Screening and Follow-up, only listings will be produced. Abnormalities of potential clinical concern will be listed for chemistry and haematology parameters.

Urinalysis dipstick results will be summarised and urinalysis data will be listed.

12.8. Other Safety Measures

12.8.1. Concomitant Medication

Concomitant medication verbatim text will be coded and classified by Anatomical Therapeutic Chemical Classification Level 1 (ATC Level 1) and preferred term using a standardized GSK coding system, GSK DRUG. Concomitant medications will be listed and will be summarized if sufficient data exist to warrant a summary.

12.8.2. Vital Signs

A summary and listing of vital signs (supine and standing) will be produced by treatment group. A summary of change from baseline in vital signs (supine and standing) will also be produced by treatment group, where the baseline value will be mean of the repeat measurements obtained pre-dose on Day 1 (See Table in Section 9.2.1). A summary of values of potential clinical concern will also be produced by treatment group and listed.

12.8.3. ABPM Measurements

Summary statistics will be provided for systolic and diastolic blood pressure and heart rate by treatment (dose level). Data will be summarised for each timepoint i.e. pre-dose, <30 minutes post-dose, 1 hour post-dose, 2 hours post-dose, etc. Summary statistics will also be provided for the corresponding pre- to post-dose changes in systolic and diastolic blood pressure and heart rate by dose level and timepoint. The pre-dose measurement at each dose level will be used to calculate the change (See Table in Section 9.2.1).

Figures will be produced displaying maximum post dose blood pressure against pre-dose blood pressure, where the pre-dose value will be the pre-dose value on the day that maximum blood pressure was recorded; one data point per subject. In addition, the same plots will be produced displaying the maximum value by pre-dose value for each dose level; up to 7 data points per subject (one per possible treatment 2 mg, 4 mg, 6 mg, 8 mg, 1 x 12 mg (fasted), 1 x 12 mg (fed) and 3 x 4 mg (fasted)). The maximum post-dose blood pressures for each subject will also be plotted by dose level (one observation per subject).

The number of subjects with systolic and diastolic blood pressure and outside the potential clinical concern ranges will be summarised by dose level, for each timepoint.

For all summaries, readings with invalid date and/or time values will not be included in the counts (identified by the variable ABSTATCD = XX, 2 digit number present).

A listing of all ABPM data will be produced. The listing will also include a column to display the time of dose for the associated visit. Information regarding reading type code (manually or automatically initiated) and status code (reason why reading could not be taken for an invalid reading) will be displayed. Invalid readings (all recorded as zero) will be set to missing for the listing.

A separate listing will be provided for patients who had an ambulatory blood pressure value of potential clinical concern at any time.

12.8.4. ECG Assessments

ECGs are collected at scheduled visits (including 2 hr, 4 hr and 24 hr collections on PK days). A summary of 12-Lead ECG findings will be produced by treatment group and timepoint. A summary of 12-Lead ECG values and change from baseline in ECG values will be produced by treatment group, where the baseline value will be mean of the triplicate readings obtained pre-dose on Day 1 (See Table in Section 9.2.1). Values collected at all other times will be in singleton. All ECG findings and values will be listed. Values of potential clinical concern will also be listed.

13. HEALTH OUTCOMES ANALYSES

Not applicable.

14. CLINICAL PHARMACOLOGY DATA ANALYSES

14.1. Pharmacokinetic Concentration Data

Plasma concentrations for ropinirole (SKF-101468) and the metabolites (SKF-104557 and SKF-89124), along with the actual blood sampling times, will be listed by subject and planned sampling time. Plasma concentrations for ropinirole (SKF-101468) and the metabolites (SKF-104557 and SKF-89124), will be summarized by treatment and planned sampling time; plasma concentrations excluded from the PK analysis will be excluded from these summaries and from the figures. Figures showing individual, mean, and median plasma concentration-time profiles (by treatment) will be produced on both semi-log and linear scales for ropinirole (SKF-101468) and the metabolites (SKF-104557 and SKF-89124). Concentrations below the quantification limit (NQ) will be handled by following GSK procedures defined in “Standard Methods for the Non-compartmental Analysis of Pharmacokinetic Data” (SOP-CPK-0001 v01), with respect to calculating mean and median values for concentration-time summaries and figures.

Dose vs individual PK parameters (AUC(0-24ss), Cmaxss, Cminss) and dose vs dose normalised PK parameters ((AUC(0-24ss), Cmaxss, Cminss), on log-log scale, will be produced and will be the responsibility of CPK/M&S. Examples of these plots are in Section 19.4

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14.2. Pharmacokinetic Parameter Derivations

The following pharmacokinetic parameters for ropinirole (SKF-101468) and its metabolites SKF-104557 and SKF-89124 will be determined:

- AUC(0-24ss): Steady-state area under the plasma concentration-time profile over the dosing interval 0 to 24 hours
- Cmaxss: Steady-state maximum observed plasma concentration
- Cminss: Steady-state observed trough concentration (average of pre-dose and 24 h concentrations for each subject)
- tmax: time taken to achieve Cmax

All PK parameters AUC(0-24ss), Cmaxss, Cminss and tmax for ropinirole (SKF-101468) and its metabolites will be summarized by treatment and data will be listed by subject. Log-transformed AUC(0-24ss), Cmaxss and Cminss values will also be summarised and listed. Tmax will not be log-transformed.

Summary statistics for all PK parameters will include: n, arithmetic mean, standard deviation, minimum, median, maximum, and 95% confidence intervals about the arithmetic mean. The geometric mean, a 95% confidence interval about the geometric mean, and the between-subject coefficient of variation (CVb) will also be provided for each treatment for all log transformed parameters (i.e., all parameters excluding tmax). The geometric mean (GM) and CVb will be estimated as follows:

$$GM = \exp(\text{mean on log scale})$$

$$CVb\ (\%) = \text{sqrt}[\exp(sd^2) - 1] \times 100$$

where sd is the standard deviation of the log-transformed data.

14.3. Pharmacokinetic Analyses

The analysis of derived pharmacokinetic parameters from plasma ropinirole (SKF-101468) concentration-time data will be the responsibility of the Discovery Biometrics. Analysis will be performed using the SAS/STAT module of the SAS System, Version 8.2 or higher (SAS and SAS/STAT are registered trademarks of the SAS Institute Inc., Cary, NC, USA) or a comparable statistical package.

Ropinirole (SKF-101468) AUC(0-24ss), Cmaxss and Cminss will be loge-transformed prior to analysis. Tmax will not be log-transformed.

Formal statistical analysis will only be conducted on the ropinirole PK parameters since the metabolites do not contribute to the pharmacological activity of ropinirole.

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Dose Proportionality Assessment

Dose proportionality of ropinirole will be assessed by fitting the loge-transformed parameters AUC(0-24ss), Cmaxss and Cminss for ropinirole 4, 8 and 12 mg (fasted) PR/XL 24h (B, D, E) to the Power Model:

$$parameter = e^{a} (dose)^{b}$$

$$ie : \quad log(parameter) = a + (b * log(dose))$$

(where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality.)

An example of SAS code is provided below:

```
proc mixed data=pk;
      class subject;
      model log(pkparm) = logdose / outp=resids solution cl alpha=0.10;
      random subject;

run;
```

Dose proportionality of ropinirole will be demonstrated if the 90% confidence interval of the estimated mean slope of AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.797 to 1.203. If the power model has failed to converge, further investigation of dose proportionality may be performed if appropriate.

Effect of Food

The effect of food (F-E) on the highest tablet strength (1 x 12 mg) will be assessed separately by fitting the loge-transformed parameters AUC(0-24ss), Cmaxss and Cminss to a mixed model analysis of variance (ANOVA), as described in the previous section. Effects associated with treatment sequence, period (or day), and treatment will be assumed fixed; effects associated with subject within each treatment sequence will be assumed random. Point estimates of the difference in least-squares means of the test minus the reference treatment will be derived and back-transformed estimates for the ratio of fed:fasted (F:E) and 90% confidence intervals will be presented.

Model and distributional assumptions underlying the analyses will be assessed by visual inspection of residuals plots. Homogeneity of variance will be assessed by plotting the studentised residuals against the predicted values from the model, whilst normality will be assessed using normal probability plots of the residuals and the random terms. If these suggest that the model is inadequate, alternative parametric or nonparametric methods will be used.

In addition, the pharmacokinetic parameter, tmax will be analysed non-parametrically. The Wilcoxon Signed Rank Test will be used to construct point estimates and 90% confidence intervals for the median difference (fed-fasted). The inclusion of zero within the confidence interval constructed is substantiating evidence that the two treatments of interest do not differ with respect to the PK parameter tmax.

Dosage Strength Equivalence

The effect of dosage strength equivalence 3 x 4 mg PR/XL 24 h and 1 x 12 mg PR/XL 24h (E-G) for ropinirole will be assessed separately by fitting the loge-transformed parameters AUC(0-24ss), Cmaxss and Cminss to a mixed effects linear analysis of variance (ANOVA) model. Effects associated with treatment sequence, period (or day), and treatment will be assumed fixed; effects associated with subject within each treatment sequence will be assumed random. Point and 90% interval estimates of the difference in least-squares means of the test minus the reference treatment will be derived using SAS code such as that described below.

```
proc mixed data=pk;
    class trt sequence period subject;
    model log(pkparm) = trt sequence period / ddfm=satterth;
    random subject(sequence);
    lsmeans trt;
    estimate 'E vs G' trt 1 -1 / cl alpha=0.1;

run;
```

These estimates will then be exponentiated (back-transformed) to express point and interval estimates on a ratio scale. The final estimates will therefore represent the ratio of the geometric least squares mean of the test treatment to the geometric least squares mean of the reference treatment.

Dosage strength equivalence will be demonstrated if the 90% confidence interval for the ratios of AUC(0-24ss), Cmaxss and Cminss are completely contained within the range 0.80 to 1.25.

An estimate of the within-subject coefficient of variation (CVw) for each loge-transformed PK endpoint will be calculated based on the log-normal distribution as follows:

$$CVw\ (\%) = \text{sqrt}[\exp(mse)-1] \times 100$$

Where mse if the residual error from the ANOVA model described above.

Model and distributional assumptions underlying the analyses will be assessed by visual inspection of residuals plots. Homogeneity of variance will be assessed by plotting the studentised residuals against the predicted values from the model, whilst normality will be assessed using normal probability plots of the residuals and the random terms. If these suggest that the model is inadequate, alternative parametric or nonparametric methods will be used.

In addition, the pharmacokinetic parameter, tmax will be analysed non-parametrically. The Wilcoxon Signed Rank Test will be used to construct point estimates and 90% confidence intervals for the median difference (E-G). The inclusion of zero within the confidence interval constructed is substantiating evidence that the two treatments of interest do not differ with respect to the PK parameter tmax.

14.4. Pharmacodynamic Analyses

Not applicable.

14.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

15. BIOMARKER DATA ANALYSIS

Not applicable.

16. PHARMACOGENETIC DATA ANALYSES

Not applicable.

17. VIRAL GENOTYPING/PHENOTYPING

Not applicable.

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18. REFERENCES

GlaxoSmithKline Document Number HM2006/00649/00. An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

GlaxoSmithKline Document Number HM2006/00649/01. An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

GlaxoSmithKline Document Number HM2006/00649/02. An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

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19. ATTACHMENTS

19.1. Table of Contents for Data Display Specifications

Note: All data will be reported using the IDSL standards indicated, where applicable. For displays where there are no IDSL standards, example displays are provided in Section 19.2 and IDSL display principles will be followed.

Note for the Clinical Pharmacology Study Report (CPSR) the following section numbering will apply:

Section 9: Study Population Results

Section 10: Safety Results

Section 11: Pharmacodynamic Results

Section 12: Pharmacokinetic Results

The format and content of in-text tables and graphs required for the CPSR are described in Section 19.4 Data for the tables will be obtainable from outputs produced in Section 19.1.6. The in-text figures will be generated using excel or similar quality graphical package.

The numbering below will be used in the final CPSR and no table re-numbering will be performed.

In the tables below, the following abbreviations have been applied;

- Stats = Discovery Biometrics Statisticians,
- Prog = Discovery Biometrics Programmers.

19.1.1. Study Population Tables

Number	IDSL ex no.	Description	Responsibility
9.01	CP_ES1	Summary of Subject Disposition	Prog
9.02	DM3	Summary of Demographic Characteristics	Prog
9.03	DM6	Summary of Race and Racial Combinations Details	Prog
9.04	CP_CM1	Summary of Concomitant Medications by Generic Term (*if appropriate*)	Prog
9.05	CP_AE1xb	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Prog
9.06	CP_RD1	Listing of Randomisation Schedule	Prog

19.1.2. SAFETY TABLES

Number	IDSL ex no.	Description	Responsibility
10.01	EX1	Summary of Exposure to Study Drug	Prog
10.02	CP_AE1xa	Summary of All Adverse Events	Prog
10.03	CP_AE1xa	Summary of Drug-Related Adverse Events	Prog
10.04	CP_AE1xb	Summary of Serious Adverse Events	Prog
10.05	CP_AE13	Summary of Adverse Events by Maximum Intensity/Grade	Prog
10.06	AE1	Summary of Adverse Events of Special Interest	Prog or Stats
10.07	SAFE2	Summary of All Adverse Events (Total Counts)	Stats
10.08	EG1	Summary of ECG Findings	Prog
10.09	EG2	Summary of ECG Values	Prog
10.10	EG2	Summary of Change from Baseline in ECG Values	Prog
10.11	VS1	Summary of Vital Signs	Prog
10.12	VS1	Summary of Change from Baseline for Vital Signs	Prog
10.13	CP_VS2	Summary of Number of Vital Signs Outside Range of Potential Clinical Concern - FDA	Prog
10.14	CP_VS2	Summary of Number of Vital Signs Outside Range of Potential Clinical Concern - Europe	Prog
10.15	UR3	Summary of Urinalysis Dipstick Results	Prog
10.16	SD1	Summary of Investigational Product Status	Prog
10.17	VS1	Summary of ABPM Measurements	Stats
10.18	VS1	Summary of Change from Baseline ABPM Measurements	Stats
10.19	SAFE1	Listing of ABPM Measurements Outside Clinical Concern Range	Stats

19.1.3. Safety Figures

Number	IDSL ex no.	Description	Responsibility
10.01	SAFE3	Maximum post dose ambulatory systolic blood pressure value vs pre-dose systolic blood pressure value on the day of the maximum post dose value (*one observation per subject*)	Stats
10.02	SAFE3	Maximum post dose ambulatory diastolic blood pressure value vs pre-dose diastolic blood pressure value on the day of the maximum post dose value (*one observation per subject*)	Stats
0.03	SAFE3	Maximum post dose ambulatory systolic blood pressure value vs pre-dose systolic blood pressure value by dose level (*up to seven observations per subject*)	Stats

Continued…

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Number	IDSL ex no.	Description	Responsibility
10.04	SAFE3	Maximum post dose ambulatory diastolic blood pressure value vs pre-dose diastolic blood pressure value by dose level (*up to seven observations per subject*)	Stats
10.05	SAFE4	Maximum systolic blood pressure for each subject by dose level when maximum occurred (*one observation per subject*)	Stats
10.06	SAFE4	Maximum diastolic blood pressure for each subject by dose level when maximum occurred (*one observation per subject*)	Stats

Note: Refer to studies SKF101468/ROR106470 and SKF101468/RRL103628 for example programs.

19.1.4. Pharmacodynamic Tables

No	IDSL ex no.	Description	Responsibility
N/A			

19.1.5. Pharmacodynamic Figures

No	IDSL ex no.	Description	Responsibility
N/A			

19.1.6. Pharmacokinetic Tables

No	IDSL ex no.	Description	Responsibility
12.01	PKCT1X	Summary Statistics by Time for Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data (ng/mL) for each regimen	Prog
12.02	PKCT1X	Summary Statistics by Time for Plasma Ropinirole (SKF-104557) Pharmacokinetic Concentration-Time Data (ng/mL) for each regimen	Prog
12.03	PKCT1X	Summary Statistics by Time for Plasma Ropinirole (SKF-89124) Pharmacokinetic Concentration-Time Data (ng/mL) for each regimen	Prog
12.04	PKPT1X	Summary Statistics by Regimen for Ropinirole (SKF-101468) Pharmacokinetic Parameters	Stats
12.05	PKPT3X	Summary Statistics by Regimen for Log-Transformed Ropinirole (SKF-101468) Pharmacokinetic Parameters	Stats
12.06	PKPL1X	Listing of Derived Ropinirole (SKF-101468) Pharmacokinetic Parameters	Stats

Continued…

No	IDSL ex no.	Description	Responsibility
12.07	PKPT1X	Summary Statistics by Regimen for Metabolite (SKF-104557) Pharmacokinetic Parameters	Stats
12.08	PKPT3X	Summary Statistics by Regimen for Log-Transformed Metabolite (SKF-104557) Pharmacokinetic Parameters	Stats
12.09	PKPL1X	Listing of Derived Metabolite (SKF-104557) Pharmacokinetic Parameters	Stats
12.10	PKPT1X	Summary Statistics by Regimen for Metabolite (SKF-89124) Pharmacokinetic Parameters	Stats
12.11	PKPT3X	Summary Statistics by Regimen for Log-Transformed Metabolite (SKF-89124) Pharmacokinetic Parameters	Stats
12.12	PKPL1X	Listing of Derived Metabolite (SKF-89124) Pharmacokinetic Parameters	Stats
12.13	ANALYSUM1 NonStd	Dose Proportionality (B, D, E): Summary of Statistical Analysis Ropinirole (SKF-101468)	Stats
12.14	ANALYSUM2 NonStd	Food Effect (F:E): Summary of Statistical Analysis Ropinirole (SKF-101468)	Stats
12.15	ANALYSUM3 NonStd	Dosage Strength Equivalence (E:G) : Summary of Statistical Analysis Ropinirole (SKF-101468)	Stats
12.16	ANALYSUM4 NonStd	Summary of Analysis of tmax Ropinirole (SKF-101468) (E vs G and F vs E)	Stats
12.17	ANALY1 NonStd	Dose Proportionality (B, D, E): Power Model ANOVA for AUC(0-24ss) Ropinirole (SKF-101468)	Stats
12.18	ANALY1 NonStd	Dose Proportionality (B, D, E): Power Model ANOVA for Cmaxss Ropinirole (SKF-101468)	Stats
12.19	ANALY1 NonStd	Dose Proportionality (B, D, E): Power Model ANOVA for Cminss Ropinirole (SKF-101468)	Stats
12.20	ANALY2 NonStd	Food Effect (F:E): ANOVA for AUC(0-24ss) Ropinirole (SKF-101468)	Stats
12.21	ANALY2 NonStd	Food Effect (F:E): ANOVA for Cmaxss Ropinirole (SKF-101468)	Stats
12.22	ANALY2 NonStd	Food Effect (F:E): ANOVA for Cminss Ropinirole (SKF-101468)	Stats
12.23	ANALY2 NonStd	Dosage Strength Equivalence (E:G): ANOVA for AUC(0-24ss) Ropinirole (SKF-101468)	Stats
12.24	ANALY2 NonStd	Dosage Strength Equivalence (E:G): ANOVA for Cmaxss Ropinirole (SKF-101468)	Stats
12.25	ANALY2 NonStd	Dosage Strength Equivalence (E:G): ANOVA for Cminss Ropinirole (SKF-101468)	Stats
12.26	ANALY3 NonStd	Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (F vs E)	Stats
12.27	ANALY3 NonStd	Wilcoxon Signed Rank Test Analysis for tmax Ropinirole (SKF-101468) (E vs G)	Stats

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19.1.7. Pharmacokinetic Figures

Number	IDSL ex no.	Description	Responsibility
12.01	PKCF2	Mean Plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*treatments B, D and E on the same plot to show dose proportionality*)	Prog
12.02	PKCF2	Mean Plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*treatments F and E on the same plot to show food effect*)	Prog
12.03	PKCF2	Mean Plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*treatments E and G on the same plot to show dosage strength equivalence*)	Prog
12.04	PKCF4	Mean ± SD Concentration-Time plots (Linear) (*A separate plot for each treatment B, D, E, F, G*)	Prog
12.05	PKCF3	Median plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*treatments B, D and E on the same plot*)	Prog
12.06	PKCF3	Median Plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*treatments F and E on the same plot to show food effect*)	Prog
12.07	PKCF3	Median Plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*treatments E and G on the same plot to show dosage strength equivalence*)	Prog
12.08	PKCF1	Individual plasma Ropinirole (SKF-101468) Concentration-Time Plots (Linear and Semi-log) (*one graph/subject – treatments B, D, E, F and G on the same plot)*	Prog
12.09	PKCF6	Individual Plasma Ropinirole (SKF-101468) Concentration-Time Plot for each Treatment (Linear and Semi-Log)	Prog
12.10	PKCF2	Mean Plasma Metabolite (SKF-104557) Concentration-Time Plots (Linear and Semi-log) (*treatments B, D, E, F and G on the same plot*)	Prog
12.11	PKCF3	Median plasma Metabolite (SKF-104557) Concentration-Time Plots (Linear and Semi-log) (*treatments B, D, E, F and G on the same plot*)	Prog
12.12	PKCF1	Individual plasma Metabolite (SKF-104557) Concentration-Time Plots (Linear and Semi-log) (*one graph/subject – treatments B, D, E, F and G on the same plot)*	Prog
12.13	PKCF6	Individual Plasma Metabolite (SKF-104557) Concentration-Time Plot for each Treatment (Linear and Semi-Log)	Prog

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Number	IDSL ex no.	Description	Responsibility
12.14	PKCF2	Mean Plasma Metabolite (SKF-89124) Concentration-Time Plots (Linear and Semi-log) (*treatments B, D, E, F and G on the same plot*)	Prog
12.15	PKCF3	Median plasma Metabolite (SKF-89124) Concentration-Time Plots (Linear and Semi-log) (*treatments B, D, E, F and G on the same plot*)	Prog
12.16	PKCF1	Individual plasma Metabolite (SKF-89124) Concentration-Time Plots (Linear and Semi-log) (*one graph/subject – treatments B, D, E, F and G on the same plot)*	Prog
12.17	PKCF6	Individual Plasma Metabolite (SKF-89124) Concentration-Time Plot for each Treatment (Linear and Semi-Log)	Prog

19.1.8. Listings

Number	IDSL ex no.	Description	Responsibility
ICH			
1	ES3	Listing of Reasons for Withdrawal	Prog
2	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	Prog
3	SD3	Listing of Study Drug Discontinuation Record	Prog
4	DM4	Listing of Demographic Characteristics	Prog
5	DM10	Listing of Race	Prog
6	EX4	Listing of Exposure Data	Prog
7	AE7	Listing of Subject Numbers for Individual Adverse Events	Prog
8	AE9	Listing of All Adverse Events	Prog
9	CP_AE9a	Listing of Serious Adverse Events	Prog
10	CP_AE9e	Listing of Adverse Events Leading to Withdrawal from Study	Prog
11	AE2	Relationship between System Organ Class and Verbatim Text	Prog
12	LB6	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance - FDA	Prog
13	LB6	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance - Europe	Prog
14	CP_LB6	Listing of All Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance - FDA	Prog
15	CP_LB6	Listing of All Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance - Europe	Prog

Continued…

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Number	IDSL ex no.	Description	Responsibility
16	LB6	Listing of Haematology Abnormalities of Potential Clinical Importance - FDA	Prog
17	LB6	Listing of Haematology Abnormalities of Potential Clinical Importance - Europe	Prog
18	CP_LB6	Listing of All Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance - FDA	Prog
19	CP_LB6	Listing of All Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance - Europe	Prog
20	UR2b	Listing of Urinalysis Data	Prog
21	CP_CM4	Listing of Concomitant Medications by Generic Term	Prog
OTHER			
22	CP_VS5	Listing of All Vital Signs for Subjects with Adverse Events of Special interest	Prog
23	AE9 (see example)	Listing of All Adverse Events of Special Interest	Prog
24	CP_EG6b	Listing of All ECG values for Subjects with a Value of Potential Clinical Importance – FDA	Prog
25	CP_EG6b	Listing of All ECG values for Subjects with a Value of Potential Clinical Importance - Europe	Prog
26	CP_EG16b	Listing of All ECG Findings for Subjects with an Abnormal Finding – FDA	Prog
27	CP_EG16b	Listing of All ECG Findings for Subjects with an Abnormal Finding - Europe	Prog
28	CP_VS5	Listing of All Vital Signs for Subjects with Values of Potential Clinical Concern - FDA	Prog
29	CP_VS5	Listing of All Vital Signs for Subjects with Values of Potential Clinical Concern - Europe	Prog
30	SAFE5	Listing of ABPM Measurements	Prog
31	PKCL1X	Listing of Individual Plasma Ropinirole (SKF-101468) Pharmacokinetic Concentration-Time Data	Prog
32	PKCL1X	Listing of Individual Plasma Metabolite (SKF-104557) Pharmacokinetic Concentration-Time Data	Prog
33	PKCL1X	Listing of Individual Plasma Metabolite (SKF-89124) Pharmacokinetic Concentration-Time Data	Prog

19.2. Data Display Specifications

Only non-standard (Non Std) templates are shown. All Clinical Pharmacology output templates (CP Std) and Core IDSL output templates can be found on the Integrated Data Standards Library database.

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19.3. Dataset Specifications

Available on request.

19.4. In-Text (CPSR) Tables and Figures

Available on request

19.4.1. Dose Proportionality

Available on request

19.4.2. Food effect

Available on request

19.4.3. Dosage Strength Equivalence (3 x 4 mg vs 1 x 12 mg)

Available on request

SYNOPSIS

Identifier: HM2007/00444/00 **Study Number:** ROP109087

Title: An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets

Investigator(s):

1. [redacted] MD, PhD [redacted]
2. [redacted] MD, [redacted] South Africa

Study centre(s):

1. [redacted] Germany.
2. [redacted] South Africa.

Publication(s):

None as of the date of this report.

Study period:

Initiation Date:	16 April 2007
Completion Date:	29 August 2007

Phase of development: II

Objectives:

Primary

- To demonstrate dose proportionality for ropinirole using an extended release (PR/CR) formulation of ropinirole over the dose range 4-12 mg when administered to subjects with a diagnosis of idiopathic Parkinson's disease (PD).
- To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PR/CR at 12 mg (highest tablet strength).
- To determine dosage strength equivalence for ropinirole PR/CR administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets.

Secondary

- To further confirm the safety and tolerability of ropinirole PR/CR over a dose range of 2-12 mg when administered to subjects with a diagnosis of idiopathic PD.

Methodology:

This was a 2-centre study employing an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and was conducted in PD subjects. PD subjects were selected as the appropriate population for this study as healthy volunteers may not tolerate ropinirole PR/CR doses of up to 12 mg as well as a dopamine deficient population.

The study included screening assessments which took place within 28 days prior to first dose, a treatment period of 37 days, a down-titration period of 4-7 days and a follow-up examination 7-14 days after the last administration of the study drug.

Subjects received ropinirole PR/CR OD starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8, and 12 mg dose levels administered). The 12 mg dose level incorporated three dosing regimens; 1 x 12 mg tablet for three days including steady state PK profile (fasted, treatment E), 1 x 12 mg tablet for three days including steady state PK profile (Food and Drug Administration (FDA) “high fat” breakfast, treatment F) and 3 x 4 mg for three days including steady state pharmacokinetic (PK) profile (fasted, treatment G).

At the 12 mg dose, subjects were randomised to one of three treatments according to six possible treatment sequences (EFG, EGF, FEG, FGE, GEF, GFE).

Blood samples were collected for PK analysis of ropinirole (SKF-101468) and its two metabolites (SKF-104557 and SKF-89124) over a 24-hour period following administration of each of the following regimens of ropinirole PR/CR: 1 x 4 mg (fasted), 1 x 8 mg (fasted), 1 x 12 mg (fasted), 3 x 4 mg (fasted) and 1 x 12 mg (high-fat fed). Bioanalysis was conducted using a validated analytical method based on HPLC-MS/MS method with a limit of quantification for SKF-101468 and SKF-89124 of 20 pg/mL and 50 pg/mL for SKF-104557.

Number of subjects:

Subject disposition and demographics are presented below:

Number of Subjects	Total
Number of subjects planned, N	36
Number of subjects randomised, N	28
Number of subjects included in the Safety population, n (%)	28 (100)
Number of subjects included in the PK population, n (%)	27 (96)
Number of subjects completed as planned, n (%)	25 (89)
Number of subjects withdrawn (any reason), n (%):	3 (11)
Reasons for subject withdrawal	
Adverse Event, n (%):	1 (4)
Other – n (%)	2 (7)
Demographics	
Age in years, Mean (SD; Range)	64.5 (8.56; 47-81)
Sex, n (%)	
Female:	14 (50)
Male:	14 (50)
BMI, Mean (SD; Range)	25.53 (3.326; 20 – 32)
Weight (kg), Mean (SD; Range)	73.4 (13.20; 54 – 96)
Height (cm), Mean (SD; Range)	169.3 (10.31; 145 – 186)
Race, n (%)	
White – White/Caucasian/European Heritage	27 (96)
White – Arabic/North African Heritage	1 (4)
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	28 (100)

Diagnosis and main criteria for inclusion:

Male and female subjects with a diagnosis of idiopathic PD, between 30 and 85 years of age with a body mass index (BMI) of 18 to 32 kg/m^2 and a body weight of at least 50 kg. All subjects were required to provide written informed consent prior to participation in the study.

Treatment administration:

Ropinirole PR/CR tablets containing ropinirole hydrochloride equivalent to 2 mg, 4 mg, 8 mg and 12 mg of active drug substance were dosed in this study.

The treatments administered during the study were:

Code	Drug/Dose/Form/Route	Batch Number
A:	Ropinirole PR/CR 2 mg/tablet/oral	[redacted]
B:	Ropinirole PR/CR 4 mg/tablet/oral	
C:	Ropinirole PR/CR 6 mg (1 x4 mg PR/CR + 1 x 2 mg PR/CR)/tablet/oral	
D:	Ropinirole PR/CR 8 mg/tablet/oral	
E:	Ropinirole PR/CR 1 x 12 mg PR/CR (fasted)/tablet/oral	
F:	Ropinirole PR/CR 1 x 12 mg PR/CR (high fat fed)/tablet/oral	
G:	Ropinirole PR/CR 3 x 4 mg (fasted)/tablet/oral	

Criteria for evaluation:

Endpoint(s)

Primary

- Ropinirole AUC(0-24), the area under the steady-state plasma concentration time curve over the dosing interval
- Ropinirole Cmax: the maximum observed steady-state plasma concentration

Secondary

- Ropinirole tmax, the time to attain ropinirole Cmax
- Cmax and AUC(0-24) for the metabolites of ropinirole, SKF-104557 and SKF-89124
- Incidence of adverse events (AEs)
- Vital signs, electrocardiogram(ECG) and clinical laboratory data

Additional Endpoint

- Ropinirole Cmin, minimum observed steady-state plasma concentration

This endpoint was not listed as an endpoint in the protocol, however, it was added as a secondary endpoint in the Reporting and Analysis Plan (RAP).

Statistical methods:

Dose proportionality of ropinirole was assessed by fitting the $\log_e$-transformed parameters AUC(0-24) and Cmax for ropinirole 1x 4 mg (fasted), 1 x 8 mg (fasted) and 1 x 12 mg (fasted) PR/CR to the Power Model. In addition, Cmin was analysed using similar methods to the primary endpoints (AUC(0-24) and Cmax).

The effect of food on the highest tablet strength 1 x 12 mg (high fat fed) versus 1 x 12 mg (fasted) was assessed by fitting the loge-transformed parameters AUC(0-24) and Cmax to a mixed model analysis of variance (ANOVA). In addition, the PK parameter, Cmin was

analysed using similar methods to the primary endpoints (AUC(0-24) and Cmax). The PK parameter tmax was analysed non-parametrically.

The dosage strength equivalence of 3 x 4 mg PR/CR and 1 x 12 mg PR/CR for ropinirole was assessed by fitting the loge-transformed parameters AUC(0-24) and Cmax to a mixed effects linear analysis of variance (ANOVA) model. In addition, the PK parameter, Cmin, was analysed using similar methods to the primary endpoints. The PK parameter, tmax was analysed non-parametrically.

Summary:

Safety:

During the treatment period, 22 (79%) of 28 subjects experienced 79 treatment emergent AEs, and 15 subjects (54%) experienced 44 AEs which were judged by the investigator to be related to the study drug. Most AEs were mild or moderate in intensity. Three subjects experienced five AEs which were of severe intensity (2x nausea, 1x abdominal pain upper; 1x syncope; 1x diarrhoea). The most frequently reported adverse events were headache, nausea and dizziness. No subjects died during the study. One subject had an serious adverse event (gastric atony), which was considered by the investigator to be unrelated to study drug. One subject discontinued from the study due to a drug-related AE (moderate orthostatic hypotension). Mean blood pressure was lower, compared to pre-dose baseline, after all doses of ropinirole with a trend for larger mean decreases at the highest dose level. No unknown or unexpected AE occurred in this study

The following table presents a summary of AEs occurring at least twice in any treatment period starting with the most frequent AE.

