Protocol C1171006

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-05221304 IN ADULT SUBJECTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO SUBJECTS WITHOUT HEPATIC IMPAIRMENT

Statistical Analysis Plan (SAP)

Version: **1.0**

Author: PPD (Cambridge, USA)

Date: 17-Aug-2017

DMB02-GSOP-RF18 2.0 STATISTICAL ANALYSIS PLAN TEMPLATE FOR HEPATIC IMPAIRMENT STUDY
30-Jun-2015

[redacted]
TMF Doc ID: 98.03

090177e190d319bc\Approved\Approved On: 29-Apr-2019 07:33 (GMT)

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	17-Aug-2017	PPD	NA

Distribution list of reviewers for this document prior to final sign-off.

Clinical Team* - List of reviewers	
Role Name	**Reviewer's Name**
Clinical Lead	PPD
Clinician	PPD
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NOTE: Italicized text within this document has been taken verbatim from the Protocol.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

This first version of the SAP reflects the C1171006 protocol (version: 08-Aug-2017)

2. INTRODUCTION

PF-05221304 is a potent, selective, orally bioavailable, and reversible dual acetyl-CoA carboxylase 1 and 2 (ACC1/2) inhibitor designed to have asymmetric distribution to the liver, CCI [redacted] *as such PF-05221304 is expected to inhibit de novo lipogenesis (DNL) and stimulate fatty acid oxidation in the liver to a greater extent than in peripheral tissues. In humans, administration of PF-05221304 has been shown to suppress hepatic DNL in a Phase 1 study in healthy adult subjects; in addition, the drug is expected to stimulate hepatic fatty acid oxidation, and consequently reduce fat accumulation in the liver. This inhibition of hepatic DNL is postulated to result in a decrease and normalization of the excessive DNL observed in nonalcoholic fatty liver disease (NAFLD). In addition, the inhibition of ACC via administration of PF-05221304 also has the potential for anti-inflammatory effects in nonalcoholic steatohepatitis (NASH).*

The primary purpose of this non-randomized, single dose, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics of PF-05221304 following administration of a single, oral, 25 mg dose. Recognizing that the target population of PF-05221304 are patients with liver disease (NASH with fibrosis) and that the major clearance mechanism of PF-05221304 is predicted to be active uptake into liver CCI [redacted] *the current study is proposed to evaluate whether there is any clinically meaningful effect of hepatic impairment on the plasma pharmacokinetics of PF-05221304.*

2.1. Study Design

This is a non-randomized, open-label, single-dose, parallel-cohort, multisite study to investigate the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (total and unbound) of PF-05221304 after a single oral 25 mg dose administered in the fed state. A total of approximately 24 subjects with varying degrees of hepatic function will be enrolled into the study to ensure that up to 6 evaluable subjects in each of the 4 hepatic function cohorts complete the study. Subjects will be selected based on their Child-Pugh score as shown in Table 1.

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Table 1. Hepatic Function Categories Based on Child Pugh Score

Cohort	*Description*	*Child-Pugh Score*	*Number of Subjects*
1	*Without hepatic impairment*	*Not Applicable*	*6*[a]
2	*Mild hepatic impairment*	*Class A (5 to 6 points)*	*6*
3	*Moderate hepatic impairment*	*Class B (7 to 9 points)*	*6*
4	*Severe hepatic impairment*	*Class C (10 to 15 points)*	*6*[b]

a. Additional subjects may be dosed to a maximum of 10 subjects to ensure mean age is ± 5 years and mean body weight ± 10 kg of this cohort is in line with pooled average assessed when ≥75% of subjects are dosed across other 3 cohorts
b. If recruitment across the sites selected proves to be prohibitive, study will dose only 4 subjects in this cohort

Child-Pugh scores will be determined as described in Table 2*, at the screening visit. Recruitment for subjects meeting the criteria for Cohorts 3 and 4 will initiate first. Recruitment for subjects in Cohort 2 will start when approximately 50% of total subjects across Cohorts 3 and 4 (ie, 6 of 12) have been dosed. Subjects in Cohort 1 will be recruited last to match the average demographics (at a minimum, age and weight; and as much as practically possible gender) across the pooled Cohorts 2 through 4.*

