Protocol C2541009

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL-COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-06865571 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Statistical Analysis Plan (SAP)

Version: **1.0**

Author: PPD MA

Date: 13-AUG-2019

Table 1. Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	13August2019	PPD	Original Version.

NOTE: Italicized text within this document has been taken verbatim from the Protocol.

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None.

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

The primary purpose of this non-randomized, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (PK) of PF-06865571 following administration of a single, oral, 100 mg dose of PF-06865571. NAFLD/NASH is associated with varying degrees of hepatic impairment. Recognizing that the target population of PF-06865571 is patients with NAFLD/NASH and that the major clearance mechanism of PF-06865571 is metabolism in the liver, the current study is proposed to evaluate whether there is any clinically meaningful effect of hepatic impairment on the plasma PK of PF-06865571.

2.1. Study Design

This is a Phase 1, non-randomized, open-label, single-dose, parallel-cohort, multicenter study to compare the pharmacokinetics of PF-06865571 in adult participants with varying degrees of hepatic impairment relative to participants without hepatic impairment after a single, oral 100 mg dose administered in the fed state. A total of approximately 24 participants with varying degrees of hepatic function will be dosed in the study as shown in Table 2.

Table 2. 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 participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this cohort is aligned with the pooled average assessed when ≥75% of participants are dosed across the other 3 cohorts.*

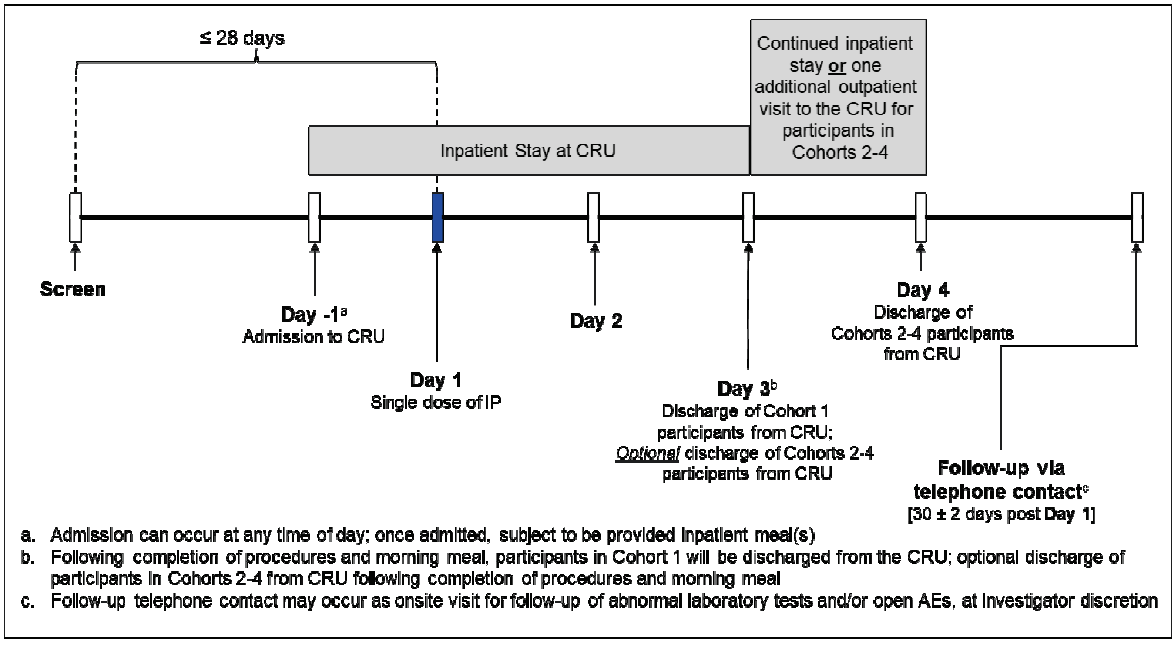
b. *If recruitment across the sites selected proves to be prohibitive, study will dose only 4 participants in this cohort.*

Categorization of participants into Cohort 2-4, inclusive, will be done based on Child-Pugh scores determined at the Screening visit. Participants will be dosed in a staged manner such that those with moderate and severe hepatic impairment (Cohorts 3 and 4) will be evaluated first. Dosing in participants with mild hepatic impairment (Cohort 2) will initiate when approximately 50% of the total participants in Cohorts 3 and 4 have been dosed. Participants without hepatic impairment (Cohort 1) will be recruited near the end of the study to match the average demographics (at a minimum, age and weight; and gender as much as practically possible) across the pooled Cohorts 2 through 4.

Participants who prematurely discontinue for non-safety related reasons may be replaced, at the discretion of the principal investigator (PI) and sponsor study team.

The overall study design is summarized in Figure 1. For individual participants, the total duration of participation from the Screening visit to the follow-up visit will range from 5 weeks (minimum) to 9 weeks (maximum).

Figure 1. Study Design



2.2. Study Objectives

Objectives	***Endpoints***
Primary:	***Primary:***
• *To compare the PK of PF-06865571 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.*	• *PF-06865571 PK parameters derived from plasma: C_{max}, AUC_{last}, and AUC_{inf}.*

Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of a single oral dose of PF-06865571 when administered to adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.*	• *Assessment of treatment-emergent adverse events, clinical laboratory tests, vital signs, and 12-lead ECGs.*
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting further clinical development.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There is no statistical hypothesis testing planned for this study.

4.2. Statistical Decision Rules

No statistical decision rules are applied.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population will be defined as all participants who received PF-06865571 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 participants dosed who have at least 1 of the PK parameters outlined in Section 6.3.1.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All participants who receive at least 1 dose of investigational product will be included in the safety analyses and listings.