System Organ Class Preferred Term	2 mg PR/CR (N=28)	4 mg PR/CR (N=28)	6 mg PR/CR (N=26)	8 mg PR/CR (N=25)	1 x 12 mg PR/CR (fasted) (N=25)	1 x 12 mg PR/CR (high fat fed) (N=25)	3 x 4 mg PR/CR (fasted) (N=25)
Any AE	7 (25%)	11 (39%)	2 (85)	8 (32%)	11 (44%)	4 (16%)	9 (36%)
Headache	1 (4%)	5 (18%)	-	3 (12%)	2 (8%)	1 (4%)	3 (12%)
Nausea	2 (7%)	2 (7%)	-	1 (4%)	2 (8%)	-	2 (8%)
Dizziness	-	1 (4%)	-	2 (8%)	3 (12%)	2 (8%)	-
Constipation	1 (4%)	2 (7%)	-	-	1 (4%)	-	-
Somnolence	-	-	-	-	1 (4%)	-	2 (8%)
Rhinitis	2 (7%)	-	-	-	-	-	-
Fatigue	-	2 (7%)	-	-	-	-	-

Pharmacokinetics:

Summaries (geometric mean, coefficient of variation between subjects (CVb%)) of the PK parameters of ropinirole and metabolites SKF-104557 and SFK-89124 are presented below:

Regimen	Ropinirole PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/CR (fasted)	27	57.1 (59.3)	3.36 (48.9)	6.00 (2.03 – 14.00)	1.64 (71.5)
1 x 8mg ropinirole PR/CR (fasted)	25	118 (46.8)	6.63 (44.6)	4.03 (2.00 – 10.00)	3.58 (58.1)
1 x 12mg ropinirole PR/CR (fasted)	25	164 (52.3)	9.06 (48.5)	4.02 (2.00 – 16.00)	4.74 (64.5)
1 x 12mg ropinirole PR/CR (fed)	25	197 (51.6)	13.1 (49.7)	10.00 (4.00 – 12.00)	4.57 (81.2)
3 x 4mg ropinirole PR/CR (fasted)	25	173 (53.8)	9.57 (52.4)	6.00 (2.00 – 14.00)	5.07 (60.9)

a. Median (range)

Regimen	SKF-104557 PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/CR (fasted)	27	78.8 (32.7)	4.02 (30.0)	9.98 (3.80 – 14.05)	2.66 (36.7)
1 x 8mg ropinirole PR/CR (fasted)	25	155 (32.8)	7.75 (37.2)	8.00 (0.00 – 14.00)	5.38 (35.5)
1 x 12mg ropinirole PR/CR (fasted)	25	219 (34.9)	10.8 (33.7)	8.00 (4.00 – 16.00)	7.60 (36.3)
1 x 12mg ropinirole PR/CR (fed)	25	250 (32.3)	13.7 (35.4)	10.00 (6.00 – 12.00)	7.70 (38.0)
3 x 4mg ropinirole PR/CR (fasted)	25	230 (24.6)	11.2 (25.5)	8.00 (2.00 – 14.00)	7.97 (26.4)

a. Median (range)

Regimen	SKF-89124 PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/CR (fasted)	27	2.78 (49.5)	0.156 (49.6)	8.00 (1.80 – 20.00)	0.092 (47.2)
1 x 8mg ropinirole PR/CR (fasted)	25	5.72 (43.3)	0.305 (49.3)	6.00 (0.00 – 20.00)	0.200 (44.7)
1 x 12mg ropinirole PR/CR (fasted)	25	8.61 (44.7)	0.463 (45.3)	6.00 (2.00 – 20.02)	0.286 (41.5)
1 x 12mg ropinirole PR/CR (fed)	25	10.2 (44.6)	0.584 (48.0)	10.00 (2.00 – 16.00)	0.315 (47.5)
3 x 4mg ropinirole PR/CR (fasted)	25	9.19 (38.5)	0.494 (40.4)	6.00 (2.00 – 20.00)	0.314 (35.0)

a. Median (range)

Statistical results of the ropinirole dose proportionality assessment (power model) are presented below:

Parameter	Slope	Standard error	90% CI
AUC(0-24) (hr*ng/mL)	0.970	0.0455	(0.893,1.046)
Cmax (ng/mL)	0.905	0.0415	(0.835,0.974)
Cmin (ng/mL)	0.986	0.0639	(0.878,1.093)

Statistical results for the effect of food on the PK of ropinirole are presented below:

Parameter	Geometric LS Mean		Ratio	90% CI
	Test (1 x 12 mg Fed)	Ref (1 x 12 mg Fasted)		
AUC(0-24) (hr*ng/mL)	196.59	163.85	1.20	(1.12, 1.28)
Cmax (ng/mL)	13.03	9.02	1.44	(1.34, 1.56)
Cmin (ng/mL)	4.54	4.72	0.96	(0.86, 1.08)
Tmax[a] (hr)	10.00	4.02	3.01	(2.00, 4.01)

a. median along with estimated median difference between treatments and 90% CI

Statistical results for ropinirole dosage strength equivalence are summarised below:

Parameter	Geometric LS Mean		Ratio	90% CI
	Test (1 x 12 mg PR/CR)	Ref (3 x 4 mg PR/CR)		
AUC(0-24) (hr*ng/mL)	163.85	173.18	0.95	(0.89, 1.01)
Cmax (ng/mL)	9.02	9.56	0.94	(0.88, 1.02)
Cmin (ng/mL)	4.72	5.07	0.93	(0.83, 1.04)
Tmax[a] (h)	4.02	6.00	0.00	(-1.00, 1.00)

a. median along with estimated median difference between treatments and 90% CI

Conclusions:

In subjects with PD

- The pharmacokinetics of ropinirole were dose proportional over the dose range 4 to 12 mg PR/CR.
- Under fed conditions ropinirole AUC(0-24) and Cmax were on average 20% and 44% higher, respectively and tmax was delayed by 3 hours compared to the fasted state.
- Dosage strength equivalence was demonstrated for 1 x 12 mg PR/CR ropinirole tablet and the 3 x 4 mg PR/CR ropinirole tablets.
- The different dose regimens of ropinirole PR/CR were well tolerated. No unknown or unexpected AEs occurred during the study.
- A lower incidence of AEs was reported following 12 mg ropinirole PR/CR in the fed state compared to the same dose fasted; the proportion of subjects that reported AEs was 16% vs 44%, respectively.

Date of Report:

February 2008

Division: Worldwide Development
Retention Category: GRS019
Information Type: Protocol Amendment

Title:	An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

Compound Number: SK&F-101468

Effective Date: 02-JUL-2007

Protocol Amendment Number: 02

Description: This amendment details an increase in patient numbers to be recruited onto the study.

Subject: SK&F101468, prolonged release for PD, pharmacokinetic, food effect, PD

Author: [redacted]

Revision Chronology:

HM2006/00649/00	2006-DEC-06	Original
HM2006/00649/01	2007-JAN-05	Amendment No.: 01. Amendment to correct inclusion/exclusion criteria and to clarify introduction section.
HM2006/00649/02	2007-JUL-02	Amendment No.: 02. Amendment to increase patient numbers to be recruited onto the study.

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Sponsor Signatory:	**Signature:**	**Date:**
Dr [redacted] Vice President, Clinical Pharmacology and Discovery Medicine, Neurology and GI CEDD	[redacted]	2nd July 2007

SPONSOR INFORMATION PAGE

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Regulatory Agency Identifying Number(s):
EudraCT: 2006-006209-94

INVESTIGATOR AGREEMENT PAGE

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

Investigator Name: _____

_____ _____
Investigator Signature Date

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ABBREVIATIONS

AE	Adverse Event
ABPM	Ambulatory blood pressure monitor
AE	Adverse Event
ALT	S-alanine aminotransferase
AST	S-aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CPDS	Clinical Pharmacology Data Sciences
CPSP	Clinical Pharmacology Statistics and Programming
CR	Controlled Release
CRF	Case report form
Cmax	Maximum observed plasma concentration
CTC	Common Toxicity Grade
CYP1A2	Cytochrome P-450 1A2 enzyme
ECG	Electrocardiogram
FDA	Food and Drug Administration
G	Gram
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HRT	Hormone Replacement Therapy
h, hrs	Hour(s)
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
IR	Immediate release
IRB	Institutional Review Board
IRLS	International Restless Legs Rating scale
IRLSSG	International Restless Legs Syndrome Study Group
IUD	Intra Uterine Device
kg	Kilogram
L	Litre
mcg	Microgram
mg	Milligram
min	Minute
mL	Millilitre
MTD	Maximum Tolerated Dose
OTC	Over-The-Counter
PCV	Packed cell volume
PD	Parkinson’s Disease
PGx	Pharmacogenetics
PLMS	Periodic Limb Movements during Sleep
PK	Pharmacokinetic

PR	Prolonged release
RBC	Red blood cells
RLS	Restless Legs Syndrome
SRM	Study Reference Manual
t.i.d.	ter in die (three times daily)
t½	Terminal phase elimination half-life
tmax	Time to achieve maximum plasma concentration
WBC	White blood cells
WCBP	Women of child-bearing potential

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PROTOCOL SUMMARY

Rationale

Ropinirole 2, 3, 4 and 8 mg ropinirole PR/CR tablets are currently available. It is proposed to develop a 12 mg tablet in order to reduce tablet burden for Parkinson's Disease (PD) patients taking higher doses of ropinirole PR/CR.

The purpose of this study is to investigate the effect of administering the 12 mg tablet of ropinirole PR/CR with a high fat meal as well as assessing the dose proportionality of ropinirole over the clinically therapeutic range of available tablet strengths (4-12mg). In addition the dosage strength equivalence for a 3 tablet combination (3x4mg vs 1x12mg) will be investigated.

Patients with PD will receive ropinirole PR/CR tablets following an up-titration dosing regimen from 2 mg to 12 mg PR/CR. For each individual patient, continuation of up-titration for study medication will be based on satisfactory tolerability at the current dose level. Pharmacokinetic assessment will be conducted during the up-titration at steady-state for the 4mg and 8mg dose levels. After achieving steady state at 12mg/day, patients will have 3 PK profiles taken.

Objective(s)

Primary

- To demonstrate dose proportionality for ropinirole using an extended release (PR/CR) formulation of ropinirole over the dose range 4-12mg when administered to patients with a diagnosis of idiopathic Parkinson's Disease.
- To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PR/CR at 12mg (highest tablet strength).
- To determine dosage strength equivalence for ropinirole PR/CR administered as 1x12mg tablet compared with 3x4mg tablets.

Secondary

- To further confirm the safety and tolerability of ropinirole PR/CR over a dose range of 2 - 12 mg when administered to patients with a diagnosis of idiopathic Parkinson's Disease.

Endpoint(s)

Primary

- Ropinirole AUC (0-24ss), the area under the steady-state plasma concentration-time curve over the dosing interval

- Ropinirole Cmaxss: the maximum observed steady-state plasma concentration

Secondary

- Ropinirole Tmax, the time to attain ropinirole Cmax
- Cmaxss and AUC(0-24ss) for the metabolites of ropinirole, SKF-104557 and SKF-89124
- Incidence of Adverse events
- Vital signs, ECG and clinical laboratory data

Study Design

This study consists of an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and will be conducted in PD patients. Patients will receive ropinirole PR/CR *od* starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and 12 mg). Patients will generally take their study medication at home and complete diary cards apart from on PK Study Days and during the 12mg dosing session when patients will remain resident in the clinic for logistical reasons.

For the 2mg dose level patients will attend the unit for dosing and safety assessments only.

For the 4 and 8 mg dose levels, patients will attend the clinic after they have received at least 5 sequential days of dosing at these dose levels, for 24-hour pharmacokinetic (PK) and safety evaluations. At these PK clinic visits, ropinirole PR/CR will be administered in the fasted state.

For the 6 mg dose level, patients will continue taking their medication at home and will attend the clinic for safety evaluations; however pharmacokinetic assessments will not be taken.

Once patients have titrated to 12mg, they will remain at this dose for the remainder of the study. At the 12 mg dose, patients will be randomised to one of three treatments according to six possible treatment sequences (EFG, EGF, FEG, FGE, GEF, GFE).

Following completion of the 12 mg dosing regimen, patients will be down-titrated according to the down titration schedule and will then attend the clinic for a follow up visit 7-14 days after completion of last administration of the study drug.

Study Population

Approximately 36 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. If practical, no further patients will be recruited to the study once 25 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

Study Assessments

Screening

Suitable patients will undergo a pre-study medical examination within 28 days before the start of the study. This will include the following: general medical history, physical examination, Epworth Sleepiness Scale assessment, 12 lead ECG, supine and standing blood pressure and pulse rate, assessments of haematology, clinical chemistry and urinalysis, HIV-1/2 test, hepatitis B and C status, urine drug screen, alcohol test and urine/serum pregnancy test (for women of child-bearing potential (WCBP) only).

Treatment Phase

Patients will be dosed once daily with ropinirole PR/CR in the morning from Day 1 to Day 37.

Assessments including pharmacokinetic sampling, 12 lead ECGs, supine and standing blood pressure and pulse rate measurements, ABPM, assessments of haematology, clinical chemistry and urinalysis, urine drug screen, alcohol test and urine/serum pregnancy test (WCBP only) will be performed throughout the treatment phase of the study.

Follow-up

A follow-up examination will be performed 7-14 days after the last administration of study drug. A physical examination will be performed; supine and standing blood pressure, pulse rate and 12-lead ECG will be recorded. Clinical chemistry, haematology and urinalysis will be assessed and adverse events (AEs) will be monitored for the preceding time interval. In addition, a urine/serum pregnancy test will be performed in WCBP.

Investigational Product

Ropinirole PR/CR tablets containing ropinirole hydrochloride equivalent to 2 mg, 4 mg, 8 mg and 12 mg of active drug substance will be dosed in this study.

1. INTRODUCTION

1.1. Background

Parkinson's disease (PD) is one of the most common neurological disorders in elderly people. It is caused by a loss of dopaminergic nerve cells in certain areas of the brain. The mainstay in the treatment of Parkinson's disease is the administration of dopaminergic agents.

Ropinirole, 4 [2 (dipropylamino)ethyl] 1,3 dihydro 2H indol 2 one, is a non ergoline dopamine agonist acting both centrally [Benham, 1988; Horton, 1988; Hieble, 1988; Herdon, 1991] and peripherally [Steinsland, 1978; Hieble, 1986] at D2/D3 receptors. It has been developed as a therapeutic agent for the treatment of the signs and symptoms of Parkinson's disease. The use of ropinirole film-coated tablets (ropinirole IR) for the treatment of Parkinson's disease is registered in more than 60 countries world-wide at doses of up to 24 mg/day.

Ropinirole IR is administered 3 times daily (tid). In order to minimise peripheral dopaminergic side effects, dosing is gradually increased in multiple steps to total daily doses of 3 mg/day or higher, according to the patient's therapeutic response. Titration may require 8 weeks or longer, depending on a given patient's responsiveness and tolerance.

A prolonged-release (PR) tablet of ropinirole has been developed. This tablet formulation was formerly termed ropinirole controlled-release (CR). The PR tablet was developed to allow once-daily dosing of ropinirole, to provide a simpler dose-titration regimen and to improve the tolerability profile by slowing the rate of absorption of ropinirole. Administration of ropinirole PR also results in fewer fluctuations in drug plasma levels throughout the day. Compliance would also be expected to be improved with a once daily regimen versus a three-times daily regimen.

1.2. Rationale

Currently, tablet strengths of 2, 3, 4 and 8 mg ropinirole PR/CR are available. It is proposed to develop a 12 mg tablet in order to reduce tablet burden for patients taking higher doses of ropinirole PR/CR.

The purpose of this study is to investigate the effect of administering the new 12 mg tablet of ropinirole PR/CR with a high fat meal as well as assessing the dose proportionality of ropinirole over the clinically therapeutic range of available tablet strengths (4-12mg). In addition the dosage strength equivalence for a 3 tablet combination (3x4mg vs 1x12mg) will be investigated.

PD patients have been selected as the appropriate population for this study as volunteers may not tolerate ropinirole PR/CR doses of up to 12 mg as well as a dopamine deficient population.

2. OBJECTIVE(S)

2.1. Primary

- To demonstrate dose proportionality for ropinirole using an extended release (PR/CR) formulation of ropinirole over the dose range 4-12mg when administered to patients with a diagnosis of idiopathic Parkinson's Disease.
- To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PR/CR at 12mg (highest tablet strength).
- To determine dosage strength equivalence for ropinirole PR/CR administered as 1x12mg tablet compared with 3x4mg tablets.

2.2. Secondary

- To further confirm the safety and tolerability of ropinirole PR/CR over a dose range of 2 - 12 mg when administered to patients with a diagnosis of idiopathic Parkinson's Disease.

3. ENDPOINT(S)

3.1. Primary

- Ropinirole AUC (0-24ss), the area under the steady-state plasma concentration-time curve over the dosing interval
- Ropinirole Cmaxss: the maximum observed steady-state plasma concentration

3.2. Secondary

- Ropinirole Tmax, the time to attain ropinirole Cmax
- Cmaxss and AUC(0-24ss) for the metabolites of ropinirole, SKF-104557 and SKF-89124
- Incidence of Adverse events
- Vital signs, ECG and clinical laboratory data

4. STUDY DESIGN

This study consists of an open, non-randomised sequential design, followed by a 3-period, randomised, crossover design and will be conducted in PD patients. Patients will receive ropinirole PR/CR *od* starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and 12 mg). Patients will generally take their study medication at home and complete diary cards apart from on PK Study Days and during the 12mg dosing session (when patients will remain resident in the clinic for logistical reasons).

For the 2mg dose level patients will attend the unit for dosing and safety assessments only.

For the 4 and 8 mg dose levels, patients will attend the clinic after they have received at least 5 sequential days of dosing at these dose levels, for 24-hour pharmacokinetic (PK) and safety evaluations. At these PK clinic visits, ropinirole PR/CR will be administered in the fasted state.

For the 6 mg dose level, patients will continue taking their medication at home and will attend the clinic for safety evaluations; however pharmacokinetic assessments will not be taken.

Once patients have titrated to 12mg, they will remain at this dose for the remainder of the study. At the 12 mg dose, patients will be randomised to one of three treatments according to six possible treatment sequences (EFG, EGF, FEG, FGE, GEF, GFE) according to the treatments defined in Table 1.

Table 1 Study Design for ROP109087

Dose Level	Dosing Days	PR/CR Dose (mg)	PK Assessments
1	1 - 7	2	-
2	8 - 14	4	Any day between Days 12-14, 4 mg steady state (fasted) (Treatment B)
3	15 - 21	6	-
4	22 - 28	8	Any day between Days 26-28, 8mg steady state (fasted) (Treatment D)
5	29 - 37	12	Assessments on Days 31, 34 and 37. Randomised, 12mg steady state: (I) Ropinirole PR/CR 1x12mg tablet (fasted) (E) (ii) Ropinirole PR/CR 1x12mg tablet (fed : standard high fat FDA breakfast) (F) (III) Ropinirole PR/CR 3x4mg tablets (fasted) (G)
	38-44	Down titration	-

On all PK assessment days, ropinirole PR/CR will be administered in the fasted state except for treatment sequence F, where dosing will occur after a standardised high fat FDA breakfast. Patients will be down-titrated according to the down titration schedule in Table 3.

Lastly, patients will attend the clinic for a follow up visit 7-14 days after completion of last administration of study drug.

4.1. Stopping criteria for up-titration

During this study a number of measures have been put in place to ensure patient safety.

For each individual patient, continuation of up-titration for study medication will be based on satisfactory tolerability at the current dose level, based upon review of the safety data (and not pharmacokinetic data). Dosing with ropinirole PR/CR will be discontinued in the following circumstances:

1. Clinically significant adverse effects considered related to administration of the study drug (see guidelines below).
2. If the systolic or diastolic blood pressure changes are of clinical concern.
3. If the ECG shows any changes from baseline which are of clinical concern.
4. Patients not wishing to continue with the study for any reason, eg unavailability, intolerance of the study procedures.

If patients are withdrawn from the study, then the follow up procedures should be carried out within 7-14 days of last dose of study medication where possible.

Table 2 Guidelines for Investigator-Initiated Premature Termination of Dosing

Symptom	Definition
Hypotension	The patient reports orthostatic symptoms such as feeling faint or dizzy that fulfil criteria common toxicity grade (CTC) grade 2 or greater for hypotension. • CTC grade 2 hypotension = requiring brief fluid replacement or other therapy; no physiologic consequences; • CTC grade 3 hypotension = requiring therapy and sustained medical attention, but resolves without persistent physiologic consequences; • CTC grade 4 hypotension = shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion) Or Clinically significant symptomatic orthostatic hypotension
Nausea	Oral intake significantly decreased (equivalent to CTC grade 2). Or No significant oral intake, requiring (i.v.) fluids (equivalent to CTC grade 3). Or Clinically significant nausea last for longer than 24 hours
Vomiting	2-5 episodes in 24 h (equivalent to CTC grade 2) Or ≥6 episodes in 24 h; or need for intravenous fluids (equivalent to CTC grade 3). Or Requiring parenteral nutrition; physiologic consequences requiring intensive care; or haemodynamic collapse (equivalent to CTC grade 4).

4.2. Postural hypotension

During this study, if symptomatic or asymptomatic postural hypotension, or significant bradycardia on standing is observed, then patients must remain in a sitting or lying position until supine and erect blood pressure and pulse are able to be re-measured and subsequently return to normal.

4.3. Extended time at dose level

Additional time at a specific dose level may be permitted to allow for further desensitisation of peripheral dopamine receptors. In previous ropinirole IR studies, this has been seen to be an important factor for improved tolerability.

If necessary, 1 or 2 days of additional dosing will be permitted at the start of each new dose level to improve tolerability if required.

If at any dose level, poor tolerability is observed on the day prior to dose escalation, dose escalation will not occur. Patients will be permitted 1 or 2 additional days of dosing at the current dose level and dose escalation will occur only if that dose level is well tolerated.

4.4. Bed-rest following first dose at new dose level and on PK assessment days

Following the first dose of study medication at each dose level, patients will remain supine or semi-supine (bed-rest) for 2 hours post-dose (excluding vital signs recordings when patients will be required to sit and then stand). Patients will remain in the clinic for 2 hours post dose on dose escalation days.

Patients will also remain in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing on PK assessment days.

5. STUDY POPULATION

5.1. Number of Patients

Approximately 36 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. If practical, no further patients will be recruited to the study once 25 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

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

1. Male or female patients aged between 30 and 85 years of age inclusive at screening.
2. Body mass index of 18 to 32 kg/m2, with a body weight of at least 50 kg.
3. Diagnosis of idiopathic Parkinson's Disease graded according to modified Hoehn & Yahr Stage I-III (Appendix 4).
4. Patients must have provided written informed consent prior to performing any Screening assessments, including any washout of concomitant medications in preparation for this study.
5. QTc interval of < 450ms at screening (or QTc < 480ms in patients with Bundle Branch Block).
6. Female patient is currently either of:

   a) non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal or any female who is surgically sterilized (via documented hysterectomy or bilateral tubal ligation).

   (For purposes of this study, postmenopausal is defined as one year without menses)

   OR

   b) child-bearing potential, has a negative urine/serum pregnancy test at the Screening Visit (prior to investigational product administration), and agrees to use acceptable contraception from one month prior to study Day 1 until one month after completion of the study (ie. one month after the follow-up visit). All hormonal birth control must have been administered for at least one monthly cycle prior to the Screening Visit. GSK acceptable contraception methods, when used consistently and in accordance with both the product label and the instructions of a physician, are as follows:

   - complete abstinence
   - sterilization of patient's male partner prior to female patient's entry into study
   - oral contraceptive (either combined or progestogen only)
   - any intra-uterine device with a documented failure rate of less than 1% per year
   - systemic contraception (eg. norplant system)
   - double barrier method if comprised of a spermicide with either a condom or diaphragm

5.2.2. Exclusion Criteria

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

1. Patients who have an abnormality on physical examination. A patient with clinical abnormality may be included only if the Investigator considers that the abnormality will not introduce additional risk factors and will not interfere with the study procedures.
2. Patients who, in the opinion of the Investigator, have medical conditions which could present a safety concern. These may include, but are not limited to, the following disorders: diabetes, peripheral neuropathy, rheumatoid arthritis, fibromyalgia syndrome, symptomatic orthostatic hypotension, hepatic or renal failure, pleuro-pulmonary fibrosis, significant and/or uncontrolled psychiatric, haematological, endocrinological, neurological (other than Parkinson's disease), or cardiovascular disease (including myocardial infarction, unstable angina pectoris, cardiac arrhythmias, cerebrovascular accident (CVA), or patients who are known to have malignancy, are being treated for malignancy or have had treatment for malignancy within the last year (other than basal cell cancer).
3. Patients having a clinically significant abnormal laboratory value, ECG, or physical examination findings not resolved by the time of the baseline examinations. Abnormal 12-lead ECG findings include, but are not limited to, the following: myocardial ischemia, clinically significant conduction abnormalities, or clinically significant arrhythmias.
4. Positive result for Hepatitis B surface antigen, Hepatitis C antibody or Human Immunodeficiency Virus (HIV) antibody at screening.
5. Positive alcohol test result and / or urine test for undeclared drugs at screening.
6. Recent history of moderate to severe dizziness, syncope, or orthostatic hypotension, defined as a fall in blood pressure, after rising from the supine to erect posture, of > 30 mmHg for systolic pressure and > 20 mmHg for diastolic pressure.
7. Significant sleep disorder or Epworth Sleep Score (Appendix 5) ≥ 9 at screening.
8. Patients with a lying/sitting diastolic blood pressure ≥110mmHg or ≤50mmHg or a systolic blood pressure ≥180mmHg or ≤90mmHg at the Screening or Baseline Visit.
9. History of any dopaminergic treatment (other than ropinirole IR and L-dopa) within 2 weeks prior to first dose.
    - Patients on dopaminergic agonists other than ropinirole IR and L-dopa may be enrolled if the agent is stopped for a 2-week wash-out period prior to first dose.
    - Patients taking ropinirole IR or L-dopa may switch to ropinirole PR/CR 2mg on study day 1, providing they have first followed the manufacturer's down titration guidelines.
    - Patients taking ropinirole IR > 4mg/day must be down-titrated according to the manufacturer's guidelines prior to study day 1.

- Patients taking ropinirole IR or L-dopa must have been on a stable dose for at least 4 weeks prior to screening; doses of ropinirole IR or L-dopa may need to be adjusted prior to or during the study.
- Patients on selegiline, amantadine, or anticholinergics may be enrolled but must have been on a stable dose for at least one month prior to study enrolment and must remain on their current dose throughout the treatment phase of the study.

10. Withdrawal, introduction, or change in dose of hormone replacement therapy and/or any drug known to substantially inhibit CYP1A2 (e.g., cimetidine, ciprofloxacin, fluvoxamine) or induce CYP1A2 (e.g., tobacco, or omeprazole) within 7 days prior to study enrolment. Patients already on these agents may be enrolled but must remain on stable doses of the agent for at least one month prior to enrolment and throughout the treatment phase of the study.
11. Patients who smoke >20 cigarettes per day and will not maintain a constant smoking habit for the duration of the study.
12. Blood donation or significant blood loss less than 90 days before Day 1 of the current study.
13. Definite or suspected personal history, or family history, of adverse reactions or hypersensitivity to ropinirole or to drugs with a similar chemical structure.
14. Use of any investigational drug (with the exception of ropinirole PR/CR) within 30 days or 5 half-lives (whichever is longer) before the start of dosing with study medication.
15. Patients who have received over-the-counter (OTC) medicine within 48 h before the first dose of study drug. Patients who have taken OTC medication may still be entered in the study, if in the opinion of the Investigator, the medication received will not interfere with the study procedures or compromise safety.
16. Recent history, or suspicion, of drug dependence or abuse of alcohol (with alcohol abuse defined as an average weekly intake of greater than 21 units or an average daily intake of greater than 3 units for men; greater than 14 units per week or greater than 2 units per day for women. One unit is equivalent to half a pint of beer, one measure of spirits, or one glass of wine).
17. Significant concern, or likelihood, that the patient will drop out of the study prematurely, will require new or prohibited concomitant medications during the study period, or will not be compliant with study procedures.
18. Women who are pregnant or breast-feeding.
19. Patients with prior or current major psychosis (eg schizophrenia or psychotic depression). Eg scoring 3 or 4 on UPDRS item 2 (thought disorder) or item 3 (depression).

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 for Ropinirole Hydrochloride Prolonged/Extended Release Tablets for Parkinson's Disease [GlaxoSmithKline Document Number ZM2004/00040/01].

6. STUDY ASSESSMENTS AND PROCEDURES

Timings of all measurements, evaluations and procedures are detailed in the Time and Events Schedule (Appendix 1). Details of dietary content of FDA "High Fat" breakfast are listed in Appendix 7.

6.1. Demographic and Baseline Assessments

Demographic and baseline data will be collected at the screening visit.

6.2. Study Procedures

6.2.1. Screening

Patients will be assessed as suitable candidates for this study using the screening inclusion and exclusion criteria. All patients will undergo a pre-study medical examination within 28 days before the start of the study. This will include the following and will be performed once informed consent has been obtained (see Appendix 1).

- General medical history including Parkinson's Disease history
- Epworth Sleepiness Scale (ESS) assessment
- Concomitant Medication history
- Adverse Event recording
- Smoking History
- Physical examination
- 12 lead ECG
- Supine and standing blood pressure and pulse rate
- Assessments of haematology, clinical chemistry and urinalysis
- HIV-1/2 test, hepatitis B and C status
- Urine drug screen
- Alcohol test
- Urine/serum pregnancy test (WCBP only)

6.2.2. Treatment phase

Patients will be dosed once daily with ropinirole PR/CR in the morning from Day 1 to Day 37.

Day 1 (2mg PR/CR)

Patients will attend the clinic on Day 1 and undergo the pre-dose procedures: urine drug screen, alcohol test, urine/serum pregnancy test (in WCBP only), triplicate 12-lead ECG assessments, supine and standing blood pressure and pulse rate measurements (3 stable sets of each required at baseline) and recording of adverse events.

Ambulatory blood pressure will be measured hourly using an ambulatory blood pressure monitor (ABPM) from pre-dose, up to and including 12-hours post dose. Patients will take the device home when leaving the unit, which will enable them to continue to monitor blood pressure up to 12 hours post-dose.

Patients will have breakfast and approximately 30 minutes later will receive their 1st dose of ropinirole PR/CR 2mg (Day 1, Time 0). Patients may be discharged from the unit 2 h after dosing following the designated bed-rest period (see Section 4.4) provided the investigator considers it safe to do so.

Days 2-7

Patients will take the study medication in the morning for Days 2-7 at home and complete a patient diary card.

Day 8 (4mg PR/CR)

Prior to dosing in the unit on Day 8, 12-lead ECG and vital signs (supine and standing blood pressure and pulse rate) will be performed. Ambulatory blood pressure will be measured hourly using an ambulatory blood pressure monitor (ABPM) from pre-dose, up to and including 12-hours post dose. Patients will take the device home when leaving the unit, which will enable them to continue to monitor blood pressure up to 12 hours post-dose.

Patients will have breakfast and approximately 30 minutes later will receive their 1st dose of ropinirole PR/CR 4mg (Day 8, Time 0). Patients may be discharged from the unit 2 h after dosing following the designated bed-rest period (see Section 4.4) provided the investigator considers it safe to do so.

Days 9-11 and 12-14 (non-PK days only)

Patients will take the study medication in the morning for Days 9-11, and in the morning on non-PK days 12-14, at home, returning to the clinic either on the evening prior to the PK day or on the morning of the PK assessment day. When dosing at home patients will complete a patient diary card. Patients will be fasted from 22:00 on the evening prior to the PK assessment day.

Day 12-14 (PK day only)

4mg PK assessment may be conducted on any day between Days 12-14.

Prior to dosing in the unit on the PK Day, vital signs (supine and standing blood pressure and pulse rate), 12-lead ECG and recording of adverse events will be performed.

Patients will then receive 4mg ropinirole PR/CR in the fasted condition in the morning. Patients will then remain in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing. Vital signs (supine and standing blood pressure and pulse rate) measurements will be made at 4, 6, 12 and 24 hours post-dose. Serial PK blood samples will be collected for analysis of ropinirole at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose.

Adverse events will be recorded at intervals post-dose and on spontaneous reporting by the patients.

All 24 hour procedures must be completed prior to the next dose of study medication.

Day 15 (6mg PR/CR)

Prior to dosing in the unit on Day 15, 12-lead ECG, vital signs (supine and standing blood pressure and pulse rate), urine drug screen and urine/serum pregnancy test (in WCBP only) will be performed. Ambulatory blood pressure will be measured hourly using an ambulatory blood pressure monitor (ABPM) from pre-dose, up to and including 12-hours post dose. Patients will take the device home when leaving the unit, which will enable them to continue to monitor blood pressure up to 12 hours post-dose.

Patients will have breakfast and approximately 30 minutes later will receive their 1st dose of ropinirole PR/CR 6mg as one 4 mg and one 2 mg tablet (Day 15, Time 0). Patients may be discharged from the unit 2 h after dosing following the designated bed-rest period (see Section 4.4) provided the investigator considers it safe to do so.

Days 16-21

Patients will take the study medication in the morning for Days 16-21 at home and complete a patient diary card.

Day 22 (8mg PR/CR)

Prior to dosing in the unit on Day 22, 12-lead ECG and vital signs (supine and standing blood pressure and pulse rate) will be performed. Ambulatory blood pressure will be measured hourly using an ambulatory blood pressure monitor (ABPM) from pre-dose, up to and including 12-hours post dose. Patients will take the device home when leaving the unit, which will enable them to continue to monitor blood pressure up to 12 hours post-dose.

Patients will have breakfast and approximately 30 minutes later will receive their 1st dose of ropinirole PR/CR 8mg (Day 22, Time 0). Patients may be discharged from the unit 2 h after dosing following the designated bed-rest period (see Section 4.4) provided the investigator considers it safe to do so.

Days 23-25 and 26-28 (non PK days only)

Patients will take the study medication in the morning for Days 23-25, and in the morning on non-PK days 26-28, at home, returning to the clinic either on the evening prior to the PK day or on the morning of the PK assessment day. When dosing at home patients will complete a patient diary card. Patients will be fasted from 22:00 on the evening prior to the PK assessment day.

Day 26-28 (PK day only)

8mg PK assessment may be conducted on any day between Days 26-28.

Prior to dosing in the unit on the PK Day, vital signs (supine and standing blood pressure and pulse rate), 12-lead ECG and recording of adverse events will be performed.

Patients will then receive 8mg ropinirole PR/CR in the fasted condition in the morning. Vital signs (supine and standing blood pressure and pulse rate) measurements will be made at 4, 6, 12 and 24 hours post-dose. Serial PK blood samples will be collected for analysis of ropinirole at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose. Patients will then remain in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing.

Adverse events will be recorded at intervals post-dose and on spontaneous reporting by the patients.

All 24 hour procedures must be completed prior to the next dose of study medication.

Days 29-37 (12mg PR/CR)

Patients will attend the unit from Day 29 and will remain in-house for the entire 12mg PR/CR treatment period (ie until completion of Day 37 assessments) due to logistical reasons.

On Day 29, Patients will be randomised to one of 6 possible treatment sequences (EFG, EGF, FEG, FGE, GEF, GFE), which will determine which of the 3 different 12mg ropinirole PR/CR treatments will be received between Days 29-31, 32-34 and 35-37 respectively. PK assessments will be performed after at least 3 sequential days of dosing of each treatment (Days 31, 34 and 37). The three 12mg PR/CR treatments are as follows;

i. Ropinirole PR/CR 12mg – fasted (Treatment E)

ii. Ropinirole PR/CR 12mg – fed (standard high fat FDA breakfast) (Treatment F) (to compare with Treatment E)

iii. Ropinirole PR/CR 12mg – 3x4mg tablets in the fasted condition (G) (to compare with Treatment E)

Prior to dosing on Day 29, 12-lead ECG and vital signs (supine and standing blood pressure and pulse rate) assessment will be performed. Patients will then receive their dose of ropinirole PR/CR 12mg according to the randomisation schedule. On Day 29, patients will have ambulatory blood pressure monitored hourly from pre-dose, up to and including 12-hours post dose.

Day 30

Patients will take the study medication in the morning at the unit. Patients will be fasted from 22:00 on the evening prior to the PK assessment day (treatments E and G only).

Day 31 (PK day)

Prior to dosing on the PK Day, vital signs (supine and standing blood pressure and pulse rate), 12-lead ECG and recording of adverse events will be performed.

Patients will then receive 12mg ropinirole PR/CR in the morning. Vital signs (supine and standing blood pressure and pulse rate) measurements will be made at 4, 6, 12 and 24 hours post-dose. Serial PK blood samples will be collected for analysis of ropinirole at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose. Patients will then remain in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing.

Adverse events will be recorded at intervals post-dose and on spontaneous reporting by the patients.

All 24 hour procedures must be completed prior to the next dose of study medication.

Day 32

Prior to dosing on Day 32, 12-lead ECG and vital signs (supine and standing blood pressure and pulse rate) will be performed.

Patients will then have breakfast if appropriate and approximately 30 minutes later will receive their dose of ropinirole PR/CR 12mg.