Table 2 *Child-Pugh Classification (CPC) of Liver Dysfunction*

Table 2-1: Scoring for Child-Pugh Classification

Cohort	*CPC*	*Level of dysfunction*	***Total Score*** *(tally based on assessment of parameters in* ***Table 2-2****)*
1	*Not Applicable*	*Without hepatic impairment*	*Not Applicable*
2	*A*	*Mild*	*5-6*
3	*B*	*Moderate*	*7-9*
4	*C*	*Severe*	*≥ 10*

Table 2-2: Derivation of Child-Pugh Classification Score

Assessment Parameters	*Assigned score for observed findings*		
	1 point	***2 point***	***3 point***
Encephalopathy grade (refer to ***Table 2-3*** *below)*	*0*	*1 or 2*	*3 or 4*[a] *(or Requiring intervention*[b]*)*
Ascites	*Absent*	*Asymptomatic*	*Requiring intervention*
Serum total bilirubin, mg/dL	*< 2*	*2 to 3*	*> 3*
Serum albumin, g/dL	*> 3.5*	*2.8 to 3.5*	*< 2.8*
Prothrombin time, sec prolonged	*< 4*	*4 to 6*	*> 6*

a. Subjects with clinically active Grade 3 or 4 encephalopathy are excluded
b. In addition, subjects with a history of Grade 3 or 4 encephalopathy who are receiving an intervention [for example: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to prevent recurrent encephalopathy should be scored as Grade 3 or 4 encephalopathy (and hence excluded from Study C1171006)

Table 2-3: Determination of Encephalopathy Grade

Encephalopathy Grade	*Definition*
0	*Normal consciousness, personality, neurological exam*
1	*Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting*

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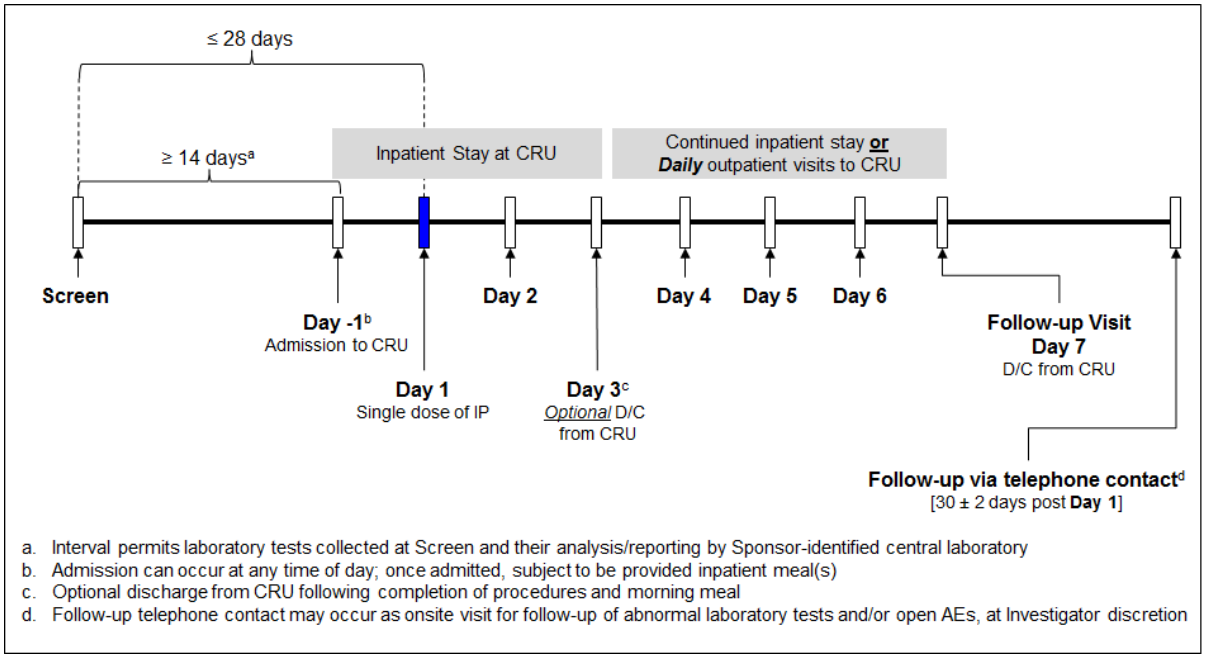
2	*Lethargic, time-disoriented, inappropriate, asterixis, ataxia*
3	*Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity*
4	*Unrousable coma, no personality/behavior, decerebrate*

The overall study design is summarized below in Figure 1. For individual subjects, the total duration of participation from the Screening Visit to the on-site Follow-up Visit (Day 7) will be a minimum of approximately 3 weeks and a maximum of approximately 5 weeks.

