Protocol *B7451020*

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE STUDY TO COMPARE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-04965842 IN ADULT SUBJECTS WITH MILD AND MODERATE HEPATIC IMPAIRMENT RELATIVE TO SUBJECTS WITH NORMAL HEPATIC FUNCTION

Statistical Analysis Plan (SAP)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	22 August 2018	PPD	Not Applicable

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

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-04965842 is a janus kinase (JAK) 1 inhibitor that is currently being developed for the treatment of atopic dermatitis (AD).

CCI [redacted]

The primary purpose of this non-randomized, single-dose, open-label study is to characterize the effect of mild and moderate hepatic impairment on the plasma PK of PF-04965842 following administration of a single 200 mg oral dose.

2.1. Study Design

This is a Phase 1 non-randomized, open-label, single-dose, parallel-cohort study to investigate the effect of mild and moderate hepatic impairment on the plasma PK, safety and tolerability of PF-04965842 after a single 200 mg oral dose.

At Screening, the Child-Pugh classification score will be utilized to assess entry criteria and to assign subjects into the appropriate hepatic-impairment group (Table 1, Table 2 and Table 3). The subjects' hepatic function will be ranked based on clinical signs and liver function test (LFT) results.

Table 1. Hepatic Function Categories Based on Child-Pugh Score

Cohort	*Description*	*Child-Pugh Score*	*Number of Subjects*
1	*Moderate hepatic impairment*	*Class B (7 to 9 points)*	*8*
2	*Mild hepatic impairment*	*Class A (5 to 6 points)*	*8*
3	*Normal hepatic function*	*Not Applicable*	*8*

Table 2. Assessment of Hepatic Impairment: Child-Pugh

Assessment Parameters	*Assigned Score for Observed Findings*		
	1 point	*2 points*	*3 points*
Encephalopathy Grade (refer to Table 3 below)	*0*	*1 or 2*	*3 or 4*
Ascites	*Absent*	*Slight*	*Moderate*
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, seconds prolonged	*<4*	*4 to 6*	*>6*

Table 3. Determination of Encephalopathy Grade

Encephalopathy Grade	*Definition*
0	*Normal consciousness, personality, neurological examination, Electroencephalogram*
1	*Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves*
2	*Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves*
3a	*Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slow waves*
4a	*Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta Activity*

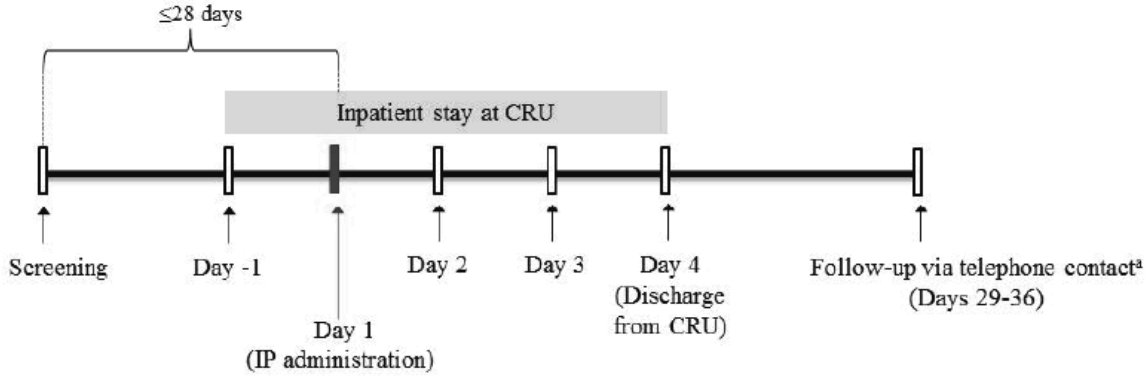
a. Subjects with clinically active Grade 3 or 4 encephalopathy are excluded.

A minimum of 24 subjects with varying degrees of hepatic function will be enrolled into the study, with approximately 8 subjects in each cohort. Subjects who withdraw/discontinue early from the study may be replaced at the discretion of the sponsor.