Day 33

Patients will take the study medication in the morning at the unit. Patients will be fasted from 22:00 on the evening prior to the PK assessment day (treatments E and G only).

Day 34 (PK day)

Prior to dosing on the PK Day, vital signs (supine and standing blood pressure and pulse rate), 12-lead ECG and recording of adverse events will be performed.

Patients will then receive 12mg ropinirole PR/CR in the morning. Vital signs (supine and standing blood pressure and pulse rate) measurements will be made at 4, 6, 12 and 24 hours post-dose. Serial PK blood samples will be collected for analysis of ropinirole at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose. Patients will then remain in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing.

Adverse events will be recorded at intervals post-dose and on spontaneous reporting by the patients.

All 24 hour procedures must be completed prior to the next dose of study medication.

Day 35

Prior to dosing on Day 35, 12-lead ECG and vital signs (supine and standing blood pressure and pulse rate) will be performed.

Patients will then have breakfast if appropriate and approximately 30 minutes later will receive their dose of ropinirole PR/CR 12mg.

Day 36

Patients will take the study medication in the morning at the unit. Patients will be fasted from 22:00 on the evening prior to the PK assessment day (treatments E and G only).

Day 37 (PK day)

Prior to dosing on the PK Day, vital signs (supine and standing blood pressure and pulse rate), 12-lead ECG and recording of adverse events will be performed.

Patients will then receive 12mg ropinirole PR/CR in the morning. Vital signs (supine and standing blood pressure and pulse rate) measurements will be made at 4, 6, 12 and 24 hours post-dose. Serial PK blood samples will be collected for analysis of ropinirole at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose. Patients will then remain in a semi-supine position (bed-rest) for a minimum of 2 hours following dosing.

Adverse events will be recorded at intervals post-dose and on spontaneous reporting by the patients.

All 24 hour procedures must be completed prior to the next dose of study medication.

Days 38-44 (Down-titration)

Patient's who complete the study or withdraw from the study prematurely and have received study medication, will be down titrated over a 4-7 day period, consisting of a reduction in the daily dose for 4 days and a further reduction as necessary for the next 3 days. Patients who cease study participation whilst at the 2 mg dose level may stop taking their study medication without the need for down-titration.

Table 3 Down-Titration Schedule for study ROP109087

PR/CR Daily Dose (mg) at the end of the treatment phase	Down Titration Schedule	
	4 Days @	3 Days @
2.0	Not applicable	Not applicable
4.0	2.0	Not applicable
6.0	4.0	2.0
8.0	6.0	4.0
12.0	8.0	4.0

Follow-up

A follow-up examination will be performed 7-14 days after the last administration of study drug. This will include a physical examination, supine and standing blood pressure and pulse rate measurements and 12-lead ECG recording. Clinical chemistry, haematology and urinalysis will be assessed and adverse events (AEs) will be monitored for the preceding time interval. In addition, a urine/serum pregnancy test will be performed in WCBP.

6.3. Safety

6.3.1. Adverse Events

Adverse event (AE) monitoring will be performed once patients start dosing with study drug. Patients will be questioned regarding the occurrence of AEs at each clinic visit.

When dosing as out-patients, the patients will record any symptoms on a diary card, which will then be recorded as AEs at their next clinic visit.

6.3.2. Vital Signs and Ambulatory Blood Pressure Monitoring (ABPM)

Blood pressure and pulse rate measurements will be recorded in both the supine and standing position at the time points indicated in the Time and Events Schedule (Appendix 1).

Supine pulse and blood pressure measurements will be made after the patient has been resting supine for a period of at least 10 minutes. The patient will then stand for one minute prior to standing blood pressure and pulse measurements being taken.

If for any technical reason the standing measurement is inaccurate the first set of standing data will be discarded, the measurement will be repeated IMMEDIATELY and this data recorded in the CRF.

At the time-point of pre-dose Day 1, to establish a stable baseline, a minimum of 3 sets (and a maximum of 6 sets) of supine and standing blood pressure and pulse rate measurements will be measured. In this instance 'stable' is defined as each supine diastolic measurement being within 15mmHg of the lowest measurement. This rule also applies for the supine systolic and standing systolic and diastolic measurements.

If blood samples and blood pressure and pulse rate measurements are scheduled to be taken at the same time-point, all blood pressure and pulse rate measurements will be completed before blood samples are drawn.

On the first day at each new dose level, patients will have their blood pressure taken hourly for 12 hours post dose, using an appropriate portable ABPM device after discharge from the unit.

6.3.3. ECG

All measurement timings are detailed in the Time and Events Schedule (Appendix 1). ECGs will be measured in triplicate (10 minutes apart) at baseline and in singleton at all other time-points.

All ECGs will be obtained after the patient has rested in a supine position for at least 15 minutes. Hot and cold drinks and food should be avoided 30 minutes before each scheduled ECG recording time-point. If asleep, patients must be woken at least 15 minutes before a scheduled ECG recording time-point.

If QTc is > 500 msec (or > 530 msec in patients with Bundle Branch Block) or uncorrected QT is >600 msec, three further ECGs will be obtained at 5 minute intervals. If the mean of the three ECGs' QTc meets the above criteria then the subject will be withdrawn (see Section 9.2.1).

6.3.4. Routine Laboratory Analysis

Laboratory safety samples to include haematology, clinical chemistry and urinalysis (full details in Appendix 6) will be performed at the time-points indicated in the Time and Events Schedule (Appendix 1).

Samples will be shipped under the appropriate conditions to the relevant local laboratory for analysis if applicable.

Any results falling outside the normal range may be repeated, at the discretion of the Investigator.

A blood sample for HIV-I/II antibodies, Hepatitis B surface antigen and Hepatitis C antibody serology will be taken at screening.

6.3.5. Urine Collection for Detection of Undeclared Drugs

A urine sample for undeclared drugs will be collected at screening and pre-dose Day 1 (see Appendix 6).

6.3.6. Alcohol test

An alcohol test will be performed at screening and pre-dose Day 1 (see Appendix 6).

6.3.7. Physical Examination

All measurement timings are detailed in the Time and Events Schedule (Appendix 1).

A physical examination will be performed to ensure suitability according to the inclusion and exclusion criteria at screening, including bodyweight, and also a medical history will be recorded.

A physical examination will also be performed at the Follow-up visit or at early termination, as appropriate, to document the health status at study completion.

6.3.8. Pregnancy

6.3.8.1. Pregnancy testing

A urine/serum pregnancy test will be performed for WCBP at the time-points indicated in the Time and Events Schedule (Appendix 1).

6.3.8.2. Time period for collecting pregnancy information

The time period for collecting and recording pregnancy information will begin upon entry into the study (i.e. screening visit) and will end 5 half lives after the last dose of the study medication.

6.3.8.3. Action to be taken if pregnancy occurs

If a patient is found to be pregnant during the study, study medication will be discontinued and the patient withdrawn from the study.

Refer to SRM for ROP109087 for further details.

6.4. Pharmacokinetics

6.4.1. Pharmacokinetic Assessments

On pharmacokinetic sampling days, serial blood samples will be collected for pharmacokinetic analysis of ropinirole and its metabolites SKF-104557 and SKF-89124 at pre-dose and at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose. During the study it is estimated that a total blood volume of approximately 400 mLs will be taken from each patient.

For details of the collection procedures, see the SRM for study ROP109087.

6.4.2. Assay Methods

Samples will be assayed for ropinirole and its metabolites (SKF-104557 and SKF-89124) using the currently approved assay methodology. Sample analysis will be the responsibility of GlaxoSmithKline Worldwide Bioanalysis, DMPK, GSK.

6.5. Pharmacogenetics

Information regarding pharmacogenetic research is included in Appendix 2. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 2). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and in most cases, the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1. Dietary restrictions

During the clinical phase of the study, (except for PK days, when caffeine and xanthine-containing beverages and foods will be avoided due to the fasting period prior to the PK day), patients should maintain their usual caffeine and xanthine intake and moderate alcohol intake to a maximum of 2 units per day for women, and 3 units per days for men.

PK sampling days will be conducted in the fasted state apart from patients randomised to a high-fat breakfast at 12 mg/day. Patients will be required to consume all the breakfast. On PK days where dosing is conducted in the fasting state, patients will fast from all food and drink from 10pm the night before until 4 hours post-dose (although a single 200mL soft drink will be allowed 2h post-dose). The only other exception is that water will be allowed up to 1 hour prior to dosing and from 1 hour after dosing. Standard meals will be provided on the PK days - lunch at approx 4 h post dose and dinner at approx 9-10 h post

dose. After 4 h fluids may be consumed ad lib (within reason). On all other dosing days, subjects will take their dose after their usual breakfast. On all other dosing days, subjects will take their dose after their usual breakfast.

As regards those foods that contain possible CYP1A2-inducing constituents (broccoli, Brussels sprouts, cabbage, etc.), patients' consumption of them, and of charcoal-broiled meat, should be "stable" – i.e., patients' diets, throughout the study, should avoid the new introduction or discontinuation of these certain food items.

Poppy seed-containing food (e.g. poppy cake) will not be allowed during the three days before the pre-study examination and three days before every treatment phase because this can falsify the urine drug screen.

7.2. Other restrictions

Strenuous physical exercise (including competitive sport) will not be allowed for 48 hours before the start of the screening, treatment or follow-up periods.

Patients who smoke must record their smoking history at screening. Patients will be asked to keep their smoking habit constant throughout the study.

Following the first dose of study medication at each dose level, patients will remain supine or semi-supine (bed rest) for 2 hours post-dose (excluding vital signs recordings when patients will be required to sit and then stand).

On PK assessment days, patients will rest in a semi-supine (bed rest) position for a minimum of 2 hours post-dose.

8. INVESTIGATIONAL PRODUCT(S)

8.1. Description of Investigational Product

Ropinirole PR/CR tablets are presented as 2 mg, 4 mg, 8 mg and 12 mg tablets containing ropinirole hydrochloride equivalent to 2 mg, 4 mg, 8 mg and 12 mg of active drug substance respectively.

8.2. Dosage and Administration

Table 4 Dosage and administration details of Study ROP109087

Dosing Days	Dose (mg/day)	Administration
1-7	2	1 x Ropinirole PR/CR 2 mg tablet/day for 7 days
8-14	4	1 x Ropinirole PR/CR 4 mg tablet/day for 7 days
15-21	6	1 x Ropinirole PR/CR 4 mg tablet/day and 1 x Ropinirole PR/CR 2 mg tablet/day for 7 days
22-28	8	1 x Ropinirole PR/CR 8 mg tablet/day for 7 days
29-37	12	On Days 29, 32 and 35 patients will be randomised to take either: 1 x Ropinirole PR/CR 12mg tablet for 3 days (fasted) *or* 1 x Ropinirole PR/CR 12mg tablet for 3 days (high fat fed) *or* 3 x Ropinirole PR/CR 4mg tablets for 3 days (fasted)
38-44	Down titration	Refer to Table 3

During the study, study medication will be taken with approximately 240 mL of room temperature water in either the fasted, normal fed (ie a light breakfast) or high-fat fed state.

8.3. Dose Rationale

Ropinirole IR is administered 3 times daily (*tid*). In order to minimise peripheral dopaminergic side effects, dosing is gradually increased in multiple steps to total daily doses of 3 mg/day or higher, according to the patient's therapeutic response. Titration may require 8 weeks or longer, depending on a given patient's responsiveness and tolerance.

A prolonged-release formulation of ropinirole PR/CR is under development. The objective of this programme is to develop a formulation that will be safe and effective in the treatment of Parkinson's disease when administered once a day (od), and that can be administered using a simpler initial dose titration regime.

It is anticipated that a PR/CR formulation will improve therapy with ropinirole by enhancing ease of dosing for the patients (once daily dosing versus 3 times daily), by permitting larger dose increments during the dose titration, and/or by potentially improving the tolerability of ropinirole as a result of lower rate of rise or peak plasma drug levels. Treatment with ropinirole PR/CR *od* is not expected to increase the daily systemic exposure to ropinirole compared to dosing with ropinirole IR *tid*.

The PR/CR formulation is currently unlicensed although an NDA is scheduled to be submitted in the coming months. The development of the 12mg tablet strength is supported by safety data from the PR/CR development programme. The mean dose of the ropinirole PR/CR formulation in the pivotal efficacy studies was around 18mg/day.

Across all PD studies, 220 patients received the PR/CR formulation at a dose of >16mg (29% of the safety population in these studies) of whom 117 patients received >16mg for 52 weeks; 234 patients received a dose between >8 and <16mg, 110 for >52 weeks.

The current study is part of the phase III plans and has been designed in order to address the following pharmacokinetic objectives: (i) definitive food effect for ropinirole PR/CR at a clinically relevant dose (12mg), (ii) dosage strength equivalence for a 3 tablet combination (3x4mg vs 1x12mg), (iii) dose proportionality of the ropinirole PR/CR tablet over the therapeutic dose range 4-12mg.

8.4. Time of dosing

Dosing will be conducted in the morning in this study as the objectives of the study are pharmacokinetic in nature and require dosing to be conducted in the fasted state. The FDA definition of fasted is that study drug should be administered at least 10h after food and no food should be taken for 4h after dosing – this is best achieved when following a morning dosing regime and therefore this will be followed for this study.

8.5. Blinding

This is an open-label study.

8.6. Treatment Assignment

Patients will be assigned to study treatment in accordance with the randomisation schedule which will be created by the Clinical Pharmacology Statistics and Programming Department (CPSP) at GSK, using RandAll, prior to study start.

All eligible patients will be randomised to receive one of six treatment sequences, ABCD**EFG**, ABCD**EGF**, ABCD**FEG**, ABCD**FGE**, ABCD**GEF**, ABCD**GFE**. The regimens are as follows:

A:	2 mg PR/CR
B:	4 mg PR/CR
C:	6 mg PR/CR (1x4 mg PR/CR + 1x2 mg PR/CR)
D:	8 mg PR/CR
E:	1 x 12 mg PR/CR (fasted)
F:	1 x 12 mg PR/CR (high fat fed)
G:	3 x 4 mg PR/CR (fasted)

9. PATIENT COMPLETION AND WITHDRAWAL

9.1. Patient Completion

A patient will be deemed to have completed the study when all protocol visits (i.e. screening, treatment phase and follow-up visit) have been successfully completed.

9.2. Patient Withdrawal

9.2.1. Patient Withdrawal from Study

Patients will be withdrawn if they experience an intercurrent illness, unacceptable adverse events or a change in status with regard to exclusion criteria.

Patients will also be withdrawn should the QTc withdrawal criteria detailed in Section 6.3.3 be met, or should the liver chemistry threshold stopping criteria be triggered (Section 10.2.1).

A patient may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the patient from participating in this study at any time. If a patient is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the evaluations planned for the follow up examinations. These data will be recorded, as they comprise an essential evaluation that needs to done prior to discharging any patient from the study.

In the event that a patient is prematurely discontinued from the study at any time due to an AE (as defined in Section 10.1, "Definition of an AE") or SAE (as defined in Section 10.2, "Definition of a SAE"), the procedures stated in Section 10 ("AEs and SAEs") must be followed.

9.2.2. Patient Withdrawal from Investigational Product

A patient may withdraw (or be withdrawn) from the study prematurely for the following reasons:

- Adverse event
- Protocol deviation (including non-compliance)
- Lost to follow-up
- Termination of the study by the sponsor
- Other (must be specified)

Once a patient has discontinued study drug, the patient may not re-enter the study.

9.3. Treatment After the End of the Study

Following completion of the study, patients will washout from study medication and return to their pre-study medication.

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

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in both this section of the protocol and in the AE/SAE section of the SRM.

10.1. Definition of an AE

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

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

10.2. Definition of a SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

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

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

d. Results in disability/incapacity, or

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

interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

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

10.2.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Liver chemistry threshold stopping criteria have been designed to assure subject safety. When subjects meet the following liver chemistry threshold criteria, investigational product must be permanently withdrawn, additional testing performed, and the subject monitored until liver chemistries resolve, stabilize, or return to baseline values. The subject must then be permanently withdrawn from the study:

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

Subjects with ALT ≥3xULN **and** bilirubin ≥1.5xULN (>35% direct bilirubin; bilirubin fractionation required) must be immediately and permanently withdrawn from investigational product. Every attempt must 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 must be reported to GSK within 24 hours of learning of its occurrence. Subjects must be monitored twice weekly until liver chemistries (ALT, AST, alkaline phosphatase,

bilirubin) resolve, stabilize or return to within baseline values. Upon completion of the safety follow-up, the subject must then be withdrawn from the study.

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

In all the above situations, every attempt must be made to 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, obtained within 24 hours or 3 half-lives of last dose. 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.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if bilirubin≥1.5xULN.
- 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 report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, putative hepatotoxins, or alcohol on the concomitant medications report form.

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.

10.3. Time Period, and Frequency of Detecting AEs and SAEs

AEs and SAEs will be collected for all patients from the time of first dose of study medication until completion of the follow-up visit. From the time a patient consents to participate in the study until he or she has completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be reported promptly to GSK.

10.4. Prompt Reporting of SAEs to GSK

SAEs will be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

10.4.1. Timeframes for Submitting SAE Reports to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	"SAE" data collection tool	24 hrs	Updated "SAE" data collection tool

10.5. AE and SAE Documentation and Follow-up Procedures

The investigator will review and adhere to the following procedures, which are outlined in detail in the AE/SAE section of the SRM:

- Method of Detecting AEs and SAEs
- Recording of AEs and SAEs
- Evaluating of AEs and SAEs
- Completion and Transmission of SAE Reports to GSK
- Follow-up of AEs and SAEs
- Post-study AEs and SAEs
- Regulatory Reporting Requirements for SAEs

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Data will be entered into a computer database system by or under the auspices of, Clinical Pharmacology Data Sciences (CPDS), GlaxoSmithKline, who are registered under the relevant data protection legislation. Appropriate checks and validations, including a 100% audit of adverse events, will be performed. The database file and all associated documentation will be retained as permanent records of the study. Statistical analyses will be performed by, or under the direct auspices of, Clinical Pharmacology Statistics and Programming (CPSP), GlaxoSmithKline.

11.1. Hypotheses

For the assessment of dose proportionality of ropinirole PR/CR over the dose range of 4-12 mg, dose proportionality will be demonstrated if the 90% confidence interval of the estimated mean slope based on the power model of AUC(0-24) and Cmax are completely contained within the range 0.797 to 1.203.

For the assessment of the effect of food on absorption of ropinirole PR/CR 12 mg, an estimation approach will be adopted. Point estimates and corresponding 90% confidence intervals will be estimated for AUC(0-24) and Cmax.

For the assessment of dosage strength equivalence of ropinirole PR/CR tablet formulations (1 x 12 mg vs 3 x 4 mg), dose strength equivalence will be demonstrated if the 90% confidence interval for the ratios of both AUC(0-24) and Cmax are completely contained within the range 0.80 to 1.25.

There are no other formal statistical hypotheses to be tested with regard to safety, tolerability and pharmacokinetics. Data for the metabolites will be summarised only.

11.2. Study Design Considerations

11.2.1. Sample Size Assumptions

Approximately thirty-six patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

Based on the results of study SK101468/165, estimates of the within-subject variability for loge-transformed ropinirole AUC(0-24) and Cmax from an analysis of dose proportionality and an analysis of dosage strength equivalence, ranged between 18% and 25%.

Using a within-subject variability of 23.5%, close to the high end of the ranges observed; it is estimated that 23 evaluable patients will be required to demonstrate dose proportionality. Sample size calculations for the assessment of dose proportionality have been based on the power model, such that the 90% confidence interval of the estimated mean slope of AUC(0-24) and Cmax are completely contained within the range 0.797-1.203. The calculation was based on a two-tailed procedure on loge-transformed data

with a power of at least 90% and a type I error of 5%. No adjustments for multiple comparisons were made.

Using a within-subject variability of 23.5%, it is estimated that 25 evaluable subjects should provide at least 90% power to demonstrate dosage strength equivalence (based on two one-sided tests). Equivalence will be demonstrated if the 90% confidence interval for the ratios of both ropinirole AUC(0-24) and Cmax are completely contained within the range 0.80 and 1.25.

Using the estimate of within subject variability of 23.5% and assuming a sample size of 25 subjects, it is estimated that the lower and upper bounds of the 90% confidence intervals for the ratio of the 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 11.7% of the point estimates for AUC(0-24) and Cmax. This calculation is based on a two-tailed type 1 error rate of 10%, with no adjustment for multiple comparisons.

11.2.2. Sample Size Sensitivity

To account for the sampling error of the within-subject variability estimates used in the sample size calculations observed in study SK101468/165, a sensitivity analysis was undertaken.

The 95th percentile of the within-subject variability estimate was 31.7%. Based on variability of 31.7%, it is estimated that 25 evaluable patients should provide at least 65% power to demonstrate dose proportionality and 59% power to demonstrate dosage strength equivalence (based on two one-sided tests). Assuming a sample size of 25 patients and variability of 31.7%, the lower and upper bounds of the 90% confidence intervals for the ratio 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 16.0% of the point estimates for AUC(0-24) and Cmax.

If the within subject variability is 23.5% and assuming a ratio of 1.05 (i.e., a deviation of 5% from unity), there would be 81% power to demonstrate dose strength equivalence with 25 evaluable subjects.

11.2.3. Sample Size Re-estimation

No sample size re-estimation will be conducted for this study.

11.3. Data Analysis Considerations

11.3.1. Analysis Populations

Safety Population: All patients who receive at least one dose of study medication.

PK Concentration Population: PK concentrations may be excluded from the pharmacokinetic analysis and/or generation of mean and/or median concentration time profiles if there is insufficient concentration data, major protocol violations, incorrect dose, emesis after dosing or patients missing days of dosing.

PK Parameter Population: All patients with evaluable pharmacokinetic data from at least one session will be included in the pharmacokinetic listings. For the assessments of dosage strength equivalence (E vs G), food effect (F vs E) and dose proportionality, all patients with evaluable pharmacokinetic data from at least one of the sessions of interest will be included in the statistical analysis.

11.3.2. Analysis Data Sets

Construction of data sets relating to the populations described above will be performed in accordance with all applicable GlaxoSmithKline standards and procedures.

Patients excluded from any analyses will be fully documented and justified within the report. All analyses will be based on the actual treatment each subject received. Any departures from the planned treatment according to the randomisation schedule will be documented in the report.

11.3.3. Treatment Comparisons

There is no intention to conduct specific analyses investigating the relationship between patient gender and the effect of repeat doses of ropinirole (SKF-101468) on pharmacokinetics. Recruitment of approximately equal numbers of male and female patients is intended to ensure inclusion of reasonable numbers of both sexes and is not for the purposes of comparative gender analysis.

11.3.3.1. Primary Comparisons of Interest

- To demonstrate dose proportionality of ropinirole PR/CR over the dose range of 4 mg to 12 mg (treatments B, D, E). The estimated mean slope and 90% confidence interval will be based on the power model and will be constructed for ropinirole AUC(0-24) and Cmax. Dose proportionality of ropinirole PR/CR will be demonstrated if the 90% confidence interval of the estimated mean slope of AUC(0-24) and Cmax are completely contained within the range 0.797 to 1.203.
- To estimate the effect of food on absorption of ropinirole PR/CR at 12 mg.

  The point estimates and 90% confidence intervals will be derived for the ratio of "fed to fasted" (F:E) for ropinirole AUC(0-24) and Cmax.
- To demonstrate dose strength equivalence of ropinirole PR/CR 1 x 12 mg tablet compared to ropinirole PR/CR 3 x 4 mg tablets.

  Point estimates and 90% confidence intervals will be derived for the ratio of "ropinirole 1 x 12 mg PR/CR : ropinirole 3 x 4 mg PR/CR" (E:G). Dose strength equivalence will be demonstrated if the 90% confidence interval for the ratios of both ropinirole AUC(0-24) and Cmax are completely contained within the range 0.80 to 1.25.

11.3.3.2. Other Comparisons of Interest

Analysis of the pharmacokinetic parameter tmax will be carried out to estimate the median difference in tmax between 1 x 12 mg fed and 1 x 12 mg fasted treatments (F vs E) and between the 1 x 12 mg tablet and 3 x 4 mg tablets (E vs G).

There are no other comparisons of interest.

11.3.4. Interim Analysis

No interim analysis is planned.

11.3.5. Key Elements of Analysis Plan

All patients who withdraw prematurely from the study or the study drug will be documented and the reason for their withdrawal will be recorded in the final study report.

Missing data will be recorded as such within patient listings and no data imputation techniques will be employed.

Ropinirole AUC(0-24) and Cmax will be loge-transformed prior to the derivation of summary statistics and statistical analysis as appropriate. Tmax will not be loge-transformed.

Any deviation from the planned analysis will be documented in the Reporting and Analysis Plan (RAP) and the final study report.

11.3.5.1. Safety Analyses

No formal statistical analysis of safety data is planned. All safety data will be listed and summarised by regimen and time-point where appropriate.

11.3.5.2. Pharmacokinetic Analyses

The ropinirole, SKF-104557 and SKF-89124 plasma concentration versus time data will be presented in tabular and/or graphical form for each treatment and appropriate comparisons made. Where the data permit, pharmacokinetic analysis of the plasma concentration-time data will be performed using appropriate non-compartmental techniques.

The following pharmacokinetic parameters for ropinirole and its metabolites, SKF-104557 and SKF-89124 will be determined:

- AUC(0-24ss): Steady-state area under the plasma concentration-time profile over the dosing interval 0 to 24 hours
- Cmaxss: Steady-state maximum observed plasma concentration
- tmax: time taken to achieve Cmax

All pharmacokinetic parameters (AUC(0-24ss), Cmaxss and tmax) will be listed and summarised using summary statistics.

The following formal statistical analyses will be conducted for ropinirole PK parameters only since the metabolites do not contribute to the pharmacological activity of administered ropinirole.

Dose Proportionality Assessment

Dose proportionality of ropinirole will be assessed by fitting the loge-transformed parameters AUC(0-24ss) and Cmaxss for ropinirole PR/CR 4 to 12 mg (B, D, E) to the Power Model:

$$parameter = e^{a} (dose)^{b}$$

$$\text{ie :} \quad \log(parameter) = a + (b * \log(dose))$$

(where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality).

Dose proportionality of ropinirole PR/CR will be demonstrated if the 90% confidence interval of the estimated mean slope of AUC(0-24ss) and Cmaxss are completely contained within the range 0.797 to 1.203. If the power model has failed to converge, further investigation of dose proportionality may be performed at the discretion of the statistician. Should results from the power model indicate a deviation from linearity (confidence limits outside of the pre-specified range for dose proportionality) then an ANOVA equivalence approach comparing each dose with the reference dose may be used to provide further information. This method will use log transformed, dose normalised AUC(0-24) and Cmax parameter data.

Effect of Food

The effect of food of ropinirole PR/CR (F-E) will be assessed separately by fitting the loge-transformed parameters AUC(0-24ss) and Cmaxss to a mixed model analysis of variance (ANOVA), as appropriate to the study design. Point estimates and 90% confidence intervals will be derived for the ratio of F:E.

In addition, tmax will be analysed using a non-parametric modelling approach. Point estimates and 90% confidence intervals for the median difference between treatment groups for the comparison of 1 x 12 mg fed with 1 x 12 mg fasted (F vs E) will be presented.

Dosage Strength Equivalence

The effect of dosage strength equivalence (E-G) of ropinirole PR/CR will be assessed separately by fitting the loge-transformed parameters AUC(0-24ss) and Cmaxss to a mixed model analysis of variance (ANOVA), as appropriate to the study design. Point estimates and 90% confidence intervals will be derived for the ratio of E:G.

In addition, tmax will be analysed using a non-parametric modelling approach. Point estimates and 90% confidence intervals for the median difference between treatment groups for the comparison of 1 x 12 mg fasted with 3 x 4 mg fasted (E vs G) will be presented.

Model and distributional assumptions underlying all analyses will be assessed by visual inspection of the residuals plots. Homogeneity of variance will be assessed by plotting the studentised residuals against the predicted values from the model, whilst normality will be assessed using normal probability plots of the residuals and the random terms. If these suggest that the model is inadequate, alternative parametric or nonparametric methods will be used.

11.3.5.3. Pharmacodynamic Analyses

No pharmacodynamic analysis is planned.

12. STUDY CONDUCT CONSIDERATIONS

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

GSK will obtain favourable 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.

The study will also be conducted in accordance with "good clinical practice" (GCP), all applicable subject privacy requirements, and, the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Subject informed consent
- Investigator reporting requirements

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

Written informed consent will be obtained for each subject before he or she can participate in the study.

12.2. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also

include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study consistent with the demands of 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

12.3. 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.

12.4. 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, GCP, and GSK procedures.

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

GSK will promptly inform all other investigators or the head of the medical institution (where applicable), and/or institutions conducting the study if the study is suspended or prematurely discontinued for safety reasons. GSK will also promptly inform 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 IEC/IRB promptly and provide the reason for the suspension or premature discontinuation.

12.5. 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, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

12.6. 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.

GSK will provide the investigator with the randomization codes for their site after the statistical analysis for the entire study has been completed.

12.7. Data Management

The data collection tool for this study will be GSK-defined case report forms (CRFs). In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Original CRFs will be retained by GSK, while the investigator will retain a copy.

13. REFERENCES

[redacted] Receptor binding studies with ropinirole in rat and bovine brain membranes: an assessment of data provided by Nova Pharmaceutical Corporation, Baltimore, USA. SK&F Report Number PW019BA, June 1988.

GlaxoSmithKline Document Number ZM2004/00040/01. Investigator Brochure for Ropinirole Hydrochloride Prolonged/Extended Release Tablets (SK&F 101468) for Parkinson's Disease (European region, REQUIP-MODUTAB™; International Region, REQUIP PD 24 HOUR™; USA, REQUIP XL 24 HOUR™).

[redacted] Effects of ropinirole and its major metabolites SK&F 89124 and SK&F 104557 on CNS, dopamine receptors in-vitro, assessed using D_1 and D_2-receptor binding assays and D_2-receptor regulation of acetylcholine release. SK&F Report Number PH/0001/SKF-101468, 1 July 1991.

[redacted] The effect of ropinirole on the pressor responses evoked by sympathetic nerve stimulation in the perfused hind limb of the dog. K&F Report Number PP 002 BA, December 1986.

[redacted] Interaction of ropinirole, SK&F 89124-A and SK&F 104557-A with central adrenergic receptors. SK&F Report Number PP011BA, July 1988.

[redacted] Interaction of ropinirole and other DA2 agonists with receptor binding sites. SK&F Report Number PW023BA, October 1988.

Steinsland O S, Hieble J P: Dopaminergic inhibition of adrenergic neurotransmission as a model for studies on dopamine receptor mechanisms. Science 1978; 199:443-445.

Appendices

Appendix 1: Time and Events Table

Study Activity	Screening	Study Day																			Down-titration	Follow-Up
		1	2-7	8	9-11	12-14[a]	15	16-21	22	23-25	26-28[a]	29	30	31	32	33	34	35	36	37	38-44	
Dosing at clinic		X		X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Dosing at home			X		X			X		X												
AE recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PK blood samples[b]						X					X			X			X			X		
Blood pressure, pulse rate[e]	X	X[c]		X		X[d]	X		X		X[d]	X		X[d]	X		X[d]	X		X[d]		X
ABPM[g]		X		X			X		X			X										
12-lead ECG[h]	X	X		X		X	X		X		X	X		X	X		X	X		X		X
Laboratory safety/Urinalysis	X																					X
Alcohol test	X	X																				
Urine screen for undeclared drugs	X	X					X															
HIV/Hepatitis serology	X																					
Pregnancy test[f]	X	X					X															X
Epworth Sleepiness Scale (ESS) assessment	X																					
Physical examination	X																					X
Smoking History	X																					
Medical History (including PD History)	X																					
Con Med History	X																					
PGx sample collection[i]	←----------																			→		

continued

Appendix 1: Time and Events Table – continued

a. PK assessment days may be conducted on any day between Days 12-14 and Days 26-28 respectively
b. Serial PK samples will be drawn pre-dose and at the following times post-dose: 1h, 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 20h and 24h
c. Vital sign measurements (supine and standing) – minimum of 3 sets required (maximum of 6 sets) to establish stable baseline at pre-dose Day 1 only
d. Vital sign measurements (supine and standing) will be taken at 4h, 6h, 12h and 24h post-dose on PK assessment days
e. Vital sign measurements conducted in supine and standing position at all time-points
f. Pregnancy test performed in WCBP only
g. Patients to be provided with ABPM device to record hourly measurements up to 12h post-dose
h. ECG measurements will be performed in triplicate (10 minutes apart) at baseline and in singleton at all other time-points
i. A pharmacogenetic sample may be taken at any time during the study after informed consent for PGx sampling has been taken and Ethics Committee approval received

Appendix 2: PGx

Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx analysis include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002 and Mallal, 2002]	HLA (human leukocyte antigen)	Caucasian males with HLA B57 variant were at increased risk for experiencing hypersensitivity to abacavir
Tranilast	Restenosis prevention following coronary bypass [Roses, 2002]	UGT1A1	Drug induced hyperbilirubinemia explained by high proportion of affected patients having 7/7 TA repeat genotype, consistent with clinically benign Gilbert's Syndrome
ABT-761	Asthma [Drazen, 1999]	ALOX5	ALOX5 Sp1 promoter genotype (x,x) associated with reduced response to 5-lipoxygenase inhibitor ABT-761

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

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

Pharmacogenetic Research Objectives

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

- Relationship between genetic variants and the pharmacokinetics of investigational product
- Relationship between genetic variants and safety and/or tolerability of investigational product
- Relationship between genetic variants and efficacy of investigational product

Study Population

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

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

In addition to any blood samples take for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. The PGx sample is labeled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

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

The need to conduct PGx analysis may be identified after a study (or a set of studies) of ropinirole has been completed and the study data reviewed. For this reason, samples may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond to ropinirole. GSK or those working with GSK (for example, other researchers) will only work with samples collected from the study for the use stated in this protocol and in the informed consent form. Samples will be stored securely. Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options concerning the PGx sample, if already collected:

- PGx research continues per the subject's consent; or,
- Any remaining sample is destroyed

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

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Pharmacogenetics Analyses

The need to conduct PGx analysis may be identified after a study (or set of studies) of ropinirole has been completed and the study data reviewed. For this reason, samples may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond to ropinirole.

Generally GSK will utilize two approaches to explore genetic variation in drug response.

1. Specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease and, thus, linked to drug response.

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

2. By evaluating large numbers of polymorphic markers (e.g., single nucleotide polymorphisms or SNPs) throughout the genome, sets of markers may be identified that correspond to differential drug response.

Hardy-Weinberg Equilibrium Testing

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

Comparison of Demographic and Baseline Characteristics by Genotype

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

Evaluation of Genotypic Effects

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

Evaluation of Treatment by Genotype and Gene-Gene Interaction

In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

Linkage Disequilibrium

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

Multiple Comparisons and Multiplicity

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

Power and Sample Size Considerations

The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete.