Figure 1. C1171006 Study Design



*In this study, subjects who prematurely discontinue for non-safety related reasons **may** be replaced, at the discretion of the principal investigator (PI) and Sponsor study team.*

2.2. Study Objectives

Primary Objective:
To compare the pharmacokinetics of PF-05221304 (both total and unbound) following administration of a single oral dose in adult subjects with varying degrees of hepatic impairment relative to age- and body weight- matched subjects without hepatic impairment
Secondary Objectives:
To compare additional pharmacokinetic parameters (both total and unbound) of PF-05221304 following administration of a single oral dose in adult subjects with varying degrees of hepatic impairment relative to age- and body weight- matched subjects without hepatic impairment

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To evaluate the safety and tolerability of a single oral dose of PF-05221304 when administered to adult subjects with varying degrees of hepatic impairment relative to age- and body weight- matched subjects without hepatic impairment.

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. The sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development. Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses testing is planned.

4.2. Statistical Decision Rules

No decision rules are planned.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population will be defined as all subjects who received 1 dose of PF-05221304 and in whom at least 1 plasma concentration value is reported.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all subjects dosed who have at least 1 of the PK parameters of primary interest.

5.2. Pharmacodynamic Analysis Set

None.

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5.3. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

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5.5. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are ultimately not dosed.

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg vomiting immediately after the dose) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.6.1. Deviations Assessed Prior to Dosing

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.6.2. Deviations Assessed Post-Dosing

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

Any events occurring following PF-05221304 dosing or increasing in severity will be counted as treatment emergent.

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Events that occur in a non-treatment period (for example Follow-up) will be counted as treatment emergent and attributed to the dose taken.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data,*
- *ECG results.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-05221304 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-05221304 (if possible) from the concentration-time data using standard non-compartmental methods:

Table 3. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-05221304	Definition
AUC_{last}	ln	A, D	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
$AUC_{last,u}$	ln	A, D	Unbound area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
AUC_{inf}*	ln	A, D	Area under the plasma concentration-time profile from time zero extrapolated to infinite time
$AUC_{inf,u}$*	ln	A, D	Unbound area under the plasma concentration-time profile from time zero extrapolated to infinite time
C_{max}	ln	A, D	Maximum plasma concentration
$C_{max,u}$	ln	A, D	Unbound maximum plasma concentration
T_{max}	R	D	Time for C_{max}
$t_{1/2}$*	R	D	Terminal half-life
CL/F*	ln	A, D	Apparent clearance
CL_u/F*	ln	A, D	Unbound apparent clearance
V_Z/F*	ln	A, D	Apparent volume of distribution
Vz_u/F*	ln	A, D	Unbound apparent volume of distribution
Fu^+	R	D	Fraction unbound

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits; u=unbound fraction
+ = Reported in eNCA as protein free fraction.

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6.3.2. Other Endpoints

None.

6.4. Covariates

No covariate for primary analysis (ie ANOVA) will be included in the model.
For secondary analysis (ie ANCOVA), age, and body weight will be included in the model. Additionally, gender may also be included as a covariate if approximately 50% of each cohort is female.

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

7.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), PK concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

In all data presentations (except listings), CP-I and CP-III concentrations below the limit of quantification (BLQ) will be set to LLQ/2. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

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In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular hepatic function cohort with ≥3 evaluable measurements. For statistical analyses (ie analysis of variance), PK parameters coded as NC will also be set to missing; and statistical analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

The effect of the hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test (impaired cohorts) and the Reference (normal hepatic function cohort) using a one-way ANOVA model based on natural log transformed data.

The relationship between PK parameters and hepatic function will be determined by a linear regression model.

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8.2. Statistical Analyses of PK Parameters

One-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-05221304 AUC_{inf}, AUC_{last} and C_{max}, unbound AUC_{inf} ($AUC_{inf,u}$), unbound AUC_{last} ($AUC_{last,u}$), and unbound C_{max} ($C_{max,u}$), as data permit, for each of the hepatic impairment classification cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean and corresponding 90% confidence intervals will be obtained from the model for each cohort. *Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model* as well. *The* adjusted mean estimates and *adjusted mean differences and 90% confidence intervals for the* estimates and *differences will be exponentiated to provide estimates* of adjusted geometric means and estimates *of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the estimates and for the ratios* respectively (see Appendix 1 for SAS code).