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

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

5.6. Protocol Deviations

Participants who experience events that may affect their PK profile (e.g. lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokinetist 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 participants against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 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; only important protocol deviations will be reported in the Clinical Study Report (CSR). 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

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.*

All events that start on or after the first dosing day and time and during the active collection period as specified in the protocol will be counted as treatment emergent adverse event (TEAE). Events that occur in a non-treatment period (for example, Follow-up) will be counted as treatment emergent and attributed to the treatment taken. For the safety endpoints Day 1 planned predose measurements will serve as baseline.

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-06865571 will be taken according to the Schedule of Activities given in the protocol. The following PK parameters will be calculated for PF-06865571 (if possible) from the concentration-time data using standard noncompartmental methods:

PK Parameter	Analysis Scale	PF-06865571	Definition
AUC_{inf}*	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}	ln	A, D	Area under the plasma concentration-time profile from time zero extrapolated to infinite time
C_{max}	ln	A, D	Maximum plasma concentration
CCI [redacted]	[redacted]	[redacted]	[redacted]

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

6.3.2. PD Endpoints

None.

6.4. Covariates

No covariate for primary analysis (i.e. ANOVA) will be included in the model.
CCI [redacted]

7. HANDLING OF MISSING VALUES

The handling of missing values for PK data is described in this section. 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), 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.

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 (i.e. not done) or NS (i.e. no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokinetist.

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 participant's concentration data, the parameter will be coded as NC (i.e. not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular hepatic function group with ≥3 evaluable measurements. For statistical analyses (i.e. analysis of variance), PK parameters coded as NC will also be set

to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual participant 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

For all outputs produced, the following ordering will be used:

Without Hepatic Impairment

Mild Hepatic Impairment

Moderate Hepatic Impairment

Severe Hepatic Impairment.

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 groups) and the Reference (normal hepatic function group) using a one-way ANOVA model based on natural log transformed data.

The relationship between PK parameters and hepatic function parameters (eg, serum albumin concentration, or prothrombin time) will be determined by a linear regression model.

8.2. Statistical Analyses

A 1-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-06865571 AUC_{inf}, AUC_{last}, and C_{max}, as data permit, for each of the hepatic impairment cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% confidence intervals, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. CCI [redacted]

CCI [redacted]

CCI [redacted]

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. 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 group:

Table 3. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, CCI [redacted]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%
CCI [redacted]	[redacted]
[redacted]	[redacted]

Box and whisker plots for individual participant parameters (AUC_{inf}, AUC_{last} and C_{max}) may be presented by hepatic function group and overlaid with geometric means.

Supporting data from the estimation of CCI [redacted] AUC_{inf} will be listed by group: 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-06865571 concentrations will include:

- a listing of all concentrations sorted by hepatic function group (from without hepatic impairment 1st, followed by mild/C2, moderate/C3 and finally severe/C4, present in heading), participant 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 group 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 group (all hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).
- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function group (all hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).
- individual concentration time plots by hepatic function group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each hepatic function group per scale).

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

8.3. Safety Analysis

A set of summary tables split by hepatic function group will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06865571.

8.3.1. Treatment and Disposition of Participants

Participant evaluation groups will show end of study participant disposition. Frequency counts will be presented for participants discontinuation(s) by hepatic function group.

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

8.3.2. Demographic and Clinical Examination Data

A summary of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by hepatic function group and 'Total Participants' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Participant discontinuations due to adverse events will be detailed and summarized by hepatic function group.

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 group.

8.3.5. Laboratory Data

Laboratory data will be listed and summarized by hepatic function group in accordance with the sponsor reporting standards. Baseline will be the planned predose measurement obtained on Day 1.

8.3.6. Vital Signs Data

Baseline value will be the planned predose measurement obtained on Day 1.

Maximum absolute values and changes from baseline for seated vital signs will be summarized descriptively by hepatic function group using categories as defined in **0.** Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose time-points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

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

8.3.7. ECG Data

Baseline value will be the planned predose measurement obtained on Day 1.

Changes from baseline for the ECG parameters QT interval, heart rate, derived QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	***Mild (msec)***	***Moderate (msec)***	***Severe (msec)***
Absolute value	*>450-480*	*>480-500*	*>500*
Increase from baseline		*30-60*	*>60*

In addition, the number of participants with uncorrected and corrected QT values >500 msec will be summarized and listed.

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.

8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, serum B-hCG for all females will be obtained at Screening. These data will only be listed.

Urine drug screen, urine B-hCG for women of child bearing potential and physical examination findings will be collected at baseline or prior to baseline visit. These data will not be brought in-house, and therefore will not be listed.

9. REFERENCES

None.

10. APPENDICES

Appendix 1: SAS CODE FOR ANALYSES

An example of the PROC GLM code is provided below:

```
proc glm data=tab.pk;
        class group;
        model l&var=group/ss3 clparm alpha=0.1;
        lsmeans group;
        estimate 'Mild vs Normal'          group -1 1 0 0;
        estimate 'Moderate vs Normal'      group -1 0 1 0;
        estimate 'Severe vs Normal'        group -1 0 0 1;

        ods output Estimates = est&var;
        ods output FitStatistics = fit&var;
        ods output ModelANOVA = tst&var;
        ods output OverallANOVA = overall&var;
run;
```

An example of the PROC REG code is provided below:

```
proc reg data=tab.pk;
        model l&var=&HepaticFunction/clb alpha=0.1;
        ods output ParameterEstimates = param&var;
        ods output FitStatistics = fit&var;
        ods output ANOVA = reg&var;
run;
```

Appendix 2: Categorical Classes for Vital Signs of Potential Clinical Concern

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Seated pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed in report.