Estimates of sample sizes required to demonstrate genotype effects vary considerably, depending on the assumptions made about allele frequency, genetic effect size, and mechanism of inheritance [Cardon, 2000]. In the work by Palmer and Cookson [Palmer, 2001], which assumed a genotype relative risk of 1.5, it was estimated that more than 300 cases and 600 controls would be needed to conduct a genetic association analysis. In contrast, McCarthy and Hilfiker [McCarthy, 2000] showed that with a genotype relative risk of 2.16 and a relatively commonly occurring genotype, only 30 cases and 30 controls would be needed to demonstrate an association.

Published PGx examples include abacavir hypersensitivity reaction [Hetherington, 2002 and Mallal, 2002] and tranilast induced hyperbilirubinemia [Roses, 2002] where genetic markers have been found to significantly associate with hypersensitivity reaction (abacavir) and hyperbilirubinemia (tranilast). These examples show that small sample sizes typically encountered in Phase I and Phase II studies may be sufficient to identify clinically relevant genetic associations.

Informed Consent

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

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

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

In general, GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results because the information generated from PGx studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstances unless required by law.

References

Cardon LR, Idury RM, Harris TJR, Witte JS, Elston RC. Testing drug response in the presence of genetic information: sampling issues for clinical trials. *Pharmacogenetics*. 2000; 10:503-10.

Drazen JM, Yandava CN, Dube L, Szcerback N, Hippensteel R, Pillari A, Israel E, Schork N, Silverman ES, Katz DA, Drajesk J. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nature Genet*. 1999; 22:168-70.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002; 359:1121-2.

Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002; 359:727-32.

McCarthy JJ, Hilfiker R. The use of single-nucleotide polymorphism maps in pharmacogenomics. *Nat Biotechnol*. 2000; 18:505-8.

Palmer LJ, Cookson WO. Using single nucleotide polymorphisms as a means to understanding the pathophysiology of asthma. *Respir Res*. 2001; 2:102-12.

Roses AD. Genome-based pharmacogenetics and the pharmaceutical industry. *Nat Rev Drug Discov*. 2002; 1:541-9.

Appendix 3: Country Specific Requirements

No country specific requirements exist.

Appendix 4: Modified Hoehn & Yahr Staging Criteria

MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

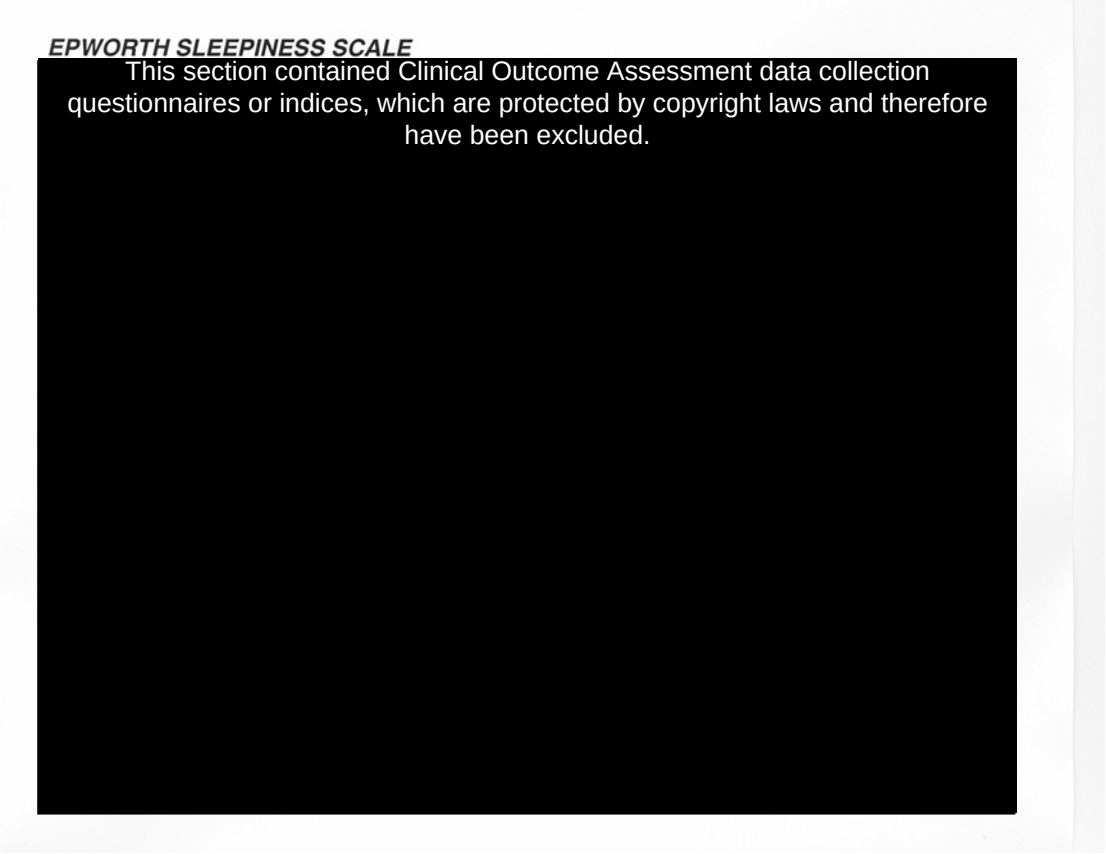
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

Appendix 5: Epworth Sleepiness Scale



Appendix 6: Clinical Laboratory Safety Assessments

Haematology, Clinical Chemistry and Urinalysis

For all patients, standard assessment for haematology, clinical chemistry and urinalysis will be performed at screening and at follow-up (see Appendix 1: Time and Events Schedule).

Haematology

1. Haemoglobin (Hb)
2. Haematocrit
3. Mean cell haemoglobin (MCH)
4. Mean cell haemoglobin concentration (MCHC)
5. Red blood cell count (RBC)
6. White blood cell count (WBC)
7. Platelets
8. Differential WBC count

Clinical Chemistry

1. Sodium
2. Potassium
3. Urea
4. Creatinine
5. Total protein
6. Albumin
7. Total bilirubin
8. Aspartate aminotransferase (AST)
9. Alanine aminotransferase (ALT)
10. Alkaline phosphatase (AP)
11. Gamma glutamyl transferase (GGT)
12. Calcium
13. Phosphate
14. Cholesterol
15. Triglycerides
16. Glucose
17. Creatine phosphokinase

18. Chloride
19. FSH/LH (screen only, female patients only, for confirmation of post-menopausal status if required)

Urinalysis

A sample of urine will be collected for urinalysis.

1. pH
2. Protein
3. Glucose
4. Bilirubin
5. Blood
6. Microscopy for cells and casts
7. Specific Gravity

Serology

A blood sample will be required at screening for serological tests for HIV-I/II antibodies, Hepatitis B surface antigen and Hepatitis C antibodies.

Urine Collection for the Detection of Undeclared Drugs

A urine sample for undeclared drugs will be collected at screening and pre-dose on Day 1. An appropriate test will be used for the detection of undeclared drugs including amphetamines, barbiturates, cannabis, cocaine, morphine and derivatives.

Pregnancy Tests

WCBP will be tested for pregnancy, using urine/serum pregnancy tests (Appendix 1: Time and Events Schedule).

Alcohol Test

An alcohol test will be performed at the study site at screening and pre-dose on Day 1.

Appendix 7: Standard Meals

FDA "High Fat" Breakfast

The High Fat meal will consist of the standardised components listed below, and will be consumed over a period of 30 minutes:

2 slices of toasted white bread with butter
2 eggs fried in butter
2 slices of bacon (15g)
4 ounces (114g) hash-browned potatoes
8 ounces (227mL) whole milk

Carbohydrate 58g, Protein 33g, Fat 67g, Calorific content approximately 1000 kcal.

Appendix 8: Protocol Changes

Rationale

Protocol Amendment 02 details the following;

- Increase in patient numbers to be recruited onto the study

Protocol Specific Changes

(A) Location in Protocol: Protocol Summary, Study Population

Changed from:

Approximately 24 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 18 patients completing the study. If practical, no further patients will be recruited to the study once 18 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 18.

Changed to:

Approximately 36 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. If practical, no further patients will be recruited to the study once 25 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

(B) Location in Protocol: Section 5 Study Population, 5.1 Number of Patients

Changed from:

Approximately 24 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 18 patients completing the study. If practical, no further patients will be recruited to the study once 18 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 18.

Changed to:

Approximately 36 male and female patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. If practical, no further patients will be recruited to the study once 25 patients have completed all study assessments. Where practical, the aim will be to recruit approximately equal numbers of male and female patients.

Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

(C) Location in Protocol: Section 11 Data Analysis and Statistical Considerations, Section 11.2 Study Design Considerations, Section 11.2.1 Sample Size Assumptions

Changed from:

Twenty-four patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 18 patients completing the study. Patients who withdraw will be replaced should the number of evaluable patients fall below 18.

Based on the results of study SK101468/165, estimates of the within-subject variability for loge-transformed ropinirole AUC(0-24) and Cmax were 18.77% and 18.07%, respectively.

Using the higher within-subject variability of 18.77%, it is estimated that 15 evaluable patients will be required to demonstrate dose proportionality. Sample size calculations for the assessment of dose proportionality have been based on the power model, such that the 90% confidence interval of the estimated mean slope of AUC(0-24) and Cmax are completely contained within the range 0.797-1.203. The calculation was based on a two-tailed procedure on loge-transformed data with a power of at least 90% and a type I error of 5%. No adjustments for multiple comparisons were made.

Using the higher within-subject variability of 18.77%, it is estimated that 17 evaluable subjects should provide at least 90% power to demonstrate dosage strength equivalence (based on two one-sided tests). Equivalence will be demonstrated if the 90% confidence interval for the ratios of both ropinirole AUC(0-24) and Cmax are completely contained within the range 0.80 and 1.25.

Using the estimates of within subject variability above and assuming a sample size of 18 subjects, it is estimated that the lower and upper bounds of the 90% confidence intervals for the ratio of the 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 11.2% of the point estimate for AUC(0-24) and within 10.8% of the point estimate for Cmax. These calculations are based on a two tailed type 1 error rate of 10%, with no adjustment for multiple comparisons.

Changed to:

Approximately thirty-six patients between 30-85 years of age will be enrolled to ensure evaluable data is obtained from a minimum of 25 patients completing the study. Patients who withdraw will be replaced should the number of evaluable patients fall below 25.

Based on the results of study SK101468/165, estimates of the within-subject variability for loge-transformed ropinirole AUC(0-24) and Cmax from an analysis of dose proportionality and an analysis of dosage strength equivalence, ranged between 18% and 25%.

Using a within-subject variability of 23.5%, close to the high end of the ranges observed; it is estimated that 23 evaluable patients will be required to demonstrate dose proportionality. Sample size calculations for the assessment of dose proportionality have been based on the power model, such that the 90% confidence interval of the estimated mean slope of AUC(0-24) and Cmax are completely contained within the range 0.797-1.203. The calculation was based on a two-tailed procedure on loge-transformed data with a power of at least 90% and a type I error of 5%. No adjustments for multiple comparisons were made.

Using a within-subject variability of 23.5%, it is estimated that 25 evaluable subjects should provide at least 90% power to demonstrate dosage strength equivalence (based on two one-sided tests). Equivalence will be demonstrated if the 90% confidence interval for the ratios of both ropinirole AUC(0-24) and Cmax are completely contained within the range 0.80 and 1.25.

Using the estimate of within subject variability of 23.5% and assuming a sample size of 25 subjects, it is estimated that the lower and upper bounds of the 90% confidence intervals for the ratio of the 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 11.7% of the point estimates for AUC(0-24) and Cmax. This calculation is based on a two-tailed type 1 error rate of 10%, with no adjustment for multiple comparisons.

(D) Location in Protocol: Section 11 Data Analysis and Statistical Considerations, Section 11.2 Study Design Considerations, Section 11.2.2 Sample Size Sensitivity

Changed from:

The 95th percentile of the variability estimates of the within-subject variability for loge-transformed ropinirole AUC(0-24) and Cmax were 22.91% and 22.05%, respectively. Using the higher variability of 22.91%, it is estimated that 18 evaluable patients should provide at least 82% power to demonstrate dose proportionality and 76% power to demonstrate dosage strength equivalence (based on two one-sided tests). Assuming a sample size of 18 patients and variability of 22.91%, the lower and upper bounds of the 90% confidence intervals for the ratio 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 13.8% of the point estimate for AUC(0-24) and 13.3% of the point estimate for Cmax.

If the within subject variability is 18.77% and assuming a ratio of 1.05 (i.e., a deviation of 5% from unity), there would be 84% power to demonstrate dose strength equivalence with 18 evaluable subjects.

Changed to:

The 95th percentile of the within-subject variability estimate was 31.7%. Based on variability of 31.7%, it is estimated that 25 evaluable patients should provide at least 65% power to demonstrate dose proportionality and 59% power to demonstrate dosage strength equivalence (based on two one-sided tests). Assuming a sample size of 25 patients and variability of 31.7%, the lower and upper bounds of the 90% confidence intervals for the ratio 1 x 12 mg (fed) : 1 x 12 mg (fasted), will be within 16.0% of the point estimates for AUC(0-24) and Cmax.

If the within subject variability is 23.5% and assuming a ratio of 1.05 (i.e., a deviation of 5% from unity), there would be 81% power to demonstrate dose strength equivalence with 25 evaluable subjects.



Case Report Form - Main

Confidential

Subject Identifier

ROP109087

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

Protocol Identifier	Subject Identifier	Centre Number	
ROP109087			

COVER SHEET - TRACKING DETAILS

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

Module Number 2

Visits included in this Module: Treatment Phase: Days 1, 8, 12-14, 15, 22, 26-28, 29, 31, 32, 34, 35, 37, Follow-up and End of Study

GlaxoSmithKline CONFIDENTIAL Final - 27 MAR 07

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
ROP109087			**Treatment Phase Day 1**

URINE DRUG SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

✓appropriate box(es)	Positive	Negative
Amphetamines	☐	☐
Barbiturates	☐	☐
Cannabis	☐	☐
Cocaine	☐	☐
Morphine and derivatives	☐	☐

If any of the above are positive, exclude subject from the study.

ALCOHOL TEST

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results *✓one:*
☐ Positive
If positive, exclude subject from the study.
☐ Negative

PREGNANCY TEST (Complete for Female Subjects of Child-bearing Potential Only)

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results
☐ Positive
If positive, exclude subject from the study.
☐ Negative

000002P ROP109087 15

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Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Treatment Phase Day 1**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg		Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
			Systolic	Diastolic		
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose 1	:			1	
2.		:			3	
3.	Pre-dose 2	:			1	
4.		:			3	
5.	Pre-dose 3	:			1	
6.		:			3	
7.	Unscheduled	:			1	
8.		:			3	
9.	Unscheduled	:			1	
10.		:			3	
11.	Unscheduled	:			1	
12.		:			3	

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Treatment Phase Day 1

12-LEAD ECG

	ECG1	ECG2	ECG3	ECG4	ECG5	ECG6
Start Date of ECG Day Month Year						
Planned Relative Time	Pre-dose 1	Pre-dose 2	Pre-dose 3	Unscheduled	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:	:	:
Ventricular Rate Beats/min						
PR Interval msec						
QRS Duration msec						
Uncorrected QT Interval msec						
QTc Interval msec						
Result of the ECG						
(enter code for result from the following list) 1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)						
[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*						

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HM2007/00444/00
ROP109087

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 1**

RANDOMISATION NUMBER

Record randomisation number.

Date of randomisation Day Month Year

Time of of randomisation Hr:Min (00:00-23:59)

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
Day 1		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_ _

_ _

_ _

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		**WORKSHEET**	**Treatment Phase** **Day 1**

AMBULATORY BLOOD PRESSURE MONITORING

Start Date	Start Time	Stop Time
Day Month Year	Hr : Min 00:00-23:59	Hr : Min 00:00-23:59
08 JAN 04	***10:20***	***10:20***
	:	**:**

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Treatment Phase Day 8**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg		Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
			Systolic	Diastolic		
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 8**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
Day 8		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		**WORKSHEET**	**Treatment Phase** **Day 8**

AMBULATORY BLOOD PRESSURE MONITORING

Start Date Day Month Year	Start Time Hr : Min 00:00-23:59	Stop Time Hr : Min 00:00-23:59
08 JAN 04	***10:20***	***10:20***
	:	**:**

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	Treatment Phase Day 12-14 (PK Assessment Day)

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	 Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	4 hrs post-dose	:			1	
4.		:			3	
5.	6 hrs post-dose	:			1	
6.		:			3	
7.	12 hrs post-dose	:			1	
8.		:			3	
9.	24 hrs post-dose	:			1	
10.		:			3	
11.	Unscheduled	:				
12.		:				
13.	Unscheduled	:				
14.		:				
15.	Unscheduled	:				
16.		:				
17.	Unscheduled	:				
18.		:				

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 12-14 (PK Assessment Day)**

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

PHARMACOKINETICS - BLOOD
INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 12-14 (PK Assessment Day)**

PHARMACOKINETICS - BLOOD

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Pre-dose		:		101
2. 1 hr post-dose		:		102
3. 2 hrs post-dose		:		103
4. 4 hrs post-dose		:		104
5. 6 hrs post-dose		:		105
6. 8 hrs post-dose		:		106
7. 10 hrs post-dose		:		107
8. 12 hrs post-dose		:		108
9. 14 hrs post-dose		:		109
10. 16 hrs post-dose		:		110
11. 20 hrs post-dose		:		111
12. 24 hrs post-dose		:		112

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087	☐☐☐☐☐☐	**WORKSHEET**	**Treatment Phase** **Day 15**

URINE DRUG SCREEN

Date and time of sample taken ☐☐ Day ☐☐☐ Month ☐☐ Year ☐☐:☐☐ Hr:Min (00:00-23:59)

✓*appropriate box(es)*	Positive	Negative
Amphetamines	☐	☐
Barbiturates	☐	☐
Cannabis	☐	☐
Cocaine	☐	☐
Morphine and derivatives	☐	☐

If any of the above are positive, exclude subject from the study.

PREGNANCY TEST (Complete for Female Subjects Only)

Date sample taken ☐☐ Day ☐☐☐ Month ☐☐ Year

Results ☐ Positive
If positive, exclude subject from the study.

☐ Negative

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	Treatment Phase Day 15

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	 Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 15**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
7. Day 12		:
8. Day 13		:
9. Day 14		:
10. Extra Dose 1 *(if required)*		:
11. Extra Dose 2 *(if required)*		:
12. Day 15		:

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_ _

_ _

_ _

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		**WORKSHEET**	**Treatment Phase** **Day 15**

AMBULATORY BLOOD PRESSURE MONITORING

Start Date Day Month Year	Start Time Hr : Min 00:00-23:59	Stop Time Hr : Min 00:00-23:59
08 JAN 04	***10:20***	***10:20***
	:	**:**

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	Treatment Phase Day 22

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	 Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 22**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
Day 22		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		**WORKSHEET**	**Treatment Phase** **Day 22**

AMBULATORY BLOOD PRESSURE MONITORING

Start Date Day Month Year	Start Time Hr : Min 00:00-23:59	Stop Time Hr : Min 00:00-23:59
08 JAN 04	***10:20***	***10:20***
	:	**:**

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	Treatment Phase Day 26-28 (PK Assessment Day)

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	Blood Pressure mmHg Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	4 hrs post-dose	:			1	
4.		:			3	
5.	6 hrs post-dose	:			1	
6.		:			3	
7.	12 hrs post-dose	:			1	
8.		:			3	
9.	24 hrs post-dose	:			1	
10.		:			3	
11.	Unscheduled	:				
12.		:				
13.	Unscheduled	:				
14.		:				
15.	Unscheduled	:				
16.		:				
17.	Unscheduled	:				
18.		:				

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 26-28 (PK Assessment Day)**

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

PHARMACOKINETICS - BLOOD
INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 26-28 (PK Assessment Day)**

PHARMACOKINETICS - BLOOD

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Predose		:		201
2. 1 hr pre-dose		:		202
3. 2 hrs post-dose		:		203
4. 4 hrs post-dose		:		204
5. 6 hrs post-dose		:		205
6. 8 hrs post-dose		:		206
7. 10 hrs post-dose		:		207
8. 12 hrs post-dose		:		208
9. 14 hrs post-dose		:		209
10. 16 hrs post-dose		:		210
11. 20 hrs post-dose		:		211
12. 24 hrs post-dose		:		212

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Treatment Phase Day 26-28 (PK Assessment Day)

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 26		:
2. Day 27		:
3. Day 28		:
4. Extra Dose 1 *(if required)*		:
5. Extra Dose 1 *(if required)*		:

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____



Protocol Identifier	ROP109087

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Treatment Phase Day 29**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg Systolic	Blood Pressure mmHg Diastolic	Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*



Protocol Identifier	ROP109087

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 29**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 29		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 29**

AMBULATORY BLOOD PRESSURE MONITORING

Start Date Day Month Year	Start Time Hr : Min 00:00-23:59	Stop Time Hr : Min 00:00-23:59
08 JAN 04	***10:20***	***10:20***
	:	**:**

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	Treatment Phase Day 31 (PK Assessment Day)

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	 Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	4 hrs post-dose	:			1	
4.		:			3	
5.	6 hrs post-dose	:			1	
6.		:			3	
7.	12 hrs post-dose	:			1	
8.		:			3	
9.	24 hrs post-dose	:			1	
10.		:			3	
11.	Unscheduled	:				
12.		:				
13.	Unscheduled	:				
14.		:				
15.	Unscheduled	:				
16.		:				
17.	Unscheduled	:				
18.		:				

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 31 (PK Assessment Day)**

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

PHARMACOKINETICS - BLOOD
INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 31 (PK Assessment Day)**

PHARMACOKINETICS - BLOOD

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Predose		:		301
2. 1 hr pre-dose		:		302
3. 2 hrs post-dose		:		303
4. 4 hrs post-dose		:		304
5. 6 hrs post-dose		:		305
6. 8 hrs post-dose		:		306
7. 10 hrs post-dose		:		307
8. 12 hrs post-dose		:		308
9. 14 hrs post-dose		:		309
10. 16 hrs post-dose		:		310
11. 20 hrs post-dose		:		311
12. 24 hrs post-dose		:		312



Protocol Identifier	ROP109087

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 31 (PK Assessment Day)**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 30		:
2. Day 31		:

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			Treatment Phase Day 32

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg Systolic	Blood Pressure mmHg Diastolic	Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
e.g., 01 JAN 03	*15 min*	*13:02*	*110*	*80*	*1*	*75*
1.	Pre-dose	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 32**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 32		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Treatment Phase Day 34 (PK Assessment Day)**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg		Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
			Systolic	Diastolic		
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	4 hrs post-dose	:			1	
4.		:			3	
5.	6 hrs post-dose	:			1	
6.		:			3	
7.	12 hrs post-dose	:			1	
8.		:			3	
9.	24 hrs post-dose	:			1	
10.		:			3	
11.	Unscheduled	:				
12.		:				
13.	Unscheduled	:				
14.		:				
15.	Unscheduled	:				
16.		:				
17.	Unscheduled	:				
18.		:				

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 34 (PK Assessment Day)**

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

PHARMACOKINETICS - BLOOD
INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 34 (PK Assessment Day)**

PHARMACOKINETICS - BLOOD

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Predose		:		401
2. 1 hr pre-dose		:		402
3. 2 hrs post-dose		:		403
4. 4 hrs post-dose		:		404
5. 6 hrs post-dose		:		405
6. 8 hrs post-dose		:		406
7. 10 hrs post-dose		:		407
8. 12 hrs post-dose		:		408
9. 14 hrs post-dose		:		409
10. 16 hrs post-dose		:		410
11. 20 hrs post-dose		:		411
12. 24 hrs post-dose		:		412



Protocol Identifier	ROP109087

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 34 (PK Assessment Day)**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 33		:
2. Day 34		:

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Treatment Phase Day 35**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg		Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
			Systolic	Diastolic		
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*



Protocol Identifier	ROP109087

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 35**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 35		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	Treatment Phase Day 37 (PK Assessment Day)

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	 Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Pre-dose	:			1	
2.		:			3	
3.	4 hrs post-dose	:			1	
4.		:			3	
5.	6 hrs post-dose	:			1	
6.		:			3	
7.	12 hrs post-dose	:			1	
8.		:			3	
9.	24 hrs post-dose	:			1	
10.		:			3	
11.	Unscheduled	:				
12.		:				
13.	Unscheduled	:				
14.		:				
15.	Unscheduled	:				
16.		:				
17.	Unscheduled	:				
18.		:				

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 37 (PK Assessment Day)**

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Pre-dose	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*



Protocol Identifier	ROP109087

PHARMACOKINETICS - BLOOD
INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Treatment Phase Day 37 (PK Assessment Day)

PHARMACOKINETICS - BLOOD

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Predose		:		501
2. 1 hr pre-dose		:		502
3. 2 hrs post-dose		:		503
4. 4 hrs post-dose		:		504
5. 6 hrs post-dose		:		505
6. 8 hrs post-dose		:		506
7. 10 hrs post-dose		:		507
8. 12 hrs post-dose		:		508
9. 14 hrs post-dose		:		509
10. 16 hrs post-dose		:		510
11. 20 hrs post-dose		:		511
12. 24 hrs post-dose		:		512



Protocol Identifier	ROP109087

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Treatment Phase Day 37 (PK Assessment Day)**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 36		:
2. Day 37		:

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS

- Check carefully for any overlapping start/stop dates.
- Ensure any deviations from investigational product are recorded correctly as outlined in the study protocol.

Protocol Identifier	Subject Identifier	Visit Date	Visit Description
ROP109087		Day Month Year	**Down -Titration Day 38-44**

INVESTIGATIONAL PRODUCT

Planned Timepoint	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
e.g., 2 hours	***05 JUN 03***	***10:54***
1. Day 38		:
2. Day 39		:
3. Day 40		
4. Day 41		
5. Day 42		
6. Day 43		

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087		WORKSHEET	Follow-up

PHYSICAL EXAMINATION

Date of Assessment ☐☐ Day ☐☐☐ Month ☐☐ Year

Indicate current physical findings by ✓ the appropriate box(es) below and if ABNORMAL, describe concisely: [different findings should be separated by either a (;) or a (/)].

	Normal	Abnormal	Not Done	
1. Hair and skin	☐	☐		_____
2. Lymph nodes	☐	☐		_____
3. Eyes	☐	☐		_____
4. Ears, Nose and Throat	☐	☐		_____
5. Breasts	☐	☐	☐	_____
6. Respiratory	☐	☐		_____
7. Cardiovascular	☐	☐		_____
8. Abdomen	☐	☐		_____
9. Urogenital	☐	☐	☐	_____
10. Pelvic	☐	☐	☐	_____
11. Rectal	☐	☐	☐	_____
12. Musculoskeletal	☐	☐		_____
13. Neurological	☐	☐		_____
14. Mental Status	☐	☐		_____

PREGNANCY TEST (Complete for Female Subjects Only)

Date sample taken ☐☐ Day ☐☐☐ Month ☐☐ Year

Results ☐ Positive

☐ Negative

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Follow-up**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure mmHg Systolic	Blood Pressure mmHg Diastolic	Subject Position (1 = Supine 3 = Standing)	Heart Rate (beats/min)
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Follow-up	:			1	
2.		:			3	
3.	Unscheduled	:				
4.		:				
5.	Unscheduled	:				
6.		:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Follow-up	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

LOCAL LABORATORY RESULT DATA (Haematology / Clinical Chemistry)

INVESTIGATOR INSTRUCTIONS

- If the laboratory changes during the study, a new set of reference ranges must be provided to GSK.
- Enter 'NR' (the abbreviation for 'No result') if the laboratory results are not available to report or if a lab error occurred.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Follow-up

LOCAL LABORATORY RESULT DATA (HAEMATOLOGY)

Date and time sample taken Day Month Year Hr:Min (00:00-23:59)

Laboratory name _

Address _

_ _

Lab ID
(For GSK use only)

Has the subject fasted?

[Y] ☐ Yes [N] ☐ No

Laboratory Test Haematology	**Result**
Haemoglobin (Hb)	
Haematocrit	
Mean cell haemoglobin (MCH)	
Mean cell haemoglobin concentration (MCHC)	
Red blood cell count (RBC)	
White blood cell count (WBC)	
Platelets	
Lymphocytes	
Neutrophils	
Monocytes	
Basophils	
Eosinophils	

Units for differential

[1] ☐ Percent [2] ☐ Absolute count

If the laboratory results meet the protocol definition of an adverse event, record the details on the Non-Serious Adverse Events page or Serious Adverse Event page.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Follow-up

LOCAL LABORATORY RESULT DATA - (CLINICAL CHEMISTRY)

Date and time sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

Laboratory name_ _

Address _

_ _

Lab ID
(For GSK use only)

Has the subject fasted?

[Y] ☐ Yes [N] ☐ No

Laboratory Test Clinical Chemistry	**Result**
Sodium	
Potassium	
Urea	
Creatinine	
Total protein	
Albumin	
Total bilirubin	
Aspartate aminotransferase (AST)	
Alanine aminotransferase (ALT)	
Alkaline phosphatase (AP)	
Gamma glutamyl transferase (GGT)	
Calcium	
Phosphate	
Cholesterol	
Triglycerides	
Glucose	
Creatine phosphokinase	
Chloride	

If the laboratory results meet the protocol definition of an adverse event, record the details on the Non-Serious Adverse Events page or Serious Adverse Event page.



Protocol Identifier	ROP109087

URINALYSIS
INVESTIGATOR INSTRUCTIONS

- If the laboratory changes during the study, a new set of reference ranges must be provided to GSK.
- If the laboratory results are not available to report or if a lab error occurred, enter "NR" (the abbreviation for 'No Result')
- If a further sample is taken, record results on the Unscheduled Page.

Code Results as shown below where appropriate:

NEG = none or negative
TRA = trace
1+ = + or 1+
2+ = ++ or 2+
3+ = +++ or 3+
4+ = ++++ or 4+
5+ = +++++ or 5+

URINALYSIS
MONITOR DATA VALIDATION CHECK

- Check that results are provided using appropriate codes as outlined in the instructions above.

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Follow-up

URINALYSIS

Date and time sample taken Day Month Year Hr:Min (00:00-23:59)

Laboratory name _____

Address _____

_____

Lab ID
(For GSK use only)

Urinalysis (Dipstick) Test	Result
pH	
Protein	
Glucose	
Bilirubin	
Blood	
Specific Gravity	

[1] *See facing page for results codes or enter numeric values as appropriate*

Note: Sedimentary microscopy should only be performed if any of the dipstick results are abnormal.

Was sedimentary microscopy performed?

[Y] ☐ Yes [N] ☐ No

Urinalysis (Microscopy) Test	Result
White blood cells	
Red blood cells	
Hyaline casts	
Granular casts	
Cellular casts	

Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) section(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE.

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Unscheduled

12-LEAD ECG ABNORMALITIES

Date of ECG Day Month Year Time of ECG Hr:Min (00:00-23:59)

Record clinically significant abnormalities below. ✓ all that apply:

A. Rhythm

[A1] ☐ Sinus bradycardia
[A21] ☐ Sinus bradycardia (heart rate 40-50 beats/min)
[A22] ☐ Sinus bradycardia (heart rate 30-39 beats/min)
[A23] ☐ Sinus bradycardia (heart rate < 30 beats/min)
[A3] ☐ Sinus pause
[A2] ☐ Sinus tachycardia (heart rate >100 beats/min)
[A4] ☐ Ectopic supraventricular beats
[A20] ☐ Ectopic supraventricular rhythm
[A17] ☐ Wandering atrial pacemaker
[A26] ☐ Multifocal atrial tachycardia (Wandering atrial pacemaker with heart rate >100 beats/min)
[A6] ☐ Supraventricular tachycardia (heart rate >100 beats/min)
[A7] ☐ Atrial flutter
[A8] ☐ Atrial fibrillation
[A5] ☐ Junctional rhythm (heart rate ≤100 beats/min)
[A25] ☐ Junctional rhythm
[A24] ☐ Junctional tachycardia (heart rate > 100 beats/min)
[A9] ☐ Ectopic ventricular beats

[A12] ☐ Ventricular couplets
[A13] ☐ Bigeminy
[A28] ☐ Trigeminy
[A14] ☐ Electrical alternans
[A29] ☐ R on T phenomenon
[A18] ☐ Ventricular fibrillation
[A19] ☐ Idioventricular rhythm (heart rate < 100 beats/min)
[A10] ☐ Sustained ventricular tachycardia
[A11] ☐ Non-sustained ventricular tachycardia
[A32] ☐ Wide QRS Tachycardia (diagnosis unknown)
[A27] ☐ Ventricular tachycardia
[A30] ☐ Monomorphic ventricular tachycardia
[A15] ☐ Torsades de Pointes (Polymorphic ventricular tachycardia with prolonged QT)
[A31] ☐ Polymorphic (sustained and non-sustained) ventricular tachycardia
[A16] ☐ Artificial pacemaker
[A99] ☐ Other abnormal rhythm

Comment _

B. P-Wave and QRS Morphology

[B1] ☐ Left atrial abnormality (P mitrale)
[B2] ☐ Right atrial abnormality (P pulmonale)
[B3] ☐ Right ventricular hypertrophy
[B5] ☐ Intraatrial conduction delay

[D14] ☐ Increased voltage consistent with left ventricular hypertrophy
[B99] ☐ Other morphology

Comment _

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Unscheduled

12-LEAD ECG ABNORMALITIES (Continued)

C. Conduction

[C1] ☐ First degree AV block (PR interval > 200 msec)
[C20] ☐ Short PR interval
[C2] ☐ Second degree AV block (Mobitz type 1)
[C3] ☐ Second degree AV block (Mobitz type 2)
[C16] ☐ 2:1 AV block
[C4] ☐ Third degree AV block
[C5] ☐ Left axis deviation (QRS axis more negative than -30°)
[C6] ☐ Right axis deviation (QRS axis more positive than +110°)
[C7] ☐ Incomplete right bundle branch block
[C13] ☐ Incomplete left bundle branch block
[C8] ☐ Right bundle branch block
[C14] ☐ Left anterior hemiblock (synonymous to left anterior fascicular block)
[C15] ☐ Left posterior hemiblock (synonymous to left posterior fascicular block)
[C9] ☐ Left bundle branch block
[C17] ☐ Bifascicular block
[C10] ☐ Non-specific intraventricular conduction delay (QRS ≥120 msec)
[C11] ☐ Accessory pathway (Wolff-Parkinson White, Lown-Ganong-Levine)
[C19] ☐ Prolonged QT interval
[C12] ☐ QT/QTc prolongation ≥ 500 msec
[C18] ☐ AV dissociation
[C99] ☐ Other conduction

Comment _

D. Myocardial Infarction

[D1] ☐ Myocardial infarction, old
[D2] ☐ Myocardial infarction, anterior
[D3] ☐ Myocardial infarction, lateral
[D4] ☐ Myocardial infarction, posterior
[D5] ☐ Myocardial infarction, inferior
[D6] ☐ Myocardial infarction, septal
[D20] ☐ Myocardial infarction, Non-Q wave
[D98] ☐ Other myocardial infarction

Comment _

E. Depolarisation/Repolarisation (QRS-T)

[D7] ☐ Non-specific ST-T changes
[D19] ☐ J point elevation
[D8] ☐ ST elevation
[D21] ☐ ST elevation-pericarditis
[D9] ☐ ST depression
[D96] ☐ ST segment abnormality, not specified
[D10] ☐ U waves abnormal
[D11] ☐ T wave inversion
[D12] ☐ T wave peaked
[D15] ☐ T waves flat
[D16] ☐ T waves biphasic
[D18] ☐ Notched T-waves
[D13] ☐ Low QRS voltage
[D17] ☐ T-wave flattening/inversion
[D97] ☐ T wave abnormality, not specified
[D99] ☐ Other depolarisation/repolarisation

Comment _

Other Abnormalities

[E99] ☐ Other abnormalities

Comment _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			**Unscheduled**

PHARMACOKINETICS - BLOOD

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Unscheduled		:		801
2. Unscheduled		:		802
3. Unscheduled		:		803
4. Unscheduled		:		804

LIVER EVENTS ASSESSMENT

If a liver event has occurred, complete the Liver Events Assessment page in the End of Study section of the CRF.