Additionally, as an exploratory analysis, age, body weight, and gender (see Section 6.4) *will be explored as a covariate/factor in the ANOVA/ANCOVA model, as appropriate* (see Appendix 1 for SAS code).

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Linear regression may be used to analyze the potential relationship between the following *PK parameters* -AUC_{inf}, and *CL/F* separately - *and the following hepatic function - serum albumin,,prothrombin time,* and total bilirubin *separately* -. *Estimates of the slope and intercept, together with their precision (90% confidence interval [CI]), and the coefficient of determination* (ie R-squared and adj-R-squared) *will be obtained from the model.*

Plots of PK parameters -AUC_{inf}, and *CL/F* separately - *versus hepatic function - serum albumin, ,prothrombin time,* total bilirubin *separately* - *will be constructed. A regression line and 90% confidence region for the PK parameters and hepatic function will be included.* (See appendix 1 for example of SAS code to produce the figure).

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Alternative model structure may also be considered. Justification for any alternative to the planned analysis will be given in the report of the study.

The following PK parameters will be summarized by hepatic function Cohort:

Table 4. PK Parameters to be Summarized Descriptively by Cohort

Parameter	Summary Statistics
C_{max}, AUC_{last}, AUC_{inf}, CL/F, V_z/F, $AUC_{inf,u}$, $AUC_{last,u}$, $C_{max,u}$, CL_u/F, and V_{zu}/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2, fu}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Box and whisker plots for *PF-05221304 AUC_{inf}, AUC_{last}, C_{max}, $AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$ individual subject parameters will be plotted by hepatic function cohort* and overlaid with geometric means.

Supporting data from the estimation of t½ and AUC_{inf} will be listed by cohort: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

Presentations for PF-05221304 concentrations will include:

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- a listing of all concentrations sorted by hepatic function cohort (present in heading), subject id and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by hepatic function cohort and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function cohort (all hepatic function cohorts on the same plot per scale, based on the summary of concentrations by hepatic function cohort and time postdose).
- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function cohort (all hepatic function cohorts on the same plot per scale, based on the summary of concentrations by hepatic function cohort and time postdose).
- individual concentration time plots by hepatic function cohort (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each hepatic function cohort per scale).

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

8.3. Safety Analysis

A set of summary tables split by hepatic function cohort will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-05221304.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, pharmacodynamics (CP-I and CP-III), as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by hepatic function cohort.

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

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8.3.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations due to adverse events will be detailed and summarized by hepatic function cohort.

Data will be reported in accordance with the sponsor reporting standards.

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by hepatic function cohort.

8.3.5. Laboratory Data

Laboratory data will be listed in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

The baseline measurement is the last predose measurement.

For each planned timepoint, baseline values and change from baseline values within each hepatic function cohort will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

8.3.7. ECG Data

The baseline measurement is the predose measurement.

For each planned timepoint, baseline values and change from baseline values within each hepatic function cohort will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

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8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations (in females), and serum β-hCG (in females), obtained at Screening, will be databased.

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9. REFERENCES

None.

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10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

```
/* Letter assignments for cohort within the estimate statement in
    the code below are as follows;
A = Severe (Test)
B = Moderate (Test)
C = Mild (Test)
D = Normal (Reference);
  */;
```

For ANOVA: An example of the PROC GLM code is provided below:

```
proc glm data=tab.pk;
        class cohort;
        model l&var = cohort / ss3 clparm alpha=0.1;
        lsmeans cohort;
        estimate 'Severe vs Normal'          cohort 1 0 0 -1;
        estimate 'Moderate vs Normal'        cohort 0 1 0 -1;
        estimate 'Mild vs Normal'            cohort 0 0 1 -1;
        ods output Estimates = est&var;
        ods output FitStatistics = fit&var;
        ods output ModelANOVA = tst&var;
        ods output OverallANOVA = overall&var;
run;
```

For ANCOVA: An example of the PROC GLM code is provided below:

```
proc glm data=tab.pk;
        class cohort;
        model l&var = cohort age weight / ss3 clparm alpha=0.1;
        lsmeans cohort;
        estimate 'Severe vs Normal'          cohort 1 0 0 -1;
        estimate 'Moderate vs Normal'        cohort 0 1 0 -1;
        estimate 'Mild vs Normal'            cohort 0 0 1 -1;
        ods output Estimates = est&var;
        ods output FitStatistics = fit&var;
        ods output ModelANOVA = tst&var;
        ods output OverallANOVA = overall&var;
run;
```

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