LOCAL LABORATORY RESULT DATA (Haematology / Clinical Chemistry)

INVESTIGATOR INSTRUCTIONS

- If the laboratory changes during the study, a new set of reference ranges must be provided to GSK.
- Enter 'NR' (the abbreviation for 'No result') if the laboratory results are not available to report or if a lab error occurred.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Unscheduled

LOCAL LABORATORY RESULT DATA (HAEMATOLOGY)

Date and time sample taken Day Month Year Hr:Min (00:00-23:59)

Laboratory name _____

Address _____

_____

Lab ID
(For GSK use only)

Has the subject fasted?

[Y] ☐ Yes [N] ☐ No

Laboratory Test Haematology	Result
Haemoglobin (Hb)	
Haematocrit	
Mean cell haemoglobin (MCH)	
Mean cell haemoglobin concentration (MCHC)	
Red blood cell count (RBC)	
White blood cell count (WBC)	
Platelets	
Lymphocytes	
Neutrophils	
Monocytes	
Basophils	
Eosinophils	

Units for differential

[1] ☐ Percent [2] ☐ Absolute count

If the laboratory results meet the protocol definition of an adverse event, record the details on the Non-Serious Adverse Events page or Serious Adverse Event page.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Unscheduled

LOCAL LABORATORY RESULT DATA - (CLINICAL CHEMISTRY)

Date and time sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

Laboratory name_ _

Address _

_ _

Lab ID
(For GSK use only)

Has the subject fasted?

[Y] ☐ Yes [N] ☐ No

Laboratory Test Clinical Chemistry	**Result**
Sodium	
Potassium	
Urea	
Creatinine	
Total protein	
Albumin	
Total bilirubin	
Aspartate aminotransferase (AST)	
Alanine aminotransferase (ALT)	
Alkaline phosphatase (AP)	
Gamma glutamyl transferase (GGT)	
Calcium	
Phosphate	
Cholesterol	
Triglycerides	
Glucose	
Creatine phosphokinase	
Chloride	

If the laboratory results meet the protocol definition of an adverse event, record the details on the Non-Serious Adverse Events page or Serious Adverse Event page.



Protocol Identifier	ROP109087

URINALYSIS
INVESTIGATOR INSTRUCTIONS

- If the laboratory changes during the study, a new set of reference ranges must be provided to GSK.
- If the laboratory results are not available to report or if a lab error occurred, enter "NR" (the abbreviation for 'No Result')
- If a further sample is taken, record results on the Unscheduled Page.

Code Results as shown below where appropriate:

NEG = none or negative
TRA = trace
1+ = + or 1+
2+ = ++ or 2+
3+ = +++ or 3+
4+ = ++++ or 4+
5+ = +++++ or 5+

URINALYSIS
MONITOR DATA VALIDATION CHECK

- Check that results are provided using appropriate codes as outlined in the instructions above.

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Unscheduled

URINALYSIS

Date and time sample taken Day Month Year Hr:Min (00:00-23:59)

Laboratory name _____

Address _____

_____

Lab ID
(For GSK use only)

Urinalysis (Dipstick) Test	Result
pH	
Protein	
Glucose	
Bilirubin	
Blood	
Specific Gravity	

[1] *See facing page for results codes or enter numeric values as appropriate*

Note: Sedimentary microscopy should only be performed if any of the dipstick results are abnormal.

Was sedimentary microscopy performed?

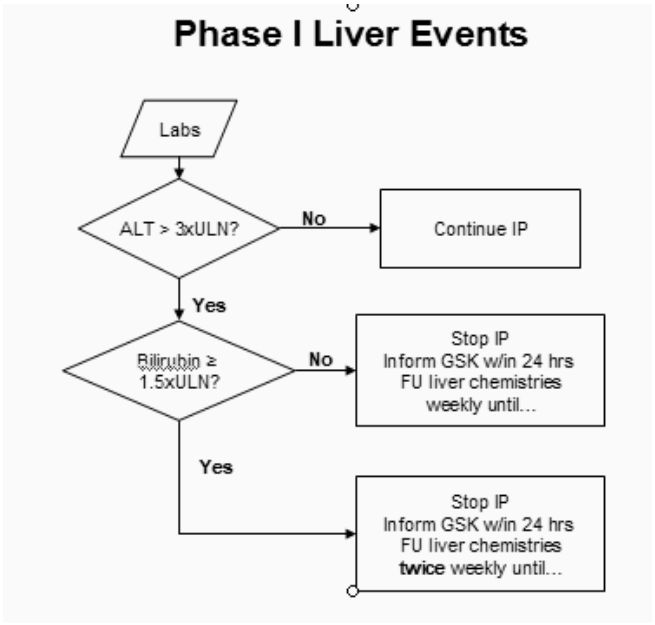
[Y] ☐ Yes [N] ☐ No

Urinalysis (Microscopy) Test	Result
White blood cells	
Red blood cells	
Hyaline casts	
Granular casts	
Cellular casts	

Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) section(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE.

LIVER EVENTS ASSESSMENT

DECISION TREE FOR LIVER EVENTS



LIVER EVENTS ASSESSMENT
INVESTIGATOR INSTRUCTIONS

- **If subject exhibits** ALT ≥3xULN, stop investigational product, complete date stopped on Investigational Product form and contact GSK within 24 hours of occurrence. Follow-up liver chemistry (ALT, AST, alkaline phosphatase, bilirubin) should be obtained at weekly intervals until values resolve, stabilize or return to within baseline values.
- **If subject exhibits** concomitant ALT ≥3xULN **and** bilirubin ≥1.5xULN, stop investigational product, complete date stopped on Investigational Product form and contact GSK within 24 hours of occurrence. Follow-up liver chemistries should be obtained at twice weekly intervals until values normalise, substantively improve, or stabilise.

Protocol Identifier	Subject Identifier	
ROP109087		

LIVER EVENTS ASSESSMENT

Have liver chemistry results reached or exceeded protocol-defined investigational product stopping criteria?

[Y] ☐ Yes [N] ☐ No

If Yes, stop investigational product, complete date stopped on Investigational Product form, contact GSK within 24 hours of occurrence, complete Liver Events Form and obtain the following tests:

- *PK blood sample within 24 hours of last dose (or 3x the investigational product half-life or t1/2).*
- *Hepatitis A: Hepatitis A IgM antibody.*
- *Hepatitis B: Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).*
- *Hepatitis C: Hepatitis C RNA.*
- *Hepatitis E IgM antibody (if subject resides or has travelled in past 3 months outside the USA or Canada).*
- *Cytomegalovirus IgM antibody (CMV)*
- *EBV (Epstein Barr viral capsid antigen IgM antibody) or if unavailable, obtain heterophile antibody or monospot testing.*
- *CPK (serum creatine phosphokinase)*
- LDH *(lactate dehydrogenase)*
- *Bilirubin fractionation, if bilirubin ≥1.5xULN*

The following are only needed when ALT ≥3xULN and bilirubin ≥1.5xULN (>35% direct)

- *Anti-nuclear antibody*
- *Anti-smooth muscle antibody*
- *Type 1 anti-liver kidney microsomal antibodies (if available)*
- *Liver Imaging (ultrasound, magnetic resonance, or computerised tomography)*



Protocol Identifier	ROP109087

INVESTIGATIONAL PRODUCT DISCONTINUATION

INVESTIGATOR INSTRUCTIONS

Complete this page when the subject completes the investigational product scheduled treatment period or when the subject prematurely discontinues investigational product.

MONITOR DATA VALIDATION CHECKS

- If the subject was withdrawn from the study at the same time as the investigational product was discontinued, ensure that the reasons for the two discontinuations are consistent.
- **If investigational product was discontinued prior to the end of the scheduled treatment period due to an adverse event**, confirm that details recorded correspond with details on the Adverse Event and Study Conclusion pages:
  - 'Withdrawal' on the AE/SAE page is recorded as 'Yes'.
  - 'Action Taken with Investigational Product(s) as a Result of the Non-Serious AE' on the AE/SAE page is recorded as 'Investigational Product Withdrawn'.
  - 'Primary Reason Investigational Product was Stopped' on the Investigational Product Discontinuation page is recorded as 'Adverse Event'.
  - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'

Protocol Identifier	Subject Identifier	
ROP109087		

INVESTIGATIONAL PRODUCT DISCONTINUATION

Was the investigational product stopped **permanently** before the end of the scheduled treatment period?

[Y] ☐ Yes [N] ☐ No

If Yes, ✓ the primary reason the investigational product was stopped:

[1] ☐ Adverse event
Record details on the Non-Serious Adverse Events or Serious Adverse Event pages as appropriate.

[2] ☐ Lost to follow-up

[3] ☐ Protocol violation

[4] ☐ Subject decided to withdraw from the study

[6] ☐ Sponsor terminated study

[Z] ☐ Other, *specify* _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _



Protocol Identifier	ROP109087

PHARMACOGENETIC (PGx) RESEARCH
INVESTIGATOR INSTRUCTIONS

CONSENT FOR PGx RESEARCH

The question "Has informed consent been obtained for PGx research?" should be completed at any time between Screening and Day 44.

- If the question is answered **No**, ✓ one box for reason and **do not** complete the remainder of the page.

WITHDRAWAL OF CONSENT

The question "Has subject withdrawn consent for PGx research?" **must be completed immediately** if the subject withdraws consent. Otherwise, it must be completed when the subject leaves the study. It must be completed for all subjects for whom informed consent was obtained for pharmacogenetic (PGx) research.

- If consent is withdrawn, the investigator will fax the completed form (Request/Notification for Destruction of Sample for Pharmacogenetic Research, F-GRD-001) to the monitor within 5 working days of destruction and retain form in the clinical study file and, where appropriate, the designated laboratory within 5 working days of the subject's premature discontinuation in the study.

BLOOD SAMPLE DESTRUCTION

Do **not** complete this section if a blood sample was not collected.

The question "Has a request been made for blood sample destruction?" must be completed immediately if there is a request for sample destruction. Otherwise, it must be completed when the subject leaves the study. It must be completed for all subjects for whom a blood sample was obtained for pharmacogenetic (PGx) research.

- If the question is answered Yes, ✓one box for reason.

Protocol Identifier	Subject Identifier	
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PHARMACOGENETIC (PGx) RESEARCH

CONSENT FOR PGx RESEARCH (DNA)

Has informed consent been obtained for PGx research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date informed consent obtained for PGx research Day Month Year

If No, ✓one reason:

[1] ☐ Subject declined
[2] ☐ Subject not asked by Investigator
[Z] ☐ Other, *specify* _____

BLOOD SAMPLE COLLECTION (DNA)

Has a blood sample been collected for PGx research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date sample taken Day Month Year

WITHDRAWAL OF CONSENT FOR PGx (DNA)

Has subject withdrawn consent for PGx research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date informed consent withdrawn for PGx research Day Month Year

BLOOD SAMPLE DESTRUCTION

Has a request been made for blood sample destruction?

[Y] ☐ Yes [N] ☐ No

If Yes, ✓one reason:

[3] ☐ Subject withdrew consent for PGx
[2] ☐ Screen failure
[Z] ☐ Other, *specify* _____

CONCOMITANT MEDICATIONS
INVESTIGATOR INSTRUCTIONS

- Record unknown months as UNK.
- The following lists of abbreviations are examples which can be used to aid the completion of the appropriate items on the Concomitant Medications page. These are not all inclusive lists and are for guidance only, other abbreviations not listed may be used if necessary.

UNITS

Abbreviation		Label
TAB	=	Tablet
MCL	=	Microlitre
ML	=	Millilitre
L	=	Litre
MCG	=	Microgram
MG	=	Milligram
G	=	Gram

FREQUENCY

Abbreviation		Label
OD/QD	=	1 x Daily
BID	=	2 x Daily
TID	=	3 x Daily
QID	=	4 x Daily
PRN	=	As required

ROUTE

Abbreviation		Label
IM	=	Intramuscular
IH	=	Inhalation
IV	=	Intravenous
NS	=	Nasal
TP	=	Topical
PO	=	Oral
VG	=	Vaginal



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CONCOMITANT MEDICATIONS
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Ensure that the spelling of the Drug Name(s) is correct (use of Trade Names is preferred).
- Check that either medication start date is completed **or** 'Taken Prior to Study?' is 'Yes'.
  - It is acceptable for start date to be missing if 'Taken Prior to Study?' is 'Yes'.
  - It is acceptable if 'Taken Prior to Study?' is 'Yes' and a start date is present, as long as the start date is prior to the date of the subject's initial visit.
- Check that either medication stop date is completed or 'Ongoing Medication?' is 'Yes'.
  - It is acceptable for stop date to be missing if 'Ongoing Medication?' is 'Yes'.
- Ensure that the 'Reason for Medication' is recorded on one of the following pages using the same terms:
  - Current Medical Conditions
  - Non-Serious Adverse Events
  - Serious Adverse Events Form

Protocol Identifier	Subject Identifier	
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CONCOMITANT MEDICATIONS

Were any concomitant medications taken by the subject prior to screening and/or during the study?

[Y] ☐ Yes [N] ☐ No

If Yes, record each medication on a separate line using Trade Names where possible. If the medication is related to a Non-Serious Adverse Event or Serious Adverse Event, details should be expressed using the same terminology.

Drug Name (Trade Name preferred)	Unit Dose	Units[1]	Frequency[1]	Route[1]	Reason for Medication	Start Date (Day Month Year)	Start Time (Hr : Min 00:00-23:59)	Taken Prior to Study? (Y=Yes N=No)	Stop Date (Day Month Year)	Stop Time (Hr : Min 00:00-23:59)	Ongoing Medication? (Y=Yes N=No)
e.g., Aspirin	***200***	***mg***	***BID***	***PO***	***Headache***	***31 MAY 03***	***14:10***	***N***	***31 MAY 03***	***23:00***	***N***
1.							:			:	
2.							:			:	
3.							:			:	
4.							:			:	
5.							:			:	
6.							:			:	
7.							:			:	
8.							:			:	

[1] *For Units, Frequency and Route see facing page for examples of acceptable abbreviations.*

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DEFINITION OF A NON-SERIOUS ADVERSE EVENT (AE) (Page 1 of 3)

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

Examples of an AE **include:**

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) 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 should not be reported as an AE/SAE).

Examples of an AE **do NOT include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen). See protocol for clarification.

IF THIS EVENT MEETS THE DEFINITION OF SERIOUS, COMPLETE THE SERIOUS ADVERSE EVENT SECTION

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NON-SERIOUS ADVERSE EVENTS (AE) (Page 2 of 3)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Start dates must be provided for the reporting of adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Non-Serious Adverse Events pages.
- Non-serious adverse event terms should be reviewed for potential SAEs per protocol.
- Confirm that any adverse events marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an adverse event, confirm that the following variables are consistent for the adverse event which resulted in withdrawal:
  - If investigational product was permanently withdrawn due to an adverse event ...
    - 'Primary Reason Investigational Product was Stopped' on the Investigational Product Discontinuation page is recorded as 'Adverse Event'.
    - Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - Withdrawal' on the Non-Serious Adverse Events page is recorded as 'Yes'.
    - Action Taken with Investigational Product(s) as a Result of the Non-Serious AE' on the Non-Serious Adverse Events page is recorded as 'Investigational Product Withdrawn'.

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INSTRUCTIONS FOR COMPLETING NON-SERIOUS ADVERSE EVENTS (AE) (Page 3 of 3)

Diagnosis	Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available, then this should be entered and the sign or symptom crossed out, initialled and dated by the investigator. If this non-serious event progresses to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date **Start Time**	Record the start date of the first occurrence of the AE. Record the start time of the AE.
Outcome	All AEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the AE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the AE was ongoing at the time of death, but was not the cause of death.
End Date **End Time**	Record the end date. This is the date the AE Recovered/Resolved. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the AE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the AE.
Frequency	Select either single episode or intermittent. Intermittent should be used if the subject experiences the same AE on multiple occasions over a period of time (e.g., dizziness). In these circumstances, the start date will be the start date of the first episode and the end date will be the date of resolution.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. 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. Not applicable = those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was stopped temporarily but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre-or post-dosing).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
Relationship to Investigational Product(s)	It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

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Protocol Identifier	Subject Identifier	
ROP109087		

NON-SERIOUS ADVERSE EVENTS (AE)

*Note: If this is a **Serious Adverse Event (SAE), do not complete this form**, go to the SAE section and complete the SAE form.*

Did the subject experience any non-serious adverse events during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

Event	Start Date	Start Time	Outcome	End Date	End Time	Frequency	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	With-drawal	Relation-ship to Investigational Product(s)
Diagnosis Only *(if known)* Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae	Day Month Year	Hr : Min 00:00-23:59	1=Single episode 2=Intermit-tent	1=Mild 2=Moderate 3=Severe X=Not appli-cable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this AE? Y=Yes[1] N=No	Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No
e.g., Headache	***25 JAN 03***	***13:25***	***1***	***27 JAN 03***	***10:20***	***1***	***1***	***4***	***Y***	***Y***
1.		:			:					
2.		:			:					
3.		:			:					
4.		:			:					
5.		:			:					
6.		:			:					

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

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Protocol Identifier	Subject Identifier	
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NON-SERIOUS ADVERSE EVENTS (AE) (Continued)

*Note: If this is a **Serious Adverse Event (SAE), do not complete this form**, go to the SAE section and complete the SAE form.*

Event	Start Date	Start Time	Outcome	End Date	End Time	Frequency	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	With-drawal	Relation-ship to Investigational Product(s)
Diagnosis Only *(if known)* Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae	Day Month Year	Hr : Min 00:00-23:59	1=Single episode 2=Intermit-tent	1=Mild 2=Moderate 3=Severe X=Not appli-cable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this AE? Y=Yes[1] N=No	Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No
e.g., Headache	***25 JAN 03***	***13:25***	***1***	***27 JAN 03***	***10:20***	***1***	***1***	***4***	***Y***	***Y***
1.		:			:					
2.		:			:					
3.		:			:					
4.		:			:					
5.		:			:					
6.		:			:					

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

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DEFINITION OF A SERIOUS ADVERSE EVENT (SAE) (Page 1 of 5)

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

a) results in death.

b) is life-threatening.

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

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation 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, diarrhoea, 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) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise 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 hospitalisation, or development of drug dependency or drug abuse.

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SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 5)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
  - If investigational product was permanently withdrawn due to an adverse event ...
    - 'Primary Reason Investigational Product was Stopped' on the Investigational Product Discontinuation page is recorded as 'Adverse Event'.
    - Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - Withdrawal' on the SAE page is recorded as 'Yes'.
    - Action Taken with Investigational Product(s) as a Result of the SAE' on the SAE page is recorded as 'Investigational Product Withdrawn'.

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THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY FAX OR TELEPHONE (FAX PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. (The original pages must remain in the Case Report Form/Study File).

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 3 of 5)

Diagnosis	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date **Start Time**	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
Outcome	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
End Date **End Time**	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/ Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. 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 everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the SAE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was temporarily interrupted but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue IP(s).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
Relationship to Investigational Product(s)	It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	
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SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

Event	Start Date	Start Time	Outcome	End date	End Time	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the SAE	With-drawal	Relationship to Investi-gational Product(s)
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Is there a reasonable possibility the SAE may have been caused by the investi-gational product? Y=Yes N=No
e.g., Anaphylaxis	***25 Jan 03***	***13:25***	***1***	***27 Jan 03***	***10:20***	***1***	***4***	***Y***	***Y***
		:			:				
		:			:				

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

If fatal, was a post-mortem/autopsy performed [Y] ☐ Yes [N] ☐ No *If Yes, summarise findings in Section 11 Narrative Remarks of this SAE form.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✓all that apply:*

[A] ☐ Results in death
[B] ☐ Is life-threatening
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation
[D] ☐ Results in disability/incapacity
[E] ☐ Congenital anomaly/birth defect
[F] ☐ Other, *specify* _____ (*see definition of SAE*)

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INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 4 of 5)

SECTION 4 **If Investigational Product was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of investigational product(s) to the subject occurred, did the reported adverse event recur?

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Protocol Identifier	Subject Identifier
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SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data

Date of birth ☐☐ ☐☐☐ ☐☐☐☐ (Day Month Year) Sex ☐ Male ☐ Female Weight ☐☐☐.☐ kg

SECTION 4 If Investigational Product(s) was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Investigational Product(s), ✓*all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _
☐ Lack of efficacy
☐ Withdrawal of investigational product(s)
☐ Concomitant medication(s) *specify* _
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries, etc. that can help explain the SAE	**Date of Onset** Day Month Year	**Condition Present at Time of the SAE?** Y= Yes N=No	***If No, Date of Last Occurrence*** Day Month Year

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INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 5 of 5)

SECTION 9 **Details of Investigational Product(s)**	Complete this section using the information in the Investigational Product page. Details of all investigational product(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of investigational product(s), including whether it was accidental or intentional.

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SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *(provide any family or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE)*

SECTION 8 RELEVANT Concomitant Medications *(include details of any concomitant medication(s) which may have contributed to the event)*

Drug Name *(Trade Name preferred)*	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	***150***	***mg***	***BID***	***PO***	***N***	***25 Jan 03***	***27 Jan 03***	***N***	***Gastric ulcer***

SECTION 9 Details of Investigational Product(s)

Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
	:

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SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *(provide details of any other tests/procedures which were carried out to diagnose or confirm the SAE e.g., laboratory data with units and normal range)*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _
(confirming that the data on the SAE pages are accurate and complete)

Date Day Month Year

Investigator's name (print) _

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PREGNANCY INFORMATION
MONITOR DATA VALIDATION CHECK

- Check that responses provided correspond with the sex of the subject.
- If the answer to the subject pregnancy question is 'Yes', ensure that a Pregnancy Notification Form has been completed for the subject.

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PREGNANCY INFORMATION

Did the subject become pregnant during the study?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not Applicable (not of childbearing potential or male)

If Yes, complete Pregnancy Notification form.

STUDY CONCLUSION
INVESTIGATOR INSTRUCTIONS

- Refer to protocol section 9 to evaluate subject completion or withdrawal from the study.
- If subject completed study:
  "Date of subject completion or withdrawal" must match the last scheduled study visit date.
- If subject withdrew and a withdrawal visit was conducted:
  "Date of subject completion or withdrawal" must match the date of subject withdrawal.
- If subject lost to follow-up:
  "Date of subject completion or withdrawal" 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
MONITOR DATA VALIDATION CHECKS

- If the investigational product was discontinued at the same time as the subject was withdrawn from the study, ensure the reasons for the two discontinuations are consistent.
- If the subject was withdrawn due to an adverse event, confirm that details recorded correspond with details on the Adverse Event and Investigational Product Discontinuation pages:
  - 'Withdrawal' on the AE/SAE page is recorded as 'Yes'.
  - 'Action Taken with Investigational Product(s) as a Result of the Non-Serious AE/SAE' on the AE/SAE page is recorded as 'Investigational Product Withdrawn'.
  - 'Primary Reason Investigational Product was Stopped' on the Investigational Product Discontinuation page is recorded as 'Adverse Event'.
  - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'.

Protocol Identifier	Subject Identifier	
ROP109087		

STUDY CONCLUSION

Date of subject completion or withdrawal ☐☐ ☐☐☐ ☐☐
Day Month Year

Was the subject withdrawn from the study?

[Y] ☐ Yes [N] ☐ No

*If Yes, ✓ the **primary** reason for withdrawal:*

[1] ☐ Adverse event → *Record details on the Non-Serious Adverse Events or Serious Adverse Event pages as appropriate.*

[2] ☐ Lost to follow-up

[3] ☐ Protocol violation

[4] ☐ Subject decided to withdraw from the study

[6] ☐ Sponsor terminated study

[Z] ☐ Other, *specify* _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Protocol Identifier	Subject Identifier	
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INVESTIGATOR COMMENT LOG

Only use this form to record explanatory information on anomalies such as missing data, sponsor waiver of inclusion/exclusion criteria, departures from planned investigational product administration or missed visits.

CRF page number if applicable	Comment

Protocol Identifier	Subject Identifier	
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INVESTIGATOR COMMENT LOG (Continued)

Only use this form to record explanatory information on anomalies such as missing data, sponsor waiver of inclusion/exclusion criteria, departures from planned investigational product administration or missed visits.

CRF page number if applicable	Comment



Protocol Identifier	ROP109087

INVESTIGATOR'S SIGNATURE

INVESTIGATOR INSTRUCTIONS

The Investigator is accountable for CRF data. However, the Principal Investigator may delegate CRF signature authority to a medically qualified Sub-investigator (as indicated on the Site Staff Signature Sheet).

Protocol Identifier	Subject Identifier	
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INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature _____ Date Day Month Year

Investigator's name (print) _____

Protocol Identifier	Subject Identifier	Centre Number	
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LIVER EVENTS

Date of assessment ☐☐ ☐☐☐ ☐☐ Day Month Year

Which liver chemistry result reached or exceeded protocol-defined investigational product stopping criteria?
✓ *all that apply*

[1] ☐ ALT (alanine aminotransferase)

[2] ☐ AST (aspartate aminotransferase)

[3] ☐ Total bilirubin

[4] ☐ Alkaline phosphatase

[OT] ☐ Other

Time period to the onset of ALT ≥2x Upper Limit Normal (ULN).

Note: Although stopping criteria is ALT ≥3x ULN, GSK are interested in capturing ALT ≥2x ULN to assess the probability of drug relatedness of liver event.

Note: Only complete dates for the treatment period applicable to the onset of ALT ≥2x ULN.	Start Date Investigational Product	End Date Investigational Product
If the liver event occurred during treatment period record start and stop date of investigational product for that treatment period.	☐☐ ☐☐☐ ☐☐ Day Month Year	☐☐ ☐☐☐ ☐☐ Day Month Year
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.	☐☐ ☐☐☐ ☐☐ Day Month Year	☐☐ ☐☐☐ ☐☐ Day Month Year

Protocol Identifier	Subject Identifier	
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LIVER EVENTS (Continued)

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.

Is the subject age 55 or older?

[Y] ☐ Yes [N] ☐ No

If female, is the subject pregnant?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not applicable

If Yes, ensure Pregnancy Notification Form has been completed.

Were any diagnostic imaging tests of the liver or hepatobiliary system performed (such as a liver ultrasound, computerized tomography or CAT scan, magnetic resonance imaging or MRI, or endoscopic retrograde cholangiopancreatography, or other)?

[Y] ☐ Yes [N] ☐ No

If Yes, were the results normal?

[Y] ☐ Yes [N] ☐ No

If No, record the details on the Non-Serious Adverse Events form or Serious Adverse Event form.

Were any liver biopsies performed?

[Y] ☐ Yes [N] ☐ No

If Yes, complete Liver Biopsy form.

Does the subject use herbals, complementary or alternative medicines, food supplements (vitamins) or illicit drugs?

[Y] ☐ Yes [N] ☐ No

If Yes, record on the appropriate Concomitant Medication form.

Did the subject fast or undergo significant dietary change in the past week?

[Y] ☐ Yes [N] ☐ No



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ALCOHOL INTAKE
INVESTIGATOR INSTRUCTIONS

ALCOHOL CONVERTER

1 unit of alcohol in US = 1.5oz hard liquor, 1 beer, 4oz wine

1 unit of alcohol in UK = 1 measure of spirits, 1/2 pint beer, 1 small glass of wine (125ml)

Round up/down to the nearest integer.

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LIVER EVENTS (Continued)

An unscheduled PK blood sample must be obtained within 24 hours of last dose (or 3x the investigational product half-life or t1/2;).

Was a pharmacokinetic blood sample obtained?

[Y] ☐ Yes [N] ☐ No

If Yes, date and time sample taken ☐☐ Day ☐☐☐ Month ☐☐ Year ☐☐:☐☐ Hr:Min (00:00-23:59)

If Yes, date and time of last investigational product dose prior to PK sample ☐☐ Day ☐☐☐ Month ☐☐ Year ☐☐:☐☐ Hr:Min (00:00-23:59)

ALCOHOL INTAKE

Record the average number of units of alcohol[1] consumed per week ☐☐☐ units per week

[1] *See facing page for conversion guidelines.*

LIVER EVENTS
DEFINITIONS

CURRENT MEDICAL CONDITIONS

Conditions from which the subject is currently suffering, regardless of how long they have been present. If the subject has had a recurring condition that is not present at the time of the assessment, it can be classed as current if, in the Investigator's opinion it is likely to recur during the study.

PAST MEDICAL CONDITIONS

Conditions from which the subject has suffered in the past, but are no longer present. A past condition may have stopped as recently as the day prior to being assessed.

NO MEDICAL CONDITION

No current or past condition.

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LIVER EVENTS (Continued)

LIVER DISEASE MEDICAL CONDITIONS

Specific Condition ✓ *only one response for each condition*		Current [1]	Past [2]	No Medical Condition [5]
1.	Acute Viral Hepatitis A			
2.	Chronic Hepatitis B			
3.	Chronic Hepatitis C			
4.	Cytomegalovirus Hepatitis			
5.	Epstein Barr Virus Infectious Mononucleosis			
6.	Herpes Simplex Hepatitis			
7.	Alcoholic Liver Disease			
8.	Non-alcoholic Steatohepatitis			
9.	Fatty Liver			
10.	Hepatic Cirrhosis			
11.	Hemochromatosis			
12.	Autoimmune Hepatitis			
13.	Gallbladder disease or biliary disease			

DRUG RELATED LIVER DISEASE CONDITIONS (All drugs including Investigational Product)

14.	Drug related liver disease			

OTHER LIVER DISEASE CONDITIONS

Specific Condition *Record only one per line for each condition and ✓ only one response for each condition*		Current [1]	Past [2]
15.			
16.			

OTHER MEDICAL CONDITIONS

Specific Condition ✓ *only one response for each condition*		Current [1]	Past [2]	No Medical Condition [5]
17.	Drug Allergies			
18.	Rheumatoid Arthritis			
19.	Psoriasis			
20.	Thyroid Disease			
21.	Inflammatory Bowel Disease			
22.	Lupus			
23.	Sjogren's Syndrome			
24.	Vitiligo			

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number
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PREGNANCY NOTIFICATION FORM (SUBJECT)

This form should be completed according to the protocol reporting requirements.
Complete this form for each subject who becomes pregnant during the study period. Send a copy of the form to GlaxoSmithKline (GSK will provide separately a list of contact names and information) by mail or fax (fax preferred) within two weeks of learning of the pregnancy. Original pages should remain with the subject's Case Report Form.
Note: This form does not routinely need to be completed for subject's partner pregnancy unless there is specific instruction to do so stated in the protocol.

MOTHER'S RELEVANT MEDICAL/FAMILY HISTORY

Mother's date of birth ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Date of last menstrual period ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Estimated date of delivery ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Was the mother using a method of contraception?

☐ Yes ☐ No

If Yes, specify _____

Type of conception, ✓*one:* ☐ Normal (includes use of fertility drugs)
☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

_____

_____

Number of previous pregnancies ☐☐ Pre-term ☐☐ Full-term

If applicable, record the number in the appropriate categories below:

☐☐ Normal births
☐☐ Stillbirths
☐☐ Children born with defects
☐☐ Spontaneous abortion
☐☐ Elective abortion
☐☐ Other

Record details of children born with defects _____

Are there any additional factors that may have an impact on the outcome of this pregnancy?

☐ Yes ☐ No

If Yes, specify _____

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PREGNANCY NOTIFICATION FORM (SUBJECT) (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_ _

_ _

DRUG EXPOSURES

*In the following table, list **all** medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). **Enter the investigational product details on the first line** (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.*

Drug Name *(Trade Name preferred)*	**Route of Admin. or For-mulation**	**Total Daily Dose**	**Units**	**Started Pre-Study** Y=Yes N=No	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Ongoing Med-ication** Y=Yes N=No	**Reason for Medication**

Was the subject withdrawn from the study as a result of this pregnancy?

☐ Yes ☐ No

***REPORTING INVESTIGATOR INFORMATION** (Forward to a more appropriate physician if needed)*

Name _Title _ _ _ Speciality _

Address _

City or State/Province _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Country _

Post or Zip Code _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Telephone No _

Fax No _

Investigator's signature _ Date ☐☐ Day ☐☐☐ Month ☐☐ Year
(confirming that the data on these pages are accurate and complete)

Investigator's name (print) _

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE)

SECTION 12 **SAE Additional/Follow-up Information**	On receipt of follow-up information, the appropriate section(s) on the SAE form must be amended/updated with any changes (i.e., diagnosis, end date or death, change in intensity, or causality). These changes must be initialled and dated with confirmation by the investigator with his/her re-signing the form and forwarded to GSK within 24 hours. The investigator and others responsible for subject care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the AE. GSK may also request extra tests or extra follow-up information. If a subject dies, any post-mortem/autopsy findings, including histopathology, must be provided to GSK.

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Case Report Form - Screening

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Subject Identifier

ROP109087

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

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Protocol Identifier	Subject Identifier	Centre Number	
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COVER SHEET - TRACKING DETAILS

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

Module Number 1

Visits included in this Module: Screening

[redacted]

[redacted] [redacted]

COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF (e.g., Height in centimetres, Weight in kilograms).
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as 0 6.
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✓.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

DATE

- If the CRF is not completed at time of subject assessment, record date of assessment, not date of CRF completion.
- Use the first three letters of each month as the abbreviation for the months (e.g., JAN, FEB, MAR).

0	1	J	A	N	0	3
Day		Month			Year	

= 1st January 2003

TIME

- Record time in 24-hour clock format unless specified otherwise, per conversion chart below.

a.m.		**p.m.**	
Midnight = 00:00	6:00 = 06:00	Noon = 12:00	6:00 = 18:00
1:00 = 01:00	7:00 = 07:00	1:00 = 13:00	7:00 = 19:00
2:00 = 02:00	8:00 = 08:00	2:00 = 14:00	8:00 = 20:00
3:00 = 03:00	9:00 = 09:00	3:00 = 15:00	9:00 = 21:00
4:00 = 04:00	10:00 = 10:00	4:00 = 16:00	10:00 = 22:00
5:00 = 05:00	11:00 = 11:00	5:00 = 17:00	11:00 = 23:00

Note: Midnight = 00:00 is the start of the new day, not the end of the previous day.

MISSING INFORMATION

- Use the following abbreviations for missing information.
  - NA not available/not applicable
  - ND not done
  - UNK unknown
  - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

GENERAL CRF
MONITOR DATA VALIDATION CHECK

All CRF pages must be reviewed for consistency, completeness, logic and legibility in line with SOP-WWD –1103, Section 6.3 and ICH GCP E6 5.18.4 to include:

- Accurate identifier information completed on every CRF page.
- Identification & completion of missing CRF pages and blank data fields in line with the instructions pre-printed in the CRF.
- Validity and chronology of recorded dates and times.
- Ensuring only one ✓ box response is completed in response to a given question (unless otherwise indicated on the CRF).
- Review of free text fields for spelling and translation errors.
- Where an option of Other; *specify* is provided, specify text should only be completed when the 'Other' option is ✓. A concise text entry, which does not match one of the alternative specified options, should be present in the space provided.
- Data is placed at the correct visit and on the correct CRF page.

DEMOGRAPHY
INVESTIGATOR INSTRUCTIONS

ETHNICITY

- **Hispanic or Latino** — A person of Cuban, Mexican, Puerto Rican, South American or other Spanish culture or origin, regardless of race

  Note: If the subject does not meet the definition above, ✓ Not Hispanic or Latino.

- **Not Hispanic or Latino** — Neither Hispanic or Latino

GEOGRAPHIC ANCESTRY

The racial groups below are based on the FDA and ICH Guidelines.

Note: In order to provide for all eventualities, it is permissible to ✓ multiple boxes.

- **African American/African Heritage** — A person having origins in any of the black racial groups of Africa
- **American Indian or Alaskan Native** — A person having origins in any of the original peoples of North and South America (including Central America) and who maintains tribal affiliation or community attachment
- **Asian - Central/South Asian Heritage** — A person having origins in Central Asia (Kazakstan, Kyrgystan, Tajikstan, Turkmenistan and Uzbekistan) and Indian Subcontinent (India, Pakistan, Bangladesh and Sri Lanka)
- **Asian - East Asian Heritage** — A person having origins in China, Korea
- **Asian - Japanese Heritage** — A person having origins in Japan
- **Asian - South East Asia Heritage** — A person having origins in Malaysia, the Philippines, Indonesia, Thailand, Vietnam, Laos, Burma or Cambodia
- **Native Hawaiian or Other Pacific Islander** — A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands, Australia (Aborigines), Papua New Guinea, New Zealand, Marshalls and other island groups west and south of Japan
- **White - Arabic/North African Heritage** — A person having origins in any of the original peoples of Middle East or North Africa
- **White - White/Caucasian European Heritage** — A person having origins in any of the original peoples of Europe

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Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
ROP109087			**Screening**

DEMOGRAPHY

Date of birth ☐☐ ☐☐☐ ☐☐☐☐ (Day Month Year)

Sex
[M] ☐ Male
[F] ☐ Female

Ethnicity ✓ *one:*
[1] ☐ Hispanic or Latino
[2] ☐ Not Hispanic or Latino

Geographic Ancestry ✓ *all that apply:*
[11] ☐ African American/African Heritage
[12] ☐ American Indian or Alaskan Native
[13] ☐ Asian - Central/South Asian Heritage
[14] ☐ Asian - East Asian Heritage
[15] ☐ Asian - Japanese Heritage
[16] ☐ Asian - South East Asian Heritage
[17] ☐ Native Hawaiian or Other Pacific Islander
[18] ☐ White - Arabic/North African Heritage
[19] ☐ White - White/Caucasian/European Heritage



Protocol Identifier	ROP109087

CHILD-BEARING POTENTIAL (Complete for Female Subjects Only)
DEFINITIONS

• **Post-menopausal**	Women who have completed menopause at least one year ago.
• **Sterile**	Pre-menopausal women who cannot conceive children. (This category includes women who have become sterile through surgical procedures such as tubal ligation. Do not include post-menopausal women in this category.)
• **Potentially able to bear children**	Women of child-bearing age who are not sterile.

Note: If the subject is sterile and is not of child-bearing age, then 'post-menopausal' will be the best choice and should be ✓.
If the subject is sterile and does not know if she is post-menopausal and is less than 62 years of age, then she is of child-bearing age and 'sterile' should be ✓.

CHILD-BEARING POTENTIAL (Complete for Female Subjects Only)
MONITOR DATA VALIDATION CHECK

Check that the Child-bearing Potential page has not been completed for male subjects.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		**WORKSHEET**	**Screening**

CHILD-BEARING POTENTIAL (Complete for Female Subjects Only)

✓ *one:*

[2] ☐ Post-menopausal

[3] ☐ Sterile (of child-bearing age)

[4] ☐ Potentially able to bear children

PREGNANCY TEST (Complete for Female Subjects of Child-bearing Potential Only)

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results ☐ Positive
If positive, exclude subject from the study.

☐ Negative

LOCAL LABORATORY RESULT DATA

Laboratory Test Clinical Chemistry	**Result**	
FSH/LH		

MEDICAL CONDITIONS

DEFINITIONS

CURRENT MEDICAL CONDITIONS

Conditions from which the subject is currently suffering, regardless of how long they have been present. If the subject has had a recurring condition that is not present at the time of the assessment, it can be classed as current if, in the Investigator's opinion it is likely to recur during the study.

PAST MEDICAL CONDITIONS

Conditions from which the subject has suffered in the past, but are no longer present. A past condition may have stopped as recently as the day prior to being assessed.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		**WORKSHEET**	**Screening**

MEDICAL CONDITIONS

Diagnosis *Only in the absence of a diagnosis, record the signs and symptoms on separate lines*	**Current** [1]	**Past** [2]
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		
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25.		
26.		
27.		
28.		

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
ROP109087			Screening

URINE DRUG SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

✓*appropriate box(es)*	Positive	Negative
Amphetamines	☐	☐
Barbiturates	☐	☐
Cannabis	☐	☐
Cocaine	☐	☐
Morphine and derivatives	☐	☐

If any of the above are positive, exclude subject from the study.

ALCOHOL TEST

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results ✓*one:*
☐ Positive
If positive, exclude subject from the study.
☐ Negative

SEROLOGY - HIV / HEPATITIS SCREEN

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

✓*appropriate box(es)*

	Positive	Negative
HIV antibody	☐	☐
Hepatitis B surface antigen	☐	☐
Hepatitis C antibody	☐	☐

*If any of the above are positive, **exclude** subject from the study.*

Protocol Identifier	Subject Identifier		Visit Description
ROP109087		WORKSHEET	Screening

PHYSICAL EXAMINATION

Date of Assessment ☐☐ Day ☐☐☐ Month ☐☐ Year

Indicate current physical findings by ✓ the appropriate box(es) below and if ABNORMAL, describe concisely: [different findings should be separated by either a (;) or a (/)].

	Normal	Abnormal	Not Done	
1. Hair and skin	☐	☐		_____
2. Lymph nodes	☐	☐		_____
3. Eyes	☐	☐		_____
4. Ears, Nose and Throat	☐	☐		_____
5. Breasts	☐	☐	☐	_____
6. Respiratory	☐	☐		_____
7. Cardiovascular	☐	☐		_____
8. Abdomen	☐	☐		_____
9. Urogenital	☐	☐	☐	_____
10. Pelvic	☐	☐	☐	_____
11. Rectal	☐	☐	☐	_____
12. Musculoskeletal	☐	☐		_____
13. Neurological	☐	☐		_____
14. Mental Status	☐	☐		_____



Protocol Identifier	ROP109087

HISTORY OF TOBACCO USE
INVESTIGATOR INSTRUCTIONS

DEFINITIONS

- **Never smoked** Never smoked/used tobacco
- **Current smoker** Currently smoking/using tobacco or has smoked/used tobacco within 6 months of screening visit
- **Former smoker** Previously smoked/used tobacco and has not smoked/used tobacco for at least 6 months prior to screening visit

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Screening

HISTORY OF TOBACCO USE

What is the subject's history of tobacco use?

[1] ☐ Never smoked[1]

[2] ☐ Current smoker[1]

[3] ☐ Former smoker[1] → When did the subject last smoke/use tobacco? ☐☐ Day ☐☐☐ Month ☐☐ Year

If current or former smoker, answer the following question:

Number of cigarettes smoked per day? ☐☐☐ cigarettes per day

[1] *See facing page for definitions.*

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
ROP109087			Screening

EPWORTH SLEEPINESS SCALE

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Used with permission. Reference: Johns MW.Sleep 1991:14(6):541

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Screening

VITAL SIGNS

Height ☐☐☐ cm Weight ☐☐☐.☐ kg

Body mass index ☐☐.☐ kg/m²

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure mmHg Systolic	 Diastolic	Subject Position 1 = Supine 3 = Standing	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***1***	***75***
1.	Screening	:			1	
2.	Screening	:			3	
3.	Unscheduled	:				
4.	Unscheduled	:				

12-LEAD ECG

	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Screening	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Ventricular Rate Beats/min			
PR Interval msec			
QRS Duration msec			
Uncorrected QT Interval msec			
QTc Interval msec			
Result of the ECG			

(enter code for result from the following list)

1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

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Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Screening

12-LEAD ECG ABNORMALITIES

Date of ECG Day Month Year Time of ECG Hr:Min (00:00-23:59)

Record clinically significant abnormalities below. ✓ all that apply:

A. Rhythm

- [A1] Sinus bradycardia
- [A21] Sinus bradycardia (heart rate 40-50 beats/min)
- [A22] Sinus bradycardia (heart rate 30-39 beats/min)
- [A23] Sinus bradycardia (heart rate < 30 beats/min)
- [A3] Sinus pause
- [A2] Sinus tachycardia (heart rate >100 beats/min)
- [A4] Ectopic supraventricular beats
- [A20] Ectopic supraventricular rhythm
- [A17] Wandering atrial pacemaker
- [A26] Multifocal atrial tachycardia (Wandering atrial pacemaker with heart rate >100 beats/min)
- [A6] Supraventricular tachycardia (heart rate >100 beats/min)
- [A7] Atrial flutter
- [A8] Atrial fibrillation
- [A5] Junctional rhythm (heart rate ≤100 beats/min)
- [A25] Junctional rhythm
- [A24] Junctional tachycardia (heart rate > 100 beats/min)
- [A9] Ectopic ventricular beats
- [A12] Ventricular couplets
- [A13] Bigeminy
- [A28] Trigeminy
- [A14] Electrical alternans
- [A29] R on T phenomenon
- [A18] Ventricular fibrillation
- [A19] Idioventricular rhythm (heart rate < 100 beats/min)
- [A10] Sustained ventricular tachycardia
- [A11] Non-sustained ventricular tachycardia
- [A32] Wide QRS Tachycardia (diagnosis unknown)
- [A27] Ventricular tachycardia
- [A30] Monomorphic ventricular tachycardia
- [A15] Torsades de Pointes (Polymorphic ventricular tachycardia with prolonged QT)
- [A31] Polymorphic (sustained and non-sustained) ventricular tachycardia
- [A16] Artificial pacemaker
- [A99] Other abnormal rhythm

Comment _

B. P-Wave and QRS Morphology

- [B1] Left atrial abnormality (P mitrale)
- [B2] Right atrial abnormality (P pulmonale)
- [B3] Right ventricular hypertrophy
- [B5] Intraatrial conduction delay
- [D14] Increased voltage consistent with left ventricular hypertrophy
- [B99] Other morphology

Comment _

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Screening

12-LEAD ECG ABNORMALITIES (Continued)

C. Conduction

[C1] ☐ First degree AV block (PR interval > 200 msec)
[C20] ☐ Short PR interval
[C2] ☐ Second degree AV block (Mobitz type 1)
[C3] ☐ Second degree AV block (Mobitz type 2)
[C16] ☐ 2:1 AV block
[C4] ☐ Third degree AV block
[C5] ☐ Left axis deviation (QRS axis more negative than -30°)
[C6] ☐ Right axis deviation (QRS axis more positive than +110°)
[C7] ☐ Incomplete right bundle branch block
[C13] ☐ Incomplete left bundle branch block
[C8] ☐ Right bundle branch block
[C14] ☐ Left anterior hemiblock (synonymous to left anterior fascicular block)
[C15] ☐ Left posterior hemiblock (synonymous to left posterior fascicular block)
[C9] ☐ Left bundle branch block
[C17] ☐ Bifascicular block
[C10] ☐ Non-specific intraventricular conduction delay (QRS ≥120 msec)
[C11] ☐ Accessory pathway (Wolff-Parkinson White, Lown-Ganong-Levine)
[C19] ☐ Prolonged QT interval
[C12] ☐ QT/QTc prolongation ≥ 500 msec
[C18] ☐ AV dissociation
[C99] ☐ Other conduction

Comment _

D. Myocardial Infarction

[D1] ☐ Myocardial infarction, old
[D2] ☐ Myocardial infarction, anterior
[D3] ☐ Myocardial infarction, lateral
[D4] ☐ Myocardial infarction, posterior
[D5] ☐ Myocardial infarction, inferior
[D6] ☐ Myocardial infarction, septal
[D20] ☐ Myocardial infarction, Non-Q wave
[D98] ☐ Other myocardial infarction

Comment _

E. Depolarisation/Repolarisation (QRS-T)

[D7] ☐ Non-specific ST-T changes
[D19] ☐ J point elevation
[D8] ☐ ST elevation
[D21] ☐ ST elevation-pericarditis
[D9] ☐ ST depression
[D96] ☐ ST segment abnormality, not specified
[D10] ☐ U waves abnormal
[D11] ☐ T wave inversion
[D12] ☐ T wave peaked
[D15] ☐ T waves flat
[D16] ☐ T waves biphasic
[D18] ☐ Notched T-waves
[D13] ☐ Low QRS voltage
[D17] ☐ T-wave flattening/inversion
[D97] ☐ T wave abnormality, not specified
[D99] ☐ Other depolarisation/repolarisation

Comment _

Other Abnormalities

[E99] ☐ Other abnormalities

Comment _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

LOCAL LABORATORY RESULT DATA (Haematology / Clinical Chemistry)

INVESTIGATOR INSTRUCTIONS

- If the laboratory changes during the study, a new set of reference ranges must be provided to GSK.
- Enter 'NR' (the abbreviation for 'No result') if the laboratory results are not available to report or if a lab error occurred.

Protocol Identifier	Subject Identifier		Visit Description
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LOCAL LABORATORY RESULT DATA (HAEMATOLOGY)

Date and time sample taken Day Month Year Hr:Min (00:00-23:59)

Laboratory name _____

Address _____

_____

Lab ID
(For GSK use only)

Has the subject fasted?

[Y] ☐ Yes [N] ☐ No

Laboratory Test Haematology	Result
Haemoglobin (Hb)	
Haematocrit	
Mean cell haemoglobin (MCH)	
Mean cell haemoglobin concentration (MCHC)	
Red blood cell count (RBC)	
White blood cell count (WBC)	
Platelets	
Lymphocytes	
Neutrophils	
Monocytes	
Basophils	
Eosinophils	

Units for differential

[1] ☐ Percent [2] ☐ Absolute count

If the laboratory results meet the protocol definition of an adverse event, record the details on the Non-Serious Adverse Events page or Serious Adverse Event page.

Protocol Identifier	Subject Identifier		Visit Description
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LOCAL LABORATORY RESULT DATA - (CLINICAL CHEMISTRY)

Date and time sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

Laboratory name_ _

Address _

_ _

Lab ID
(For GSK use only)

Has the subject fasted?

[Y] ☐ Yes [N] ☐ No

Laboratory Test Clinical Chemistry	**Result**
Sodium	
Potassium	
Urea	
Creatinine	
Total protein	
Albumin	
Total bilirubin	
Aspartate aminotransferase (AST)	
Alanine aminotransferase (ALT)	
Alkaline phosphatase (AP)	
Gamma glutamyl transferase (GGT)	
Calcium	
Phosphate	
Cholesterol	
Triglycerides	
Glucose	
Creatine phosphokinase	
Chloride	

If the laboratory results meet the protocol definition of an adverse event, record the details on the Non-Serious Adverse Events page or Serious Adverse Event page.



Protocol Identifier	ROP109087

URINALYSIS
INVESTIGATOR INSTRUCTIONS

- If the laboratory changes during the study, a new set of reference ranges must be provided to GSK.
- If the laboratory results are not available to report or if a lab error occurred, enter "NR" (the abbreviation for 'No Result')
- If a further sample is taken, record results on the Unscheduled Page.

Code Results as shown below where appropriate:

NEG = none or negative
TRA = trace
1+ = + or 1+
2+ = ++ or 2+
3+ = +++ or 3+
4+ = ++++ or 4+
5+ = +++++ or 5+

URINALYSIS
MONITOR DATA VALIDATION CHECK

- Check that results are provided using appropriate codes as outlined in the instructions above.

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Protocol Identifier	Subject Identifier		Visit Description
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URINALYSIS

Date and time sample taken Day Month Year	Hr:Min (00:00-23:59)	
Laboratory name_ _ _ _

CONCOMITANT MEDICATIONS

Record details of the subject's ongoing concomitant medications in the appropriate Concomitant Medications section.



Protocol Identifier	ROP109087

INCLUSION AND EXCLUSION CRITERIA
MONITOR DATA VALIDATION CHECK

- Confirm that the subject is eligible to participate in the study and if not, that all the failed criteria have been marked.

Protocol Identifier	Subject Identifier		Visit Description
ROP109087			Screening

ELIGIBILITY QUESTION

Did the subject meet all the entry criteria?

[Y] ☐ Yes [N] ☐ No

If No, ✓ all boxes corresponding to violations of any inclusion/exclusion criteria.

*Do **not** enter the subject into the study if they failed any inclusion or exclusion criteria below.*

INCLUSION CRITERIA

✓ the boxes corresponding to any of the inclusion criteria the subject failed.

1. ☐ Male or female patients aged between 30 and 85 years of age inclusive at screening.
2. ☐ Body mass index of 18 to 32 kg/m2, with a body weight of at least 50 kg
3. ☐ Diagnosis of idiopathic Parkinson's Disease graded according to modified Hoehn & Yahr Stage I-III (Appendix 4 of protocol).
4. ☐ Patients must have provided written informed consent prior to performing any Screening assessments, including any washout of concomitant medications in preparation for this study.
5. ☐ QTc interval of < 450ms at screening (or QTc < 480ms in patients with Bundle Branch Block).
6. ☐ Female patient is currently either of:

   a) non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal or any female who is surgically sterilized (via documented hysterectomy or bilateral tubal ligation).

      (For purposes of this study, postmenopausal is defined as one year without menses)

   OR

   b) child-bearing potential, has a negative urine/serum pregnancy test at the Screening Visit (prior to investigational product administration), and agrees to use acceptable contraception from one month prior to study Day 1 until one month after completion of the study (ie. one month after the follow-up visit). All hormonal birth control must have been administered for at least one monthly cycle prior to the Screening Visit. GSK acceptable contraception methods, when used consistently and in accordance with both the product label and the instructions of a physician, are as follows:

      - complete abstinence
      - sterilization of patient's male partner prior to female patient's entry into study
      - oral contraceptive (either combined or progestogen only)
      - any intra-uterine device with a documented failure rate of less than 1% per year
      - systemic contraception (eg. norplant system)
      - double barrier method if comprised of a spermicide with either a condom or diaphragm.

Protocol Identifier	Subject Identifier		Visit Description
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EXCLUSION CRITERIA

✓ *the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.*

1. ☐ Patients who have an abnormality on physical examination. A patient with clinical abnormality may be included only if the Investigator considers that the abnormality will not introduce additional risk factors and will not interfere with the study procedures.

2. ☐ Patients who, in the opinion of the Investigator, have medical conditions which could present a safety concern. These may include, but are not limited to, the following disorders: diabetes, peripheral neuropathy, rheumatoid arthritis, fibromyalgia syndrome, symptomatic orthostatic hypotension, hepatic or renal failure, pleuro-pulmonary fibrosis, significant and/or uncontrolled psychiatric, haematological, endocrinological, neurological (other than Parkinson's disease), or cardiovascular disease (including myocardial infarction, unstable angina pectoris, cardiac arrhythmias, cerebrovascular accident (CVA), or patients who are known to have malignancy, are being treated for malignancy or have had treatment for malignancy within the last year (other than basal cell cancer).

3. ☐ Patients having a clinically significant abnormal laboratory value, ECG, or physical examination findings not resolved by the time of the baseline examinations. Abnormal 12-lead ECG findings include, but are not limited to, the following: myocardial ischemia, clinically significant conduction abnormalities, or clinically significant arrhythmias.

4. ☐ Positive result for Hepatitis B surface antigen, Hepatitis C antibody or Human Immunodeficiency Virus (HIV) antibody at screening.

5. ☐ Positive alcohol test result and / or urine test for undeclared drugs at screening.

6. ☐ Recent history of moderate to severe dizziness, syncope, or orthostatic hypotension, defined as a fall in blood pressure, after rising from the supine to erect posture, of > 30 mmHg for systolic pressure and > 20 mmHg for diastolic pressure.

7. ☐ Significant sleep disorder or Epworth Sleep Score (Appendix 5) ≥9 at screening.

8. ☐ Patients with a lying/sitting diastolic blood pressure ≥110mmHg or ≤50mmHg or a systolic blood pressure ≥180mmHg or ≤90mmHg at the Screening or Baseline Visit.

9. ☐ History of any dopaminergic treatment (other than ropinirole IR and L-dopa) within 2 weeks prior to first dose.
   - Patients on dopaminergic agonists other than ropinirole IR and L-dopa may be enrolled if the agent is stopped for a 2-week wash-out period prior to first dose.
   - Patients taking ropinirole IR or L-dopa may switch to ropinirole PR/CR 2mg on study day 1, providing they have first followed the manufacturer's down titration guidelines.
   - Patients taking ropinirole IR > 4mg/day must be down-titrated according to the manufacturer's guidelines prior to study day 1.
   - Patients taking ropinirole IR or L-dopa must have been on a stable dose for at least 4 weeks prior to screening; doses of ropinirole IR or L-dopa may need to be adjusted prior to or during the study.
   - Patients on selegiline, amantadine, or anticholinergics may be enrolled but must have been on a stable dose for at least one month prior to study enrolment and must remain on their current dose throughout the treatment phase of the study.

Protocol Identifier	Subject Identifier		Visit Description
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EXCLUSION CRITERIA (Continued)

✓ *the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.*

10. ☐ Withdrawal, introduction, or change in dose of hormone replacement therapy and/or any drug known to substantially inhibit CYP1A2 (e.g., cimetidine, ciprofloxacin, fluvoxamine) or induce CYP1A2 (e.g., tobacco, or omeprazole) within 7 days prior to study enrolment. Patients already on these agents may be enrolled but must remain on stable doses of the agent for at least one month prior to enrolment and throughout the treatment phase of the study.

11. ☐ Patients who smoke >20 cigarettes per day and will not maintain a constant smoking habit for the duration of the study.

12. ☐ Blood donation or significant blood loss less than 90 days before Day 1 of the current study.

13. ☐ Definite or suspected personal history, or family history, of adverse reactions or hypersensitivity to ropinirole or to drugs with a similar chemical structure.

14. ☐ Use of any investigational drug (with the exception of ropinirole PR/CR) within 30 days or 5 half lives (whichever is longer) before the start of dosing with study medication.

15. ☐ Patients who have received over-the-counter (OTC) medicine within 48 h before the first dose of study drug. Patients who have taken OTC medication may still be entered in the study, if in the opinion of the Investigator, the medication received will not interfere with the study procedures or compromise safety.

16. ☐ Recent history, or suspicion, of drug dependence or abuse of alcohol (with alcohol abuse defined as an average weekly intake of greater than 21 units or an average daily intake of greater than 3 units for men; greater than 14 units per week or greater than 2 units per day for women. One unit is equivalent to half a pint of beer, one measure of spirits, or one glass of wine).

17. ☐ Significant concern, or likelihood, that the patient will drop out of the study prematurely, will require new or prohibited concomitant medications during the study period, or will not be compliant with study procedures.

18. ☐ Women who are pregnant or breast-feeding.

19. ☐ Patients with prior or current major psychosis (eg schizophrenia or psychotic depression). Eg scoring 3 or 4 on UPDRS item 2 [thought disorder] or item 3 [depression].

Protocol Identifier	Subject Identifier		Visit Description
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INVESTIGATOR COMMENT LOG

Only use this form to record explanatory information on anomalies such as missing data, sponsor waiver of inclusion/exclusion criteria, departures from planned investigational product administration or missed visits.

CRF page number if applicable	Comment

LIST OF INVESTIGATORS AND IECS/IRBS FOR ROP109087 (HM2007/00444/00)

Investigator	Investigator/ Site no.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[redacted] PD Dr. med.	[redacted]	[redacted] Germany	Dr. Med. [redacted] Germany
[redacted] Dr	[redacted]	[redacted] South Africa.	Dr [redacted] South Africa

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Written Informed Consent Form

Study Title	An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

Patient Information Sheet Version: 1
Patient Information Sheet Date: 29.01.2007

EUDRACT Nr.: 2006-006209-94

Sponsor: GlaxoSmithKline
New Frontiers Science Park
Third Avenue
Harlow, Essex CM19 5AW, UK
[redacted]

Investigator: PD Dr. med. [redacted]

Research Unit: [redacted]

Phone number (weekdays 8 a.m. – 5 p.m.) [redacted]

Emergency number [redacted]
(5 p.m. – 8 a.m. weekdays, all day weekends and public holidays)

Patient Identification: _____

Written Information Sheet

What does giving consent mean?

Dear Patient
You have been invited to take part in a clinical study. Before agreeing to participate in this clinical study, it is important that you take time to read this document. This document includes this "written information sheet" and a "consent form". The patient information sheet provides information about the clinical study in which you have been invited to take part and what will happen if you participate. It also provides information about the purpose of the clinical study, the benefits and financial payments you will receive as well as information about the possible risks and discomforts that may be associated with taking part.

You will be asked to give your consent to participate by signing the "consent form" at the end of this document. Before doing so, you will be given adequate time to read the document and to ask the study team to explain anything that you don't fully understand. You will also be given time to think about the study at home with persons who you trust before agreeing to participate.

Your participation in this study is completely voluntary. You may withdraw your consent at anytime and leave the study. You do not need to explain your decision and your medical care will not be affected.

You will be immediately informed if any information becomes available that may affect your willingness to continue participating in the study. You will be kept informed of any significant changes of study duration or procedures.

If you agree to take part in the study you will be provided with a signed copy of this written information and the consent form.

Why is this study being carried out and are there any alternative treatments?

Parkinson's disease (PD) belongs to a group of conditions called movement disorders and is one of the most common neurological disorders in elderly people. The symptoms are caused by a loss of certain dopamine-producing brain cells. The mainstay in the treatment of Parkinson's disease is the administration of dopaminergic agents. Ropinirole is a dopaminergic drug, mimicking the role of dopamine in the brain, causing nerve cells in the brain to react as they would to dopamine. Ropinirole is currently available in tablets, which have to be administered three times a day. In order to reduce tablet burden for Parkinson's disease patients taking higher doses of ropinirole, it is proposed to develop a 12 mg tablet with a special prolonged–release formulation (PR/CR) to provide a once a day medication. It is anticipated that this will improve therapy with ropinirole by enhancing ease of dosing for the patients (once daily dosing versus 3 times daily).

The purpose of this study is to investigate the effect of administering the new 12 mg tablet of ropinirole PR/CR with a high fat meal. In addition, the dosage strength equivalence for a 3 tablet combination (3x4mg vs. 1x12mg) will be investigated.

Accordingly, the main focus of this study is pharmacokinetics (PK), which is the study of how a drug is taken up into the body, how it is metabolised, which blood concentration of the drug is found in-between the dosing periods and how the drug is removed from the body. PK is mostly assessed by measuring the blood level of pre-defined substances at certain time points after dosing. As food intake can influence the PK of a substance, this will be an aspect of the study, too.

As there are other treatment options for Parkinson's disease (including commercially available ropinirole), there is no need for you to participate. You may choose not to take part in this study.

What does the study involve?

This is an open-label study with only one treatment group. That means that all volunteers will receive the same study drug.

The study activities are broken down into a number of different sections or procedures. These procedures are:

- Screening & Pre-study Procedures
- Study Procedures
- Post-study Procedures

What happens in each of these is described below:

Screening & Pre-study Procedures
All patients will undergo a pre-study medical examination within 28 days before the start of the study. Once you signed the informed consent form, this will include the following:

- obtaining your general medical history including Parkinson's disease history and assessment of the so-called Epworth Sleepiness Scale (ESS)
- obtaining information on concomitant medication and smoking history
- adverse event recording
- a physical examination and 12 lead ECG
- recording your supine and standing blood pressure and pulse rate
- assessments of haematology, clinical chemistry, HIV-1/2 test, hepatitis B and C status
- urinalysis, urine drug screen and alcohol test
- urine/serum pregnancy test (if applicable)

Study Procedures
Day 1-37, up-titration and steady state period
You will receive ropinirole PR/CR tablets following an up-titration dosing regimen from 2 mg to 12 mg PR/CR (up-titrating period) Up-titration means a stepwise increase of the dose of the drug over time until one arrives at the highest dose (12 mg in this study), to help the body adapt to it better.

You will be dosed once daily with ropinirole PR/CR in the morning from day 1 to day 37. It will be started with 2mg PR/CR on day 1 with weekly up-titration to 4mg, 6mg, 8mg and 12mg. Continuation of up-titration for study medication will be based on satisfactory

tolerability at the current dose level. At day 1 and on every first day of up-titration (day 8, 15, 22, 29) dosing will be done in the research unit. You will attend the research unit on these days and undergo following pre-dose procedures: ECG assessments, blood pressure and pulse rate measurements and recording of adverse events, urine drug screen (day 1 and 15 only), alcohol test (day 1 only), urine/serum pregnancy test (if applicable, day 1 and 15 only).

You will have breakfast at the unit and receive ropinirole PR/CR approximately 30 minutes later. Your blood pressure will be measured hourly from pre-dose up to and including 12 hours post dose. This will be done with an ambulatory blood pressure monitor (ABPM). The ABPM is a portable device (about the size of a very small handbag or purse) that is connected to a cuff around your arm. It will measure your blood pressure automatically every hour. You will take the device home when leaving the unit, which will enable you to monitor your blood pressure at home up to 12 hours post dose. You will bring back the device for evaluation at the next opportunity. You may leave the unit 2 h after dosing following a bed-rest period provided that the investigator believes it is safe for you to do so.

The rest of the week (day 2-7, day 9-14, day 16-21, day 23-28) you will take the study medication at home (except for PK assessment days, see below). You will document the dosing at home and your health status in a diary card.

PK assessment will be conducted during the 4mg (any day between day 12-14) and the 8mg (any day between day 26-28) dosing weeks, where you have to attend and remain in the research unit for at least 24 hours. After dosing in the morning, which takes place in a fasted state (you consume no food or beverages except for water from 22:00 in the evening before), you have to remain for 2 hours in a semi-supine position (comfortable position between lying and sitting in your bed). Vital signs, ECGs and serial blood draws will be taken at various time points during these 24 hours. You may attend the research unit in the evening prior to the PK assessment days.

Beginning with the 12 mg dose on day 29 (steady state period) you will attend the unit and will remain in-house for the entire 12mg PR/CR treatment period (i.e. until completion of day 37 assessments). You may attend the research unit in the evening prior to the start of the 12 mg dosing period. On day 29, you will be randomised to a treatment sequence which will determine in which order you will receive the 3 different 12mg ropinirole PR/CR treatments between Days 29-31, 32-34 and 35-37 respectively. These three 12mg PR/CR treatments are as follows:

- Ropinirole PR/CR 12mg – fasted
- Ropinirole PR/CR 12mg – fed (standard high fat breakfast)
- Ropinirole PR/CR 12mg – 3x4mg tablets in the fasted condition

PK assessments will be performed after at least 3 sequential days of dosing of each treatment (Days 31, 34 and 37) with similar conditions and assessments to the PK days in the up-titration period. You will leave the research unit on the morning of day 38, if the investigator believes it is safe for you to do so.

Post-study Procedures
Days 38-44, down-titration period

Patients who complete the study or withdraw from the study prematurely and have received study medication will be down titrated over a 4-7 day period, consisting of a reduction in the daily dose for 4 days and a further reduction as necessary for the next 3 days. Down-titration means to slowly stepwise reduce the dose of a drug to avoid symptoms of withdrawal.

Follow-up examination

A follow-up examination will be performed 7-14 days after the last administration of study drug. This will include a physical examination, supine and standing blood pressure and pulse rate measurements and ECG recording. Clinical chemistry, haematology and urinalysis will be assessed and adverse events (AEs) will be monitored for the preceding time interval. When applicable, a urine/serum pregnancy test will be performed.

There will be approximately 62 blood draws in the study. The total volume of blood drawn, including screening, predose, study and post study procedures will be about 400 ml, equivalent to approximately 24 tablespoons.

The study will take place at the research unit of [redacted] under the control of Priv.-Doz. Dr. med. [redacted] (the Investigator). It is physically located at:

[redacted]

To take part in the study *you must* (among other considerations)

- be a male or female patient between 30 and 85 years of age inclusive
- have a body mass index of 18 to 32 kg/m2, with a body weight of at least 50 kg
- have an diagnosis of Parkinson's disease (graded according to modified Hoehn & Yahr Stage I-III)
- Female patients must be either of:
- non-childbearing potential (i.e., physiologically incapable of becoming pregnant, post-menopausal or surgically sterilized, or of
- child-bearing potential, having a negative urine/serum pregnancy test at the Screening Visit (prior to investigational product administration), and agrees to use acceptable contraception from one month prior to study Day 1 until one month after completion of the study (ie. one month after the follow-up visit). All hormonal birth control must have been administered for at least one monthly cycle prior to the Screening Visit. Acceptable contraception methods, when used consistently and in accordance with both the product label and the instructions of a physician, are as follows:
    - complete abstinence
    - sterilization of patient's male partner prior to female patient's entry into study
    - oral contraceptive (either combined or progestogen only)
    - any intra-uterine device with a documented failure rate of less than 1% per year
    - systemic contraception (e.g. norplant system)

- double barrier method if comprised of a spermicide with either a condom or diaphragm

You can not participate *if you have* (among other considerations)

- serious medical conditions which could represent, in the opinion of the investigator, a safety concern; for example symptomatic orthostatic hypotension, hepatic or renal failure, psychiatric, rheumatic, haematological, endocrinological, oncological, cardiovascular, or neurological diseases (other than Parkinson's disease),
- a clinically significant abnormal laboratory value, ECG, or physical examination finding,
- a positive result for Hepatitis B, Hepatitis C or Human Immunodeficiency Virus (HIV) at screening,
- a positive alcohol test result and / or urine test for undeclared drugs at screening,
- a recent history of moderate to severe dizziness, syncope, or orthostatic hypotension,
- a lying/sitting diastolic blood pressure ≥110mmHg or ≤50mmHg or
- a systolic blood pressure ≥180mmHg or ≤90mmHg at the screening or baseline visit,
- received certain other medications to treat Parkinson´s disease (other than ropinirole or L-Dopa) within 2 weeks prior to first dose in this study. This will be discussed in detail with your study physician.
- a withdrawal, introduction, or change in dose of hormone replacement therapy and/or certain drugs and/or change in your smoking habits,
- a prior or current major psychiatric disease (eg schizophrenia or depression).
- Women who are pregnant or breast-feeding can not participate.

If you agree and qualify to participate, it is expected that you will take part in the study for approximately 5-6 weeks from your first study visit to your last study visit, not including the screening and the post-study visits which will take place within 28 days before and 7-14 days after the study itself.

How many other patients are there in the study?

It is planned that 24 patients will participate in this study, approximately 12 of those will take part at this location.

Do I have to stay in the study?

You can withdraw your consent to participate and leave the study at any time. You do not have to provide a reason or justification for your decision to leave the study. Please inform a study physician or member of the study team if you wish to leave the study or send a written notice to:

[redacted]

If you decide to leave the study early you will still be invited to attend a post-study visit to check on your safety and well being. During this visit the same assessments as for the regular follow-up examination will take place.

The [redacted] or the Sponsor may also decide to withdraw you from the study if:

- It is subsequently discovered that you do not meet the study requirements
- the study physician believes it is in your best interests to leave the study,
- if you do not follow the requirements of the study or the instructions given,
- if the study is stopped for any reason,
- for any other reason determined by the Investigator or the Sponsor

If you withdraw your consent or leave the study early then:

- you won't be able to participate any further in the study,
- [redacted] will not collect any more information about you,
- [redacted] will still be able to use and share information it collected about you before you withdrew your consent, if this is needed to ensure the study is completed properly or for other reasons permitted or required by law
- the Sponsor will still be able to use the information about you that was collected before you withdrew your consent.

What are the foreseeable risks for taking part in the study?

Experience with the study drug

Ropinirole has been widely used as a therapy for Parkinson´s disease since 1996 (marketed in over 60 nations worldwide, in Germany branded as "Requip®"). Recently the substance was approved for therapy of so-called "Restless Legs Syndrome" as well.

To date, ropinirole (both IR and PR/CR tablets) has been administered to 2553 unique subjects in the PD clinical trials (2079 subjects have received the IR tablet, 641 subjects have received the PR/CR tablet, and 167 subjects have received both ropinirole PR/CR and ropinirole IR tablets).

The PR/CR formulation is currently unlicensed, but has been tested in healthy volunteers in four clinical studies to date. Six additional studies have been completed in subjects with PD. A further two studies are ongoing in subjects with PD and one study has been terminated. No new safety concerns have been identified for ropinirole PR/CR tablets compared with ropinirole IR tablets. During these studies most adverse events were of mild or moderate intensity.

Known side effects of the substance are listed below, whereas

very common means	>1/10,
common	>1/10 - >1/100,
occasional	>1/100 - >1/1000,
seldom	>1/1000 - >1/10000,
very seldom	>1/100000.

Organ System	Occurrence	Side Effect
Psychiatric	common	Hallucination
	occasional	Psychotic reactions (other than hallucination) including delirium, delusional symptoms, paranoia, pathologic gambling, increased libido
Nervous system	very common	Significant somnolence, syncope
	common	Drowsiness including vertigo
	occasional	Sudden onset of sleep
	very seldom	extreme somnolence
Vascular system	common	Peripheral oedema (including leg oedema)
	occasional	Hypotension, postural hypotension (in rare cases serious)
Gastrointestinal system	very common	Nausea, dyspepsia, constipation
	occasional	Abdominal pain, vomiting, pyrosis
Liver	very seldom	Increase of liver enzymes

In general, tolerability improves during up-titration of the dose. Please inform your study doctor immediately if you experience any adverse events during the study conduct.

Study procedures
Some of the procedures performed during the course of the study may cause some discomfort:

- Single blood samples will typically be taken with a disposable needle.
- Where more frequent blood samples are to be taken, an intravenous cannula will be used. An intravenous cannula is a thin tube made of flexible plastic that is inserted via a metal cannula. It is most commonly inserted into a forearm vein or a cubital vein (where the arm bends at the elbow). Once inserted it remains there for a period of time (for instance, the remainder of the day) until the required blood sampling is completed.

Puncturing veins with either a disposable needle or a cannula does not generally carry any risk. However, in some rare cases there may be a risk of bleeding into the surrounding tissue. Very rarely there may be some inflammation of the vein, formation of blood clots (thrombosis) or nerve injury.

Other examinations performed during the study, such as ECG recording, measurement of vital signs (blood pressure, pulse rate) carry no risk.

Every first day of a new up-titration period your blood pressure will be monitored hourly by an ambulatory device. You will take this device to your home, take it off in the evening and bring it back to the research unit at the next opportunity. Whilst the hourly automatic measurements of the device might be distracting, they are of no risk.

Unknown Risks
It is possible that the study drug may cause other undesirable or unwanted effects which are not known at this time. You will be immediately informed if any information becomes available that may affect your willingness to continue participating in the study.

If you agree and are selected to take part in this study, then it is very important that:

- you follow all instructions given by the study team,
- you come to the research unit for all scheduled visits or other visits requested by the study team,
- if you have a problem in keeping an appointment at the research unit, then please inform the study team in advance,
- you follow all instructions given to you about the use of other medications during the study and keep a record of any other medications that you take. Do not take any medications without the permission of the study team,
- you report any undesirable, unwanted or unusual symptoms you experience (adverse events),
- you report any changes in or worsening of existing conditions
- you do not consume food containing poppy-seeds
- you maintain your usual intake of coffee or other caffeine-containing beverages (e.g. black tea or cola)
- you maintain your usual smoking habit
- you avoid strenuous physical exercise
- you do not bring food and beverages to the unit, you will be provided with standardized meals at the unit
- you must not have participated in any other clinical study within the previous month and you must not do so during your participation in this study
- you must not have donated blood or plasma during the last 3 months
- you do not take any illegal drugs (e.g. cannabis or cocaine)

Are there any benefits for taking part in the study?

If you participate in this study you will undergo many study related procedures and medical examinations. These will include a thorough evaluation of your health status. The information obtained from your participation in this study may be of help to patients in the future.

Please be aware that there is no guarantee that participating in this study will be of any medical benefit to you. You do not have to participate in this study to receive treatment for your condition.

Further treatment with ropinirole PR/CR won't be available to you after the end of the trial. Your neurologist will decide about how to continue with your regular treatment.

What payments will be made for the study?

You will receive financial compensation for participating in this study. If you are accepted into the study and complete all study procedures and visits you will receive the sum of 2635,- Euro.

Please be aware that if you decide to leave the study early, or are withdrawn from the study, you will be paid a proportion of this amount. This will be based on how long and in how many procedures you participated.

If you complete the screening procedures but are found not to be eligible to take part in the study, then you will receive only a small compensation of 25,- Euro.

The first payment will be issued on the last day of the study (or later if necessary), a second payment when the study physician has reviewed all findings and no further controls are necessary. No interim payments will be made.

If you do not comply with the study requirements or subject responsibilities, which compromises the purpose of the study, the compensation you receive may be reduced as the respective data cannot be used for evaluation.

The [redacted] does not make any deductions for tax. Financial compensation is generally subject to income tax if your entire annual income exceeds the personal allowance specified in the tax schedule.

Who should I contact to answer any questions on the study?

The study team will be happy to answer any questions you may have about this study or your participation in it. You are free to ask questions at any time during the study. Please call if you have any questions about the study.

If you experience an injury, illness or develop any undesirable or unwanted symptoms (adverse events) during the study, immediately call:

weekdays 8 a.m. – 5 p.m.:	[redacted]
5 p.m. – 8 a.m. weekdays, all day weekends and public holidays:	[redacted]

For more information about your rights as a study volunteer, to ask any questions about participation in a study or to make a complaint about this study, you may also contact:

The Subjects Information Center at the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM – Federal Institute for Drugs and Medical Devices)

Bundesinstitut für Arzneimittel und Medizinprodukte
Fachgebiet Klinische Prüfung / Inspektionen
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn

Telefon: [redacted]
Fax: [redacted]

E-Mail: [redacted]

In the event if you are injured in the study what compensation will be available?

For this clinical study a liability insurance policy has been taken out in accordance with § 40, Paragraph 1, Clause 3, No. 8 and Paragraph 3 AMG (German Drug Law). This insurance covers damage to the health of the participants which occurs during the performance of the clinical study. In the event that a subject is killed or the body or the

health of the subject is harmed during the performance of the study, the insurance coverage will also take over liability if no other party will assume responsibility.

The insurance does not apply to health disorders, or their worsening, which would have occurred or persisted without your participation in this study. Nor does it cover genetic damage (changes of the genetic material [genome], of the chromosomes, of the genes or of individual nucleotides). However, the insurance cover will be provided in cases of organic health damage to the insured with effects on the clinical picture (phenotype).

The insurance cover is only guaranteed if you have not contravened the instructions and the conditions in the patient information. In particular, you are obliged:

- not to undergo any other medical treatment – **except in case of emergencies** - unless it is in agreement with the study physician,
- to immediately notify the insurer (the insurance company) about any damage to your health which could have occurred as a consequence of the clinical study.

In accordance with the law, after inclusion into the study you will be handed out the "General Insurance Conditions for Clinical studies" (for subject liability insurance), confirmation of the insurance coverage, the patient information and the informed consent form.

For this clinical study the insurance policy (policy no. [redacted]
has been taken out with

Alte Leipziger Versicherung AG
Alte Leipziger-Platz 1
61440 Oberursel
Tel.: [redacted]
Fax: [redacted]

to the amount EURO 500.000,- per subject, which is the legally recommended amount. Accordingly, you are insured up to a maximum of EURO 500.000,- in case of health damage, death or permanent disability.

The insurance does not cover accidents on the way to and from the research unit, nor compensation for injury resulting from your personal conduct or participation in activities outside the scope of the study protocol. Punitive payments and compensation for intangible damage (e.g. pain and suffering) are excluded.

Who will have access to medical and personal information about me that is collected in this study?

We need your permission to use your personal information and to collect information about you during the study. As such, you cannot participate in this study unless you sign the informed consent form which contains the "Consent to Data Protection" according to German Drug Law (AMD).

By signing the informed consent form, you are giving [redacted] permission to provide your personal information to these groups:

- The sponsor and anyone working on the sponsor's behalf,
- Government health authorities,
- An Institutional Review Board (IRB) or Ethics Committee that oversees the study,
- Other government or regulatory organisations that oversee the study,
- Other organisations such as central laboratories or central data readers.

These groups may use your records to check the information collected in this study, to check how the study is conducted, to monitor your safety, or for other uses allowed by law. [redacted] will also have to share your personal health information if the law requires it to.

[redacted] will collect information about you (such as study records, information about your general health, how you have responded to the drug, side effects you may have experienced, and the results of any tests done during the study) in a Case Report Form (CRF) or study chart.

All those samples, medical data and all results of the different tests will be encrypted (i.e. coded with a subject number only; not with your name or your initials). All transmissions or further evaluations of the data (done by the sponsor or third parties on behalf of the sponsor) will be performed in this so-called pseudonymous manner, which means no one except for the investigator can relate your subject number to your name. However, this coding does not completely exclude the risk of your personal identification.

In accordance with the German Drug Law (AMG § 40, Paragraph 2a, Clause 2, No. 1, Character a-d), you are informed herewith that, where necessary, the collected data:

- will be kept available for inspection by the supervisory authority or Sponsor's representative in order to verify the proper conduct of the clinical trial,
- will be passed on in a pseudonymised version to the Sponsor or to an agency commissioned by the latter for the purpose of scientific evaluation,
- will be passed on, in a pseudonymised version, to the applicant and the competent authority for the marketing authorisation if an application for a marketing authorisation is filed,
- will be passed on, in a pseudonymised version, to the sponsor and the competent authority and subsequently by the latter to the European database in the event of undesirable events in connection with the investigational medicinal product.

Your informed consent for the collection, processing and transmission of your personal data is irrevocable. If you withdraw your informed consent the stored data may be used further, if required, to evaluate effects of the study drug, to ensure that your interests are not affected, or for ensuring that complete data is available for marketing authorizations.

Furthermore, foreign regulatory authorities (e.g. Food and Drug Administration, FDA, in the USA) may inspect your personal data recorded during this study. Such inspections are also in your own interest. They are strictly confidential and are performed by specially authorized persons.

All the above mentioned representatives of the Sponsor and [redacted] are subject to professional secrecy. Your personal data will be treated with absolute confidentiality and will not be made available to the public; i.e. your name will not appear in any publication.

The sponsor assures that all data from this clinical study, including the case report forms, will be archived for at least 10 years after completion or discontinuation of the study.

You have the right of disclosure for all your personal data stored with the study physician or the study sponsor. Furthermore, you have the right to the correction of inaccuracies in your personal data. If you wish to request information, please ask your study physician. He will contact the study sponsor and provide information about your stored personal data.

If you agree to participate in this study, you agree to be tested for HIV (Human Immunodeficiency Virus), the virus that causes AIDS (Acquired Immunodeficiency Syndrome). You also agree to be tested for the presence of the Hepatitis viruses B and C.

Any subject who has a positive HIV or Hepatitis test may not participate in this study.

In accordance with the German law, positive HIV test results will be reported anonymously to the Robert-Koch Institute. A positive result for Hepatitis B or Hepatitis C will be reported by name to the responsible health authority. By agreeing to participate in this study, you agree that this information may be reported in the event it is necessary.

What will GlaxoSmithKline (GSK) do with the information it gets?

GSK may use the information that the study doctor gives it (i.e. the coded information):

- By storing and analyzing it electronically to find out what this study is telling us.
- By sharing it with regulatory authorities that approve new medicines, or with groups that check that research is done properly
- By publishing the results of the study (this will not include any information that directly identifies you)
- By sharing it as part of research with other companies or universities for the purpose of further understanding or developing this drug and with other GSK offices in this country and in other countries. If the information is sent to another country, GSK will apply the same level of protection to your information, to the extent permitted by local law
- By using it to plan new studies or other types of research or other medical purposes related to the development of the drug.

What will happen to tissue samples from this study?

Samples collected during the course of the study will be sent to the sponsor for further analysis. Your samples will be treated confidentially and in a way which does not identify you by name. The sponsor may contract other third parties (e.g. laboratories) to support the processing and analysis of your samples. The sponsor or any third parties that it works with will only process your samples for the intended purpose of this study.

If you decide at a later date to withdraw your consent and not to participate in the study, you have the right to request the destruction of your samples. However, the results from analysis of your samples that were obtained up to this time may still be used. The

sponsor or third parties will keep the generated results for at least 10 years. Your samples will be used only for the purposes mentioned in this patient information sheet.

How is GlaxoSmithKline involved?

This study is being performed on behalf of GSK, which is the study "Sponsor". The sponsor is paying for the study to be conducted.

THANK YOU FOR CONSIDERING PARTICIPATING IN THIS CLINICAL STUDY!

Consent Form

An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets.

GlaxoSmithKline
VERSION 1, DATED 29.01.2007
EUDRACT Nr. 2006-006209-94

Investigator: PD Dr. [redacted]

Patient's Name: _____ Date of Birth: _____
(Full name in BLOCK CAPITALS) (Day/Month/Year)

Data protection: Explanation of Data Protection Requirements

I understand that in this clinical study personal data relating to me, in particular medical findings, will be collected, stored and analyzed. The utilization of information relating to my health is done in accordance with legal requirements and I must give my free consent to this. Without that consent I cannot take part in the clinical study.

Consent to Data Protection (German Drug Law)

1. **I give consent that data recorded in this clinical study, in particular relating to my health, can be stored in paper and electronic form by [redacted] If necessary the pseudonymised (encoded) data may be transferred:**
   a. **To the sponsor GlaxoSmithKline or to their designee (GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK) for the purpose of scientific evaluation.**
   b. **In the case of a marketing authorization: to the applicant and to the authorizing authority (Bundesinstitut für Arzneimittel und Medizinprodukte, FDA).**
   c. **In the case of adverse events: to GlaxoSmithKline, to the responsible ethical committee, to the competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte) and furthermore, to the European Database.**
   d. **To authorities in Europe and non-European countries (e.g. Laboratories).**

2. **I give consent that designated representatives of GlaxoSmithKline who are bound to confidentiality and the competent national and international authorities may examine my personal data, in particular relating to my health, which are stored with my study physician for as long as this is necessary for auditing that the study is being performed correctly. For this purpose I release the study physician from his requirement to patient/physician confidentiality.**

3. **My consent to collect and analyze my personal data, in particular relating to my health, is irrevocable. It has been explained to me that I can end my participation in the clinical study at anytime. In the case that I revoke my consent to participate in the study, I give consent that all data stored up until that point in time can be used in the future without reference to my name if it is necessary for:**
   a. **The evaluation of the effectiveness of the study medication**

b. Ensuring that my interests are not affected
c. Ensuring that complete data is available for marketing authorization

4. I give consent that my data after completion or cancellation of the clinical study may be stored for at least 10 years, as is required by laws governing clinical studies of test substances. After that period my personal data will be destroyed, except when this is not possible for legal or contractual reasons.

5. I have been informed about the following regulations: in the case that I revoke my consent to participate in the clinical study, all authorities or parties who have stored my personal data, in particular relating to my health, must immediately review the need to retain my personal data for the purposes which are outlined in §3 a to c. Data which is not required must be destroyed immediately.

6. I confirm that _____
(Name of person obtaining consent in BLOCK CAPITALS)
has informed me of the nature and objectives of this clinical study and the possible risks related to it.
7. I have been provided with a copy of the "General Insurance Conditions for Clinical Trials" and the Insurance confirmation as well as of the Patient Information Sheet. I have understood the information given orally and in writing and I agree to comply with the clinical study and its terms as laid out in the Patient Information Sheet. This includes effective birth control (if applicable).
8. I understand that my participation is entirely voluntary and that I may withdraw from this clinical study at any time without affecting my future medical care or legal rights.
9. I understand that all specimens and samples obtained from me during the study are the property of GlaxoSmithKline.
10. **I hereby declare my voluntary agreement to participate in this clinical study.** I have received a copy of this consent form.

Subject's Signature _____ Date: _____
DD/ MM/ YY

Printed name of Subject _____

Statement of Person Obtaining Informed Consent:
I, the undersigned, have fully explained the details of this clinical study as described in the Patient Information Sheet to the patient named above.

Signature of Person conducting Consent _____ Date: _____
DD/ MM/ YY

Printed name of Person conducting Consent _____

Initials | | | | **Screening No.** **S** | | | |

PATIENT INFORMATION LEAFLET AND CONSENT FORM

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets

[redacted] **Study No:** [redacted]

[redacted]

[redacted]

Sponsor Name: GlaxoSmithKline

Sponsor No: ROP109087

INTRODUCTION

You are being invited to volunteer to participate in a research study being conducted on behalf of the sponsor GlaxoSmithKline. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your own doctor if you wish. Ask us if there is anything that is not clear to you or if you would like more information. Take time to decide whether or not you wish to take part.

The screening procedures form part of the study and therefore we need to obtain your consent before we undertake any screening tests. The results of these tests will determine whether you are eligible to participate in the treatment phase of the study.

WHY IS THE STUDY BEING DONE?

Parkinson's disease (PD) is one of the most common neurological disorders in elderly people. It is caused by a loss of a certain type of nerve cells, called dopaminergic nerve cells. The mainstay in the treatment of Parkinson's disease is the administration of dopaminergic agents. The drug that will be tested in this research project, called ropinirole, is one of the dopaminergic agents.

Ropinirole immediate release film-coated tablets (called ropinirole IR) is registered for use of treating Parkinson's disease in more than 60 countries world-wide at doses of up to 24 mg/day. These tablets (ropinirole IR) are administered 3 times daily. A prolonged-release (PR/CR) tablet formulation of ropinirole has been developed to provide a once a day formulation for the benefit of patients.

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The prolonged-release formulation of Ropinirole (PR/CR) is currently available in tablet strengths of 2, 4 and 8 mg. Since some patients require doses higher than 8mg, a 12 mg tablet has now also been developed.

The purpose of this study is:

- To compare the concentrations of ropinirole in the blood following treatment with the different strengths, i.e 4mg, 8mg and 12mg.
- To establish whether the body will get the same exposure to ropinirole if the patient takes 3x4mg tablets as opposed to taking 1x12mg tablet.
- To establish whether the body will get the same exposure to ropinirole when the tablet (12mg strength) is taken in the prescence or absence of food.

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HOW LONG WILL THE STUDY LAST?

If you agree to take part, you will first undergo the screening procedures as detailed overleaf. These procedures will help the study doctor decide whether you can take part in this study and are part of the study itself. The study will consist of three periods: a screening, treatment and follow-up period. The duration of the three periods is described overleaf:

Period	*Duration*	*Number of visits*
Screening	1 day (within 28 days of start of the treatment period)	1 visit (up to 3 hours)
Treatment	Approximately 44 days	* 3 x clinic visits of 4h duration with 3 x short visits within 24 hours to return blood pressure measuring equipment * 1 x short admission of 40h duration with 1x short visit within 24 hours of discharge to return blood pressure measuring equipment * 1 x long admission of 11 nights and 10 days
Follow-up	1 day (within 14 days after last administration of the study drug)	1 visit (1 hour)

The entire study, from screening to follow-up, will take approximately eleven (11) weeks to complete.

WHY HAVE I BEEN CHOSEN?

You are being asked to take part in this study because you have Parkinson's Disease. The basic requirement for people to join this study are men and women aged between 30 and 85 years who have Parkinson's Disease and who fulfil certain criteria at the screening visit, such as: a body mass index between 18 and 32kg/m^2 and a body weight of at least 50kg; normal blood pressure and electrocardiogram (ECG - which is a tracing of your heart rhythm).

You are being invited to volunteer for this study because we think that you might meet the description above. However, until all screening checks have been carried out and reviewed by the doctor at the beginning of the study, your participation in the study is not guaranteed.

The study will be conducted in two countries, South Africa and Germany. [redacted] will conduct the study in South Africa. A total of approximately 24 patients will be enrolled into the study.

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DO I HAVE TO TAKE PART?

Your participation is completely voluntary. It is up to you to decide whether or not to take part. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect your access to other medical care. If you do decide to take part you will be given this information leaflet to keep and will be asked to sign the consent form (pages 14 and 17 of this document).

Withdrawal from the study:
Your safety and well being is our primary concern. You may therefore be withdrawn from the study at any time if any of the following occur:

- at your request, irrespective of the reason
- if it is found that you did not give an accurate history
- if you do not adhere to the requirements of the study
- if the study doctor believes it will be in your best interests, at which stage he/she will discuss the reason with you
- if you have a symptom or illness, or a change in your blood tests which would rule out your further participation in the study

The study doctors and/or the Sponsor Company retain the right to stop the study, or stop your participation in the study at any time, for any reason, without your consent. If it is detected that you did not give an accurate history or did not follow the guidelines of the trial and the regulations of the trial facility, you may be withdrawn from the trial at any time.

If you withdraw from the study, or are withdrawn, you will be required to attend an Early Termination Visit after withdrawal for the same tests as described in the Follow-up visit above.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

Screening

There will be a screening examination within 28 days of the date that the study medication is to be given. This examination involves some medical tests, which usually take 2 – 3 hours, to help the study doctors decide if you are suitable to take part in the study.

You will be asked about your health, if you are taking any treatment for a medical condition or illness and about any operations or illnesses you have had in the past. A full medical history will be performed, including information about how much alcohol you drink and any previous smoking habits. The study doctor will do a physical examination which will include measuring your height and weight, as well as measurement of your blood pressure, pulse and body temperature. An electrocardiogram (ECG) will also be performed to check the rhythm of your heart.

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At this visit a nurse will collect blood and urine samples from you for laboratory tests of full blood count, liver and kidney function test and urinalysis. A serum pregnancy test will be conducted on female subjects of child bearing potential. The urine sample will also be used to screen for substances of abuse (such as cannabis, cocaine and opiates) and you will not be able to participate if this is positive. A saliva alcohol test will also be performed.

You will also be tested for HIV 1 and 2 antibodies, as well as indications of Hepatitis B or C infection in your blood. Please refer to the Addendum to the Volunteer Information Leaflet which you also need to sign prior to testing.

These tests are to check that you are well and eligible to take part in this study.

If the results of the screening examination show that you are a suitable candidate for the study, you will be given an appointment for the next clinic visit and will be told how to prepare for that visit.

Treatment period (Day 1 to Day 44)

The following table gives a day by day overview of study procedures that you will asked to undergo:

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Study day and visit time	**Study visit procedures**
Day 1 – Clinic visit in the morning **1st dose of 2mg tablet** **(Treatment A)**	• Pre-dosing assessments: Urine substance abuse screening and alcohol test, 12 lead ECG, Blood pressure and pulse rate monitoring, pregnancy test (on women of child bearing potential), Health inquiry. • An Ambulatory Blood Pressure Monitor (ABPM) device will be connected to record the blood pressure over the next 12 hours. • Breakfast. 30 Minutes later dosing with 2mg Ropinirole PR/CR tablet • Discharge 2 hours after dosing if the investigator is satisfied, with the ABPM device connected for another 10 hours. • The ABPM device must be returned to the clinic by the next morning.
Day 2-7	Home dosing with 2mg Ropinirole PR/CR tablets and completion of diary card
Day 8 – Clinic visit in the morning **1st dose of 4mg tablet** **(Treatment B)**	• Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, Health inquiry. • An Ambulatory Blood Pressure Monitor (ABPM) device will be connected to record the blood pressure over the next 12 hours. • Breakfast. 30 Minutes later dosing with 4mg Ropinirole PR/CR tablet • Discharge 2 hours after dosing if the investigator is satisfied, with the ABPM device connected for another 10 hours. • The ABPM device must be returned to the clinic by the next morning.
Day 9-13	Home dosing with 4mg Ropinirole PR/CR and completion of diary card
Evening of Day 13 until Mid morning on Day 15 **Day 14 24-hour blood sampling profile at 4mg dose level**	• Admission to the Clinic on the evening before the profile day. Fasting from 10pm that night. Plain water is allowed up to one hour before dosing. • Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, health inquiry, and insertion of an intravenous canula for collection of blood samples • Dosing with 4mg Ropinirole PR/CR • Blood sampling: up to 12 blood samples over 24 hours • Regular monitoring of blood pressure and pulse, health inquiry

Day 15 – **1st dose of 6mg tablet** **(Treatment C)**	• Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, Health inquiry. • An Ambulatory Blood Pressure Monitor (ABPM) device will be connected to record the blood pressure over the next 12 hours. • Breakfast. 30 Minutes later dosing with 6mg Ropinirole PR/CR tablet • Discharge 2 hours after dosing if the investigator is satisfied, with the ABPM device connected for another 10 hours. • The ABPM device must be returned to the clinic by the next morning.
Day 16 - 21	Home dosing with 6mg Ropinirole PR/CR and completion of diary card
Day 22 – Clinic visit in the morning **1st dose of 8mg tablet** **(Treatment D)**	• Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, Health inquiry. • An Ambulatory Blood Pressure Monitor (ABPM) device will be connected to record the blood pressure over the next 12 hours. • Breakfast. 30 Minutes later dosing with 8mg Ropinirole PR/CR tablet • Discharge 2 hours after dosing if the investigator is satisfied, with the ABPM device connected for another 10 hours. • The ABPM device must be returned to the clinic by the next morning.
Day 23-27	Home dosing with 8mg Ropinirole PR/CR and completion of diary card
Admission on the Evening of Day 27 until the morning of Day 37 **Day 28 – 24-hour blood sampling profile 8mg dose level**	• Admission to the Clinic on the evening before the profile day. Fasting from 10pm that night. Plain water is allowed up to one hour before dosing. • Day 28 - Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, health inquiry, and insertion of an intravenous canula for collection of blood samples • Dosing with 8mg Ropinirole PR/CR • Blood sampling: up to 12 blood samples over 24 hours • Regular monitoring of blood pressure and pulse, health inquiry

Treatment E (Days 29-31) or (Days 32-34) or (Days 35-37) **Ropinirole PR/CR 12mg - fasted**	**Treatment F** (Days 29-31) or (Days 32-34) or (Days 35-37) **Ropinirole PR/CR 12mg - fed**	**Treatment G** (Days 29-31) or (Days 32-34) or (Days 35-37) **Ropinirole PR/CR 3x4mg tablets - fasted**

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Day 29 – **Randomisation** to treatment regimen **1st dose of 12mg (either 1x12mg tablet or 3x4mg tablets)**	• Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, Health inquiry. • An Ambulatory Blood Pressure Monitor (ABPM) device will be connected to record the blood pressure over the next 12 hours. • Breakfast. 30 Minutes later dosing with 1x12mg Ropinirole PR/CR tablet or 3x4mg Ropinirole PR/CR tablets
Days 30	• Drug intake in the morning • Fasting from 10pm the night before dosing. Plain water is allowed up to one hour before dosing
Days 31 24-hour blood sampling profile at 12mg dose level	• Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, health inquiry, and insertion of an intravenous canula for collection of blood samples • Dosing according to randomized treatment • Blood sampling: up to 12 blood samples over 24 hours • Regular monitoring of blood pressure and pulse, health inquiry
Day 32	• Pre-dosing assessments: 12 lead ECG, Blood pressure and pulse rate monitoring, Health inquiry. • Breakfast (if applicable), dosing
Days 33 to 37	Day 33 – see program for Day 30 Day 34 – see program for Day 31 – **24-hour blood sampling profile** Day 35 – see program for Day 32 Day 36 – see program for Day 30 Day 37 – see program for Day 31 – **24-hour blood sampling profile**
Days 38 to 44 **Down titration (at home)** **Or in the event of withdrawal from the study**	• Discharge from the clinic on the morning of Day 38 • Patients will be provided with medication to be taken in specific doses for a specified number of days, to prevent adverse events due to rapid discontinuation of the study drug

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To make it as comfortable as possible for you during the collection of the blood samples on a blood profile day, a doctor or nurse will insert an intravenous cannula (a small plastic tube) into one of the veins of your forearm on the morning before study medication administration. Blood samples will be collected through this cannula which remains in your vein so that you can move around quite easily. The cannula will be removed before you are discharged from the unit.

Follow-up period

Seven (7) to 14 days after the last study medication administration, a post-study follow-up examination will be done to ensure that you are well. This visit will include the same type of investigations as during the screening period.

The study doctor will review your medication and will ask about any changes in your health and about any symptoms you might have experienced.

WHAT ELSE DO I HAVE TO DO?

You will be required to adhere to the following restrictions:

Medicines: The study doctor will review all the medication that you are currently using. There are certain medications that are not allowed during the study, and it is therefore essential that you provide as much information as possible about the medication that you are currently receiving, and that you do not use other medication during the study without consulting the study doctor. **Female volunteers using hormone replacement therapy should be on the same treatment and dose for at least 1 month before Day 1.**

The following are examples of medications not allowed during the study: Pergolide, Mirapex, Rifampicicn, Omeprazole, ciprofloxacin, etc.

If you are taking a medication that is allowed during the study, you will be allowed to continue these if you have been taking the same dose for at least 7 days before the first dose administration. If you are taking medication for PD which is not allowed under the protocol (such as Pexola) it will need to be stopped at least 7 days prior to your first dose of study medication. However, it will be stopped only if you are eligible for study participation.

If you have a problem and you think you will need some medication, please telephone one of the [redacted] doctors **before** you take anything, on [redacted] or on the mobile phone [redacted] or [redacted] One of the doctors can always be contacted on one of these telephone numbers.

Diet: You will have to refrain from consuming any food or drink containing caffeine during the 10 hours before study medication administration on a profile day (Days 14, 28, 31, 34, 37). On other days during the study you should maintain your usual caffeine intake. Caffeine is present in food and beverages such as: Coffee, Tea, Cola-flavoured drinks (e.g. Coke®) Cocoa, Chocolate, Caffeine-containing beverages (e.g. Red Bull®).

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You are requested to consult the labels on food products to determine if they contain alcohol and/or caffeine.

Poppy seed-containing food (e.g. poppy cake/muffins) will not be allowed during the three days before the screening visit and three days before every treatment phase because this can falsify your urine substance of abuse screening result.

For profile days you will have to be fasted from 10pm the night before until four hours after study medication administration. You will be allowed to drink water up to 1 hour prior to dosing and from 1 hour after dosing. You will receive standardized meals whilst you are admitted to the study unit.

You will receive a High Fat Meal 30 minutes before dosing on either Day 31, 34 or 37. You will have to consume the whole meal over a period of 30 minutes. This High Fat meal will consist of:

2 slices of toasted white bread with butter
2 eggs fried in butter
2 slices of bacon (15g)
1 helping (114g) hash-browned potatoes
1 glass (227mL) whole milk

The consumption of food that contain broccoli, Brussels sprouts, cabbage, etc. or charcoal-broiled meat should be kept stable throughout the study and you should avoid new introduction or discontinuation of these food items.

On the days when you take your study medication at home, you can take this after your normal breakfast.

Alcohol: Moderate alcohol intake to a maximum of 2 units per day for women, and 3 units per days for men is allowed. You will have to refrain from consuming any alcohol during the 3 days before each admission to the study unit and for the time admitted to the unit. One unit of alcohol is equivalent to a can of beer (340ml), a small glass of wine (200ml) or a one tot drink of spirits (25ml).

Smoking: Your smoking habit will be recorded in your medical history during the screening visit. Only patients who smoke 20 cigarettes per day or fewer will be allowed to take part in the study. You should keep your smoking habit constant throughout the study.

Exercise: Strenuous physical exercise (including competitive sport) will not be allowed 48 hours before the screening, treatment, and follow-up periods.

Postural restriction: After the first dose of study medication at each dose level (up-titration days 1, 8, 15, 22, 29), you will have to remain in a supine or semi-supine (bed rest) position for 2 hours after dosing.

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Study identification card: You will be given a small card at the screening day. This has information about the study on it and it is important that you keep this card with you at all times until you have completed the whole study. It is important to show this to any medical doctor who might treat you in an emergency situation, or if you visit another doctor, because it may be important for the doctor to know what medication you took and that you are on a clinical trial.

WHAT IS THE MEDICATION THAT IS BEING TESTED?

If you qualify and agree to take part in the study, you will receive Ropinirole controlled release tablets which are being developed for the treatment of PD.

WHAT ARE THE SIDE EFFECTS AND RISKS OF TAKING PART?

Your condition may not improve, or it may worsen, while taking the study medication.

All drugs may cause side effects in some people. There may be some risks, inconveniences, or side effects from study drugs or study procedures that are not known at this time. Side-effects of Ropinirole PR/CR are generally mild and may become less after you have taken the medicine for a short time. Ropinirole (as an immediate release formulation, also called Requip®) has been marketed in South Africa since 1999 as a treatment for Parkinson's disease. The PR/CR tablet which is being tested in this study is a slow release formulation of the same medication and its side effects are expected to be similar to the immediate release formulation as follows:

The most common side effects of ropinirole IR known to GlaxoSmithKline from clinical trials with patients with RLS and volunteers without RLS are:

Very common side effects:

- feeling sick (nausea and vomiting)

Common side effects:

- feeling drowsy or sleepy
- dizziness (or spinning sensation)
- abdominal pain
- fainting
- fatigue (tiredness)
- nervousness

Headache and upper respiratory tract infections have also been reported commonly as adverse events in these clinical studies, but at a similar frequency in patients treated with either ropinirole IR or placebo.

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Additional side effects of ropinirole known to GlaxoSmithKline from clinical trials with patients with Parkinson's disease and post-marketing experience are:

Very common side effects:

- unwanted, fidgity movements (when ropinirole is taken in combination with Levodopa/L-Dopa)

Common side effects:

- a drop in blood pressure that may make you feel dizzy or faint especially when standing up from a sitting or lying position.
- experiencing hallucinations
- swelling of the hands, ankles or feet
- constipation
- dyspepsia (e.g. feeling full up and bloated, experiencing heartburn)
- confusion (when ropinirole is taken in combination with Levodopa/L-Dopa)

Uncommon side effects:

- increased sexual desire
- other psychotic reactions in addition to hallucinations, such as severe confusion (delirium), irrational ideas (delusions) and irrational suspiciousness (paranoia)
- A small number of patients taking ropinirole have developed a problem with gambling. It is not known if this problem is directly related to the medicines or is due to other reasons. If you or your family notices that you have an unusual urge to gamble, talk to your doctor.

Very rare side effects:

- fall asleep suddenly without apparently feeling sleepy. If you feel extremely tired during the day or fall asleep suddenly without apparently feeling sleepy you should see your doctor.

There is always the possibility of any adverse event occurring. You may, for example, experience an allergic reaction after taking the study medication, but this type of reaction is always a possibility if you take any foreign substance.

If you experience any new symptoms while on the study, it is important that you tell the nurses or doctors even if you do not think they are related to the study medication. It does not matter how mild the effect is - even if it is only a sore throat, this should be reported. It is very important that you are honest about any symptoms you have so that the safety of the medicines being tested can be accurately assessed.

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WHAT ARE THE DISADVANTAGES OF TAKING PART?

Drawing of blood samples can result in discomfort. It may cause bruising where the needle is inserted or less commonly, swelling of the vein, infection or bleeding from the site. For your protection, all blood sampling is performed under clean conditions by experienced personnel. The total volume of blood collected during the study will be approximately
360 ml (approximately 1 and a half cupfuls – less than the volume collected when you donate blood).

During the study you will be required to give blood samples as described earlier. As your safety is of the greatest importance, we may need to take a few extra samples if we see any changes in the results of your blood tests. This is a summary of the number of samples and the volume of blood to be taken at the study visits:

Screening	7 tubes – 37mL which is just over 2 tablespoonfuls
Day 14	12 tubes – 60mL which is approximately 4 tablespoonfuls
Day 28	12 tubes – 60mL which is approximately 4 tablespoonfuls
Day 31	12 tubes – 60mL which is approximately 4 tablespoonfuls
Day 34	12 tubes – 60mL which is approximately 4 tablespoonfuls
Day 37	12 tubes – 60mL which is approximately 4 tablespoonfuls
Follow-up	5 tubes – 22mL which is just under 2 tablespoonfuls

If you have private medical insurance you should check with the insurance company before you agree to participate to make sure that doing the study will not affect your insurance cover.

Occasionally, during the screening examinations, a medical condition is found which the participant did not know about, such as high blood pressure, abnormal heart function or anaemia. If any condition is found which you did not know you had, the study doctor will advise you of the best thing to do and, with your written permission, will contact your own doctor to inform him or her of the finding. All such information will be treated with the strictest confidence. The only exception to this rule will be cases where a law exists compelling us to report individuals infected with a communicable disease. In this event, you will be informed of our intent to disclose such information to the authorised state agency.

ARE THERE ANY ALTERNATIVE TREATMENTS AVAILABLE?

If you decide not to take part in this trial, you will continue to use the medication that you are currently taking for treatment of your Parkinson's Disease. These may include, but are not limited to treatment such as levodopa (e.g. Sinemet®, MAO-B inhibitors (e.g. selegiline), COMT-inhibitors (e.g. entacapone), or other medications that work in a similar way to the study medication, called dopamine agonists.

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ARE THERE ANY BENEFITS FOR ME FROM TAKING PART IN THIS TRIAL?

You may already be receiving treatment with ropinirole as part of your maintenance therapy. You may get benefit from treatment with ropinirole during the study, but this cannot be guaranteed. The effectiveness of ropinirole in the treatment of Parkinson's Disease is not the focus of this study; instead, the information we get from this trial may help us to improve treatment regimens for people with Parkinson's Disease in the future.

CHILDBEARING POTENTIAL

Experimental medications may have unforeseen side effects. Birth defects, including physical deformities, mental retardation and other problems, as well as premature birth, are known risks of some medications. While the results from studies in animals are important and may be relevant to what happens in humans, the effects of ropinirole on the growth and development of an unborn baby are not known because testing of ropinirole is still incomplete. There may be unknown risks to the fetus (unborn baby) if you are a female participant or if your female partner (if you are a male participant) becomes pregnant while participating in this study or to an infant if you are nursing.

The effects of ropinirole on the unborn child or the nursing baby are not known, therefore, pregnant or breastfeeding women cannot participate in this study. If you are a female of childbearing potential, you will be tested to make sure you are not pregnant at the Screen, Day 1 and Follow-Up Visits.

For the reasons outlined above, if you choose to participate in this study, you must use one of the allowed contraceptive methods (a way to prevent you or your partner from becoming pregnant) before you enter the study and for one month after you complete the study:

Female participants: If you are female of child bearing potential you will have to use an accepted method of contraception such as oral contraception, surgical sterilization, Intra-uterine device (IUD), diaphragm in conjunction with spermicidal foam, condom on the male partner in conjunction with spermicidal foam. ***Women who are breastfeeding may not take part in this study.***

Male participants: You and/or your partner use birth control in the form of a barrier method i.e. condoms, while you are on the study. Your partner should not become pregnant for at least 3 months after the start of study and should therefore be using an effective method of contraception, i.e. oral contraception or a diaphragm with spermicide.

Ask your doctor if you have any questions about these choices and which might be best for you.

Pregnancy: If you find that you or your partner (in the case of male volunteers) fall pregnant, while you are participating in the study you should inform the study investigator immediately. You will be required to withdraw from the study. In this event the pregnancy will be followed up to determine the outcome. Follow-up will be no longer than 6 to 8 weeks past the expected delivery date.

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Your study doctor will help to make sure you get medical advice for the proper care of you and your unborn baby. Your study doctor will continue to collect information about you.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

Sometimes during the course of a research project, new information becomes available about the medication that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, the study doctor will wish to give you a brief health check before discharging you. If you decide to continue in the study you will be asked to sign an updated consent form. Also, the study doctor might decide from the new information that it is in your best interest to withdraw you from the study. In such circumstances, the study doctor will explain why and will give you a brief health check.

WHAT IF SOMETHING GOES WRONG?

The sponsor undertakes that in the event of you suffering any significant deterioration in health or well being, or from any unexpected sensitivity or toxicity caused by your participation in the study, it will provide immediate medical care.

The sponsor has appropriate insurance cover to provide prompt payment of compensation for any reasonable and customary medical expenses in accordance with the Association of the British Pharmaceutical Industry in *Clinical Trial Compensation Guidelines*, ABPI January 1991, **in the event of an injury resulting directly from participation in the trial**.

Broadly speaking, the ABPI guidelines recommend that the sponsor of the study, without any legal commitment, should compensate you, without you having to prove that it is at fault, for any injury resulting from giving the study medication or other procedures carried out in accordance with the protocol for this study.

The sponsor will not be liable for any loss, injuries and/or damages which you may sustain to the extent that such loss is caused by:

- The use of other medicine during the study
- Any injury caused by a departure on your part from the study protocol, the requirements of the study/and or any instructions or indication which the study doctor may give to you
- Any injury arising from any act or omission on the part of a third party to deal adequately with an adverse event or reaction to the study medication
- An injury arising from negligence on your part

During the course of the clinical study you may not participate in any other study.

You must notify the study doctor immediately of any side effects and/or injuries during the trial; whether they are research related injuries or other related complications. Any

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deterioration in your health during or directly after the clinical study must be reported to the doctor at once.

Should you have to receive any medical care not pertaining to the study in question, this must be reported to the doctor.

The sponsor company reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right at law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

All information collected about you and your participation in this study, including hospital/clinic records, personal data and research data will be kept strictly confidential. The data will be stored, processed and summarised both manually and using computer technology and will be handed over to the Sponsor Company WITHOUT any means of identification. The Sponsor Company is legally bound to respect the laws concerning the use of any data containing personal information that it receives. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

This information will be reviewed by authorised representatives of GlaxoSmithKline.

The information might also be inspected by the [redacted] the South African Medicines Control Council (MCC) and/or other foreign regulatory authorities such as the United States Food and Drug Administration (FDA), as well as your personal doctor. Therefore, you hereby authorise the study doctor to release your medical records to GlaxoSmithKline, its employees or agents, domestic and foreign regulatory health authorities, the South African Medicines Control Council and the [redacted]

These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

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You will have the right to inspect you own personal information to ensure that it accurate, and to correct any inaccuracies. The right to correct your personal information does not extend to study data gathered during the actual study period.

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PERSONAL DOCTOR / SPECIALIST NOTIFICATION

Please indicate below, whether you are willing for the study doctor to notify your personal doctor or your specialist of your participation in this study:

Tick		**Initials**
☐	YES I want you to inform my personal doctor / specialist of my participation in this study.	
☐	NO, I do not want you to inform my personal doctor / specialist of my participation in this study but accept receipt of an information letter addressed to my general practitioner regarding participation in this study should I undertake to forward this to my GP.	
☐	I do not have a personal doctor / specialist	

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results will be reported by the Sponsor Company for use in further development of Ropinirole PR/CR. The report will not include any means of identification of the volunteers who have taken part in the study. The Sponsor Company may use the data in scientific publications but this will not include any identity of the study volunteers.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

The study is funded by GlaxoSmithKline and will be conducted by [redacted] You will be compensated for the time that you spent at the research site for the study as well as the screening and follow-up visits. If you complete the entire study, or the investigator withdraws you for your own safety, you will receive R12,770.00 (Twelve thousand, seven hundred and seventy Rand). If you decide to withdraw from the study, you will receive a pro-rata payment at the discretion of the research site management. There will be no cost to you for your participation in this study. All study medication and study procedures performed during the study will be funded by the Sponsor.

WHO HAS REVIEWED THE STUDY?

The Clinical Trial Protocol for this study was submitted to the [redacted] and written approval has been granted by that committee. The South African Medicines Control Council has also provided written approval of the conduct of the study. The study has been structured in accordance with the Declaration of Helsinki, a copy of which may be obtained from the investigator should you wish to read it. The study will be conducted according to Good Clinical Practice Guidelines as specified by Guidelines for Good Practice in the conduct of Clinical Trials in Human Participants in South Africa.

SOURCE OF ADDITIONAL INFORMATION

Initials | | | | **Screening No.** **S** | | | |

For the duration of the trial, you will be under the care of Drs [redacted] and [redacted] If, at any time between your visits, you feel that any of your symptoms are causing you problems, or if you have any questions during the trial, please do not hesitate to contact any of them on telephone numbers [redacted] or [redacted]

If you have questions about this trial, please ask the study coordinator or study doctors (Dr [redacted] or Dr [redacted] If you have questions about your rights as a research subject, you may call The Chairperson, [redacted] tel. [redacted] If you believe you have sustained a research related injury, you may call Dr. [redacted]

After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

1.1.1.

1.1.2. The Registrar

SA Medicines Control Council

Department of Health

Private Bag X828

PRETORIA, 0001

Fax: [redacted]

Email: [redacted]

Initials | | | | **Screening No.** **S** | | | |

Informed Consent Form

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets

[redacted] **Study No:** [redacted]

[redacted]

[redacted]

Sponsor Name: GlaxoSmithKline

Sponsor No: ROP109087

2.	3. PRINCIPAL INVESTIGATOR DR [redacted]	4.	PLEASE INITIAL BOX	
1.	I hereby agree to undergo the screening procedures as described above in order to determine my eligibility for participation in a clinical study. I understand that until all pre-dose checks have been carried out and reviewed by the doctor before the first dosing day, my participation in this study is not guaranteed.	5. ☐	6.	7.
2.	I confirm that I have read and understood the information leaflet dated **07 December 2006** for the above study. I have been informed by Dr _____ about the nature, conduct, potential benefits and risks of this clinical trial with Ropinirole PR/CR and have had the opportunity to ask questions and they were answered to my satisfaction.	8. ☐	9.	10.
3.	I have been given time to discuss the information with others and to decide whether or not to take part in this study.	11. ☐	12.	13.
4.	I understand that my participation is given of my own free will and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	14. ☐	15.	16.
5.	I understand that sections of any of my personal data concerning this study may be looked at by responsible individuals from [redacted] GlaxoSmithKline, the [redacted] or from regulatory authorities. I give permission for these individuals to have access to and reproduce my records on condition that national legislature with respect to the protection of personal data is adhered to. I am aware that the results of the trial, including personal details regarding my sex, age, date of birth and initials will be anonymously processed into a trial report.	17. ☐	18.	19.
6.	I agree to take part in this study and understand the instructions relating to my participation in this study which have been communicated to me both verbally and in writing. I have been informed that disobeying the instructions may result in my exclusion from the study and forfeiture of the agreed remuneration.	20. ☐	21.	22.

Initials | | | | **Screening No.** **S** | | | |

7. For **female** participants of child bearing potential: I use a accepted method of contraception such as oral contraception, surgical sterilization, Intra-uterine device (IUD), diaphragm in conjunction with spermicidal foam, condom on the male partner in conjunction with spermicidal foam. I am not currently breastfeeding. 23 | | 24. 25.

8. For **male** participants of child bearing potential: I understand that to participate in this study, I should use contraception (condom in conjunction with spermicidal foam, diaphragm on the female partner in conjunction with spermicidal foam) during this study **26** | | 27. 28.

9 I will receive a signed copy of the Information Leaflet and Consent Form dated **07 December 2006**. 29 | | 30. 31.

		dd mm yyyy	hh mm
Signature: Volunteer	**Print all initials and Surname**	**Date**	**Time**
Signature: of person assisting with the consent discussion	**Print all initials and Surname**	**Date**	**Time**
Signature: Investigator	**Print all initials and Surname**	**Date**	**Time**

Initials | | | | **Screening No.** **S** | | | |

ADDENDUM TO
Information Leaflet and Consent Form

An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets

[redacted] **Study No:** [redacted]

[redacted]

[redacted]

Sponsor Name: GlaxoSmithKline

Sponsor No: ROP109087

INTRODUCTION

Please take time to read the following information carefully and discuss it with friends, relatives and your own doctor if you wish. Ask us if there is anything that is not clear to you or if you would like more information.

As part of the screening procedures and to be eligible to participate in the study we need to obtain your consent before we collect a blood sample from you to test for HIV 1 and 2 antibodies and Hepatitis B and C antibodies in your blood. The results of these tests will not only determine whether you are eligible to continue into the treatment phase of the study, but could also have a profound influence on your health and life style:

- Initially after infection with the HIV, the HIV-test may be falsely negative (for up to 6 months after infection) and this is referred to as the "window period";
- If you are involved in high risk behavior for the transmission of the HIV-virus (i.e. unprotected sex, multiple sexual partners, intravenous substance user, sharing of needles) you are more likely to be in the "window period" if your HIV-test is negative and you should, therefore, not take part in the study.
- The test results may, in some cases, yield a false positive (indicate that a person has antibodies to the virus when the person does not) or yield a false negative (fail to detect that a person has antibodies to the virus when the person has antibodies). A positive blood test result does not mean that you have AIDS and in order to diagnose AIDS other means must be used in conjunction with the blood test.

Initials | | | | **Screening No.** **S** | | | |

HIV (AIDS) TEST INFORMATION

This test is performed to ensure that you are healthy in all respects. Any underlying disease might give rise to symptoms that could be misinterpreted as side-effects of the medication being tested. This would make accurate analysis of the information gathered during the study impossible. In addition to this, the taking of a new and experimental medication might pose additional risks to your health if you were suffering from an underlying disease of which the study doctors were not aware.

Should your HIV screen test result be positive, you will be informed as such in person by the study doctor. He/she will also arrange for further confirmatory blood tests. Should these also result in a positive test, counselling will be arranged for you by the study doctor. It should be known that a positive test result may have a psychological impact on you and may profoundly influence your lifestyle. Knowing one's HIV status may have important advantages and disadvantages.

Initials | | | | **Screening No.** **S** | | | |

Advantages may include:

- Availing oneself to health care and counseling for HIV and hepatitis which has many benefits;
- Preventing the transmission of HIV and hepatitis to sexual partners;
- Informing one's partner so that he / she can also prevent the spread of HIV;
- Avoiding blood donations; and
- Preventing mother to child HIV transmission.

Disadvantages may include:

- Mental stress, depression and despair;
- Stigmatisation;
- Discrimination; and
- Rejection by family, friends, sexual partners and / or spouse.

These should be carefully considered before signing this consent document.

All information will be treated as strictly confidential. You are free to discuss any questions confidentially with the study doctor. Advice is also available at the nearest AIDS Information Centre, where HIV testing can be done.

Important notice:

It is important for you to note, that should you be tested during the screening period, and it is found that you are HIV positive, you cannot hold [redacted] or the sponsor of the study liable for any HIV treatment or care.

Initials | | | | **Screening No.** **S** | | | |

ADDENDUM TO
INFORMATION LEAFLET AND CONSENT FORM
An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12mg tablets

[redacted] **Study No:** [redacted]

[redacted]

[redacted]

Sponsor Name: GlaxoSmithKline

Sponsor No: ROP109087

32. **33. PRINCIPAL INVESTIGATOR DR** [redacted] **34. PLEASE INITIAL BOX**

1. I hereby agree to have blood drawn in order to undergo the HIV and hepatitis tests as described above in order to determine my eligibility for participation in a clinical study. I understand that until all pre-dose checks have been carried out and reviewed by the doctor before the first
2. I confirm that I have read and understood the information leaflet addendum dated **07 December 2006** for the above study. I have been informed by Dr about the nature, conduct, potential benefits and
3. I do not consider myself to be in a high-risk group for contracting the HIV- or hepatitis B and C virus and have no reason to believe that I have been previously exposed to these viruses. I understand that, if I consider myself to be at risk for HIV- or hepatitis-transmission, I should
4. I understand that I will be informed of the results of the test in person and in confidence, and that I will be advised regarding further counselling should the results be positive.
5. I understand that should I be tested and found to be HIV positive during the screening period, I cannot hold [redacted] or the Sponsor of the study liable for any HIV treatment or care
6. I will receive a signed copy of the Volunteer Information Leaflet and Consent Form Addendum, dated **07 December 2006**

35. 36. 37. 38. 39. 40. 41. 42. 43. 45. 51.

Initials | | | | **Screening No.** **S** | | | |

		dd mm yyyy	hh mm
Signature: Volunteer	**Print all initials and Surname**	**Date**	**Time**
		dd mm yyyy	hh mm
Signature: of person assisting with the consent discussion	**Print all initials and Surname**	**Date**	**Time**
		dd mm yyyy	hh mm
Signature: Investigator	**Print all initials and Surname**	**Date**	**Time**

Master Schedule Report

StudyID: *ROP109087*
Description: *An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12mg tablets.*

Treatments and Sequences defined for study

	Treatments		
Sequence	**Code**	**Description**	**Period**
A/B/C/D/E/F/G	A	2mg PR/XL 24h	1
	B	4mg PR/XL 24h	2
	C	6mg PR/XL 24h (1x4mg PR/XL 24h + 1x2mg PR/XL 24h)	3
	D	8mg PR/XL 24h	4
	E	1x12mg PR/XL 24h (fasted)	5
	F	1x12mg PR/XL 24h (high fat fed)	6
	G	3x4mg PR/XL 24h (fasted)	7
A/B/C/D/E/G/F	A	2mg PR/XL 24h	1
	B	4mg PR/XL 24h	2
	C	6mg PR/XL 24h (1x4mg PR/XL 24h + 1x2mg PR/XL 24h)	3
	D	8mg PR/XL 24h	4
	E	1x12mg PR/XL 24h (fasted)	5
	G	3x4mg PR/XL 24h (fasted)	6
	F	1x12mg PR/XL 24h (high fat fed)	7
A/B/C/D/F/E/G	A	2mg PR/XL 24h	1
	B	4mg PR/XL 24h	2
	C	6mg PR/XL 24h (1x4mg PR/XL 24h + 1x2mg PR/XL 24h)	3
	D	8mg PR/XL 24h	4
	F	1x12mg PR/XL 24h (high fat fed)	5
	E	1x12mg PR/XL 24h (fasted)	6
	G	3x4mg PR/XL 24h (fasted)	7
A/B/C/D/F/G/E	A	2mg PR/XL 24h	1
	B	4mg PR/XL 24h	2
	C	6mg PR/XL 24h (1x4mg PR/XL 24h + 1x2mg PR/XL 24h)	3
	D	8mg PR/XL 24h	4
	F	1x12mg PR/XL 24h (high fat fed)	5
	G	3x4mg PR/XL 24h (fasted)	6
	E	1x12mg PR/XL 24h (fasted)	7
A/B/C/D/G/E/F	A	2mg PR/XL 24h	1

Master Schedule Report

StudyID: *ROP109087*
Description: *An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12mg tablets.*

	Treatments		
Sequence	**Code**	**Description**	**Period**
	B	4mg PR/XL 24h	2
	C	6mg PR/XL 24h (1x4mg PR/XL 24h + 1x2mg PR/XL 24h)	3
	D	8mg PR/XL 24h	4
	G	3x4mg PR/XL 24h (fasted)	5
	E	1x12mg PR/XL 24h (fasted)	6
	F	1x12mg PR/XL 24h (high fat fed)	7
A/B/C/D/G/F/E	A	2mg PR/XL 24h	1
	B	4mg PR/XL 24h	2
	C	6mg PR/XL 24h (1x4mg PR/XL 24h + 1x2mg PR/XL 24h)	3
	D	8mg PR/XL 24h	4
	G	3x4mg PR/XL 24h (fasted)	5
	F	1x12mg PR/XL 24h (high fat fed)	6
	E	1x12mg PR/XL 24h (fasted)	7

Master Schedule Report

StudyID: *ROP109087*
Description: *An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12mg tablets.*

Schedule No: 1
Stratum Site 2 (South Africa)

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/E/G/F
	A/B/C/D/G/F/E
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	A/B/C/D/G/F/E
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/G/E/F
	A/B/C/D/F/G/E
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	Schedule
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E

Master Schedule Report

StudyID: *ROP109087*
Description: *An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12mg tablets.*

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/E/G/F
	A/B/C/D/G/F/E
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	A/B/C/D/G/F/E
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/G/F/E
	A/B/C/D/G/E/F
	A/B/C/D/F/G/E
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G

Master Schedule Report

StudyID: *ROP109087*
Description: *An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12mg tablets.*

Schedule No: 1
Stratum Site 1 (Germany)

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/F/G/E
	A/B/C/D/E/G/F
	A/B/C/D/G/E/F
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	A/B/C/D/F/E/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/F/G/E
	A/B/C/D/F/G/E
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/G/E/F

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/E/G/F
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/G/E
	A/B/C/D/F/E/G
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/G/E/F
	A/B/C/D/F/G/E
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
Schedule	
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	A/B/C/D/F/G/E
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E

Master Schedule Report

StudyID: *ROP109087*
Description: *An open label, repeat dose, dose escalation study conducted in Parkinson's Disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL 24h) 12mg tablets.*

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/F/G/E
	A/B/C/D/E/G/F
	A/B/C/D/G/E/F
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G
	A/B/C/D/F/E/G
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/F/G/E
	A/B/C/D/F/G/E
	A/B/C/D/F/E/G
	A/B/C/D/G/F/E
	A/B/C/D/E/F/G
	A/B/C/D/E/G/F
	A/B/C/D/G/E/F
	A/B/C/D/E/G/F
	A/B/C/D/G/E/F
	A/B/C/D/G/F/E
	A/B/C/D/F/E/G
	A/B/C/D/F/G/E
	A/B/C/D/E/F/G
	A/B/C/D/G/F/E
	A/B/C/D/E/G/F
	A/B/C/D/F/G/E
	A/B/C/D/F/E/G
	A/B/C/D/E/F/G
	A/B/C/D/G/E/F
	A/B/C/D/F/E/G

Randomisation Number	Treatment / Sequence
[redacted]	A/B/C/D/G/F/E
	A/B/C/D/G/E/F
	A/B/C/D/F/G/E
	A/B/C/D/E/G/F
	A/B/C/D/E/F/G

GlaxoSmithKline

PHARMACEUTICAL DEVELOPMENT
USE BY DATE CERTIFICATE

Protocol No.:	ROP109087	Job No.:	J113845
Countries:	Germany and South Africa		

Pack Description	Batch Details	Storage Conditions	Use by Date (Date that appears on label)
Bottles containing 33 x SKF101468 (Ropinirole) 2mg tablets	Input Batch No.: [redacted] Lot No: [redacted]	Store at 20 - 25°C	**31 October 2007** **(10/2007)**
Bottles containing 33 x SKF101468 (Ropinirole) 4mg tablets	Input Batch No.: [redacted] Lot No: [redacted]	Store at 20 - 25°C	**30 June 2008** **06/2008**
Bottles containing 33 x SKF101468 (Ropinirole) 8mg tablets	Input Batch No.: [redacted] Lot No: [redacted]	Store at 20 - 25°C	**31 October 2008** **(10/2008)**
Bottles containing 33 x SKF101468 (Ropinirole) 12mg tablets	Input Batch No.: [redacted] Lot No: [redacted]	Store at 20 - 25°C	**31 May 2009** **(05/2009)**

Created by: [redacted]	Date: 09 Feb 2007	Checked by: [redacted]	Date: 09 Feb 2007

This is to certify that the above Job and associated input batches have been manufactured, packaged and tested in compliance with current Good Manufacturing Practice in accordance with EU Directive 2003/94/EC and compliance with registered details will be assured prior to shipment in accordance [redacted] EU Directive 2001/20/EC.

Signed by: [redacted]	Print Name [redacted]	Date 10 APR 2007

Qualified Person, Pharmaceutic[redacted]evelopment Quality Assurance, Harlow, UK

New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW
Telephone: [redacted] Fax [redacted]

CONFIDENTIAL

CONFIDENTIAL

COA No.: [redacted]
Product: Ropinirole Hydrochloride CR Tablets 2mg (pfb)

GlaxoSmithKline

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline Research & Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel. [redacted]
Fax
www.gsk.com

Product: Ropinirole Hydrochloride CR Tablets 2mg (pfb)

Strength / Dose Form: 2mg/Tablet

Batch Number: [redacted]

Date of Manufacture: 07-October-2005

Site of Manufacture: GSK, Crawley, UK

Test	Acceptance Criteria	Results
Description	White, biconvex, capsule-shaped, film coated tablet, debossed with 'SB' on both sides	White, biconvex, capsule-shaped, film coated tablet, debossed with 'SB' on both sides
Identification of Ropinirole by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram
Ropinirole Content by HPLC (mg per tablet as pfb)	95.0 to 105.0% label claim (1.90 – 2.10 mg ropinirole pfb / tablet)	99.1% label claim (1.99 mg pfb / tablet)
Uniformity of Content by HPLC	Complies with USP <905> and Ph.Eur 2.9.40	Mean = 97.9% Range = 94.4-100.7% RSD = 1.8% L1 = 4.7
Drug-related impurities by HPLC (% w/w) SK&F 104557 SK&F 96266 SK&F98959 Any other individual degradation product Total degradation products[1]	 Not greater than 0.3 Not greater than 0.4 Not greater than 0.3 Not greater than 0.2 Not greater than 1.0	 0.06 0.13 0.09 0.07 0.34

Registered in England & Wales
No. 835139
Registered office
980 Great West Road
Brentford, Middlesex. TW8 9GS

gsk.0066a

CONFIDENTIAL

COA No.: [redacted]
Product: Ropinirole Hydrochloride CR Tablets 2mg (pfb)

Dissolution (% Ropinirole released)	Complies with USP <724> for extended release articles. The acceptance ranges of % Ropinirole released for the specified timepoints are:		
	After 2 hours	Not more than 20%	11 (11-11)
	After 12 hours	45 to 65%	48 (46-51)
	After 24 hours	Not less than 80%	87 (82-91)
This material conforms to Specification S0004920/1			

1. Total degradation includes all degradation products that have been detected at a level above the quantification limit.

This material was manufactured and tested in accordance with current Good Manufacturing Practices

Approved by: [redacted] **Date:** 06-DEC-2006

Qualified Person
Quality Assurance
GSK, Harlow, UK

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COA No.: [redacted]
Product: Ropinirole Hydrochloride CR Tablets 4mg (pfb)

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Product: Ropinirole Hydrochloride CR Tablets 4mg (pfb)

Strength / Dose Form: 4mg/ Tablets

Batch Number: [redacted]

Date of Manufacture: 17-June-2005

Site of Manufacture: GSK, Crawley, UK

Test	Acceptance Criteria	Results
Description	White, biconvex, capsule-shaped, film coated tablet, debossed with 'SB' on both sides	White, biconvex, capsule-shaped, film coated tablet, debossed with 'SB' on both sides
Identification of Ropinirole by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram
Ropinirole Content by HPLC (mg per tablet as pfb)	95.0 to 105.0% label claim (3.80 – 4.20 mg ropinirole pfb / tablet)	97.6% label claim (3.90 mg pfb / tablet)
Uniformity of Content by HPLC	Complies with USP <905> and Ph.Eur 2.9.40	Mean = 96.8% Range 94.3-99.4% RSD = 1.9% L1 = 6.1

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COA No. [redacted]
Product: Ropinirole Hydrochloride CR Tablets 4mg (pfb)

Test	Acceptance Criteria		Results
Drug-related impurities by HPLC (% w/w)			
SK&F 104557	Not greater than 0.3		0.05
SK&F 96266	Not greater than 0.4		0.16
SK&F98959	Not greater than 0.3		<0.05
Any other individual degradation product	Not greater than 0.2		0.06
Total degradation products[1]	Not greater than 1.0		0.32
Dissolution (% Ropinirole released)	Complies with USP <724> for extended release articles. The acceptance ranges of % Ropinirole released for the specified timepoints are:		
	After 2 hours	Not more than 20%	11 (10-11)
	After 12 hours	45 to 65%	50 (47-52)
	After 24 hours	Not less than 80%	88 (82-94)
This material conforms to Specification S0004922/1			

1. Total degradation includes all degradation products that have been detected at a level above the quantification limit.

This material was manufactured and tested in accordance with current Good Manufacturing Practices.
Approved by: [redacted] **Date:** 06-Dec-2006

Qualified Person,
R&D Quality Assurance
GSK, Harlow, UK

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COA No. [redacted]

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Product: Ropinirole Hydrochloride CR Tablets 8mg (pfb)

Strength / Dose Form: 8mg/Tablet

Batch Number: [redacted]

Date of Manufacture: 11-OCT-2005

Site of Manufacture: GSK, Crawley, UK

Test	Acceptance Criteria	Results
Description	White, biconvex, capsule-shaped, film coated tablet, debossed with 'SB' on both sides	White, biconvex, capsule-shaped, film coated tablet, debossed with 'SB' on both sides
Identification of Ropinirole by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram
Ropinirole Content by HPLC (label claim)	95.0 to 105.0% label claim (7.600 – 8.400 mg ropinirole pfb / tablet)	96.8% (7.741 mg pfb / tablet)
Uniformity of Content by HPLC	Complies with USP <905> and Ph.Eur 2.9.40	Mean = 96.0% Range = 93.5-99.2% RSD = 1.7% L1 = 6.4

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COA No. [redacted]

Drug-related impurities by HPLC (%w/w) SK&F 104557 SK&F 96266 SK&F 98959 Any other individual degradation product Total degradation products[1]	 Not greater than 0.3 Not greater than 0.4 Not greater than 0.3 Not greater than 0.2 Not greater than 1.0		 <0.05 0.08 <0.05 <0.05 0.08
Dissolution (% Ropinirole released)	Complies with USP <724> for extended release articles. The acceptance ranges of % Ropinirole released for the specified timepoints are:		
	After 2 hours After 12 hours After 24 hours	Not more than 20% 45 to 65% Not less than 80%	12 (11-12) 51 (49-52) 86 (81-89)
This material conforms to Specification S0004924 /1			

1. Total degradation includes all degradation products that have been detected at a level above the quantification limit.

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] **Date:** 09 February 2007

[redacted] BPharm MSc MRPharmS MIQA
Qualified Person
GSK R&D Quality Assurance, Harlow, Essex, UK

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COA No.: [redacted]
Product: Ropinirole Hydrochloride XL-24 Hour Tablets 12mg (pfb)

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New Frontiers Science Park
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Fax.
www.gsk.com

Product: Ropinirole Hydrochloride XL-24 Hour Tablets 12mg (pfb)

Strength / Dose Form: 12mg/Tablet

Batch Number: [redacted]

Date of Manufacture: 05-May-2006

Site of Manufacture: GSK, Crawley, UK

Test	Acceptance Criteria	Results
Description	Green, biconvex, capsule shaped, film coated tablet, debossed with 'GS' on one face and 'YX7' on the other face.	Green, biconvex, capsule shaped, film coated tablet, debossed with 'GS' on one face and 'YX7' on the other face.
Identification of Ropinirole by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the Ropinirole reference material chromatogram
Ropinirole Content by HPLC (mg per tablet as pfb)	11.4 – 12.6 (95.0 to 105.0% label claim)	11.8 (98.5 % label claim)
Uniformity of Dosage Units by HPLC	Complies with USP <905> and Ph.Eur 2.9.40	Mean = 97.6% Range = 95.6 – 100.2% RSD = 1.9% L1 = 5.3

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COA No. [redacted]
Product: Ropinirole Hydrochloride XL-24 Hour Tablets 12mg (pfb)

Drug-related impurities by HPLC (%w/w) SK&F 104557 SK&F 96266 SK&F98959 Any other individual impurity Total impurities[1]	 Not greater than 0.3 Not greater than 0.4 Not greater than 0.3 Not greater than 0.2 Not greater than 1.0		 <0.05 0.14 <0.05 <0.05 0.14
Dissolution (% Ropinirole released)	Complies with USP <724> for extended release articles. The acceptance ranges of % Ropinirole released for the specified timepoints are:		
	After 2 hours After 12 hours After 24 hours	Not more than 20% 45 to 65% Not less than 80%	13 (13 - 13) 55 (54 - 58) 89 (86 - 91)
This material conforms to Specification S0007980/2			

1. Total includes all synthetic and degradation products that have been detected at a level above the quantification limit.

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] **Date:** 08 March 2007

[redacted] BPharm MSc MRPharmS MCQI
Qualified Person
GSK R&D Quality Assurance, Harlow

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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****.*

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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: An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.ROP109087 HM2007/00444/00

Name of Investigator: [redacted] MD, PhD

Affiliation: [redacted] Germany

Signature of Investigator: [redacted]

Date: 08 FEB 2008

SIGNATORY SIGNATURE PAGE

STUDY TITLE: An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets

Study: ROP109087 Development Phase: II

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: Director, Clinical Pharmacology and Discovery Medicine, Neurology CEDD

Signature: [redacted]

Date: 11th Feb 08

SIGNATORY SIGNATURE PAGE

STUDY TITLE: An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets

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Title of Sponsor Signatory: Director, Clinical Pharmacology and Discovery Medicine, Neurology CEDD

Signature: [redacted]

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Title of Sponsor Signatory: Director, Clinical Pharmacology and Discovery Medicine, Neurology CEDD

Signature: [redacted]

Date: 11th Feb 08