*Recruitment for subjects with moderate and mild hepatic impairment (Cohorts 1 and 2) will initiate first and these subjects will be enrolled in parallel. Subjects with normal hepatic function (Cohort 3) will be enrolled after the completion of subjects in Cohorts 1 and 2 (in-patient portion of the study) to match the median demographics (at a minimum, age [±10 years] and body weight [±15 kg]; and as much as practically possible gender) across the pooled Cohorts 1 and 2. Approval from the sponsor must be obtained **before** proceeding with dosing subjects in Cohort 3.*

The overall study design is summarized below in Figure 1. For individual subjects, the total maximum duration of study participation from the Screening visit to the end of clinical research unit (CRU) stay is approximately 31 days and approximately 63 days from the Screening visit to the Follow-up contact.

Figure 1. Study Design



Abbreviations: CRU = clinical research unit; IP = investigational product.

a. Follow-up telephone contact may occur as onsite visit for follow-up of clinically significant abnormal laboratory tests and/or ongoing AEs.

2.2. Study Objectives

Primary Objective:

- *To estimate the effect of mild and moderate hepatic impairment on the PK of PF-04965842 following single oral administration in adult subjects with hepatic impairment relative to age- and body weight-matched subjects with normal hepatic function.*

Secondary Objective:

- *To evaluate the safety and tolerability of a single oral dose of PF-04965842.*

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[redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. However, 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 dose-escalation decisions, facilitating PK/PD 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 are required.

4.2. Statistical Decision Rules

No decision rules are required.

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-04965842 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 one of the PK parameters of primary interest.

5.2. Pharmacodynamic Analysis Set

None.

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.

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 subjects who are allocated to a cohort but not treated.

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg, lack of compliance with dosing, vomiting immediately after dosing, etc) 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 based on the potential important protocol deviation (PIPD) document will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.6.1. Deviations Assessed Prior to Randomization

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-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol based on the PIPD document 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 start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Follow-up) will be counted as treatment emergent and attributed to the previous treatment 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 (blood pressure and pulse rate);*
- *ECG results;*
- *physical examination.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-04965842 CCI [redacted] will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-04965842 CCI [redacted] (if possible) from the concentration-time data using standard noncompartmental methods:

Table 4. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-04965842	CCI [redacted]		
AUC_{inf}*	ln	A, D			
CCI [redacted]					
C_{max}	ln	A, D			
CCI [redacted]					

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

CCI [redacted]

[redacted]

6.4. Covariates

None.

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), 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 (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).

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 (ie, 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 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 for PF-04965842 will be assessed by constructing 90% confidence intervals (CI) around the estimated difference between each of the Test (hepatic impairment cohorts) and the Reference (normal hepatic function cohort) using a one-way ANOVA model based on natural log transformed data.

CCI [redacted]

8.2. Statistical Analyses

ANOVA will be used to compare the natural log transformed AUC_{inf}, CCI [redacted] *and C_{max} of PF-04965842, for each of the hepatic impairment cohorts (Test) to the normal hepatic function cohort (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.*

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 (as data permit) for PF-04965842 CCI [redacted] ill be summarized by hepatic function cohorts:

Table 5. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
CCI AUC_{inf}*, C_{max}, C CI	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
CCI	
CCI	

Supporting data from the estimation of C CI and AUC_{inf} will be listed by group and analyte: 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-04965842 CCI concentrations will include:

- 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-04965842.

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, 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 break-down 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.

8.3.3. Discontinuation(s)

Subject discontinuations 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 from each planned timepoint including Day -1 will be listed and summarized in accordance with the sponsor reporting standards.

For laboratory parameters which are collected only at Screening for inclusion/exclusion criteria, data will not be captured for inclusion into the study database and therefore will not be listed or summarized.

8.3.6. Vital Signs Data

Vital sign data will include blood pressure and pulse rate. 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, frequency count and percentage of patients with normal and abnormal ECG evaluation will be provided using sponsor default standards.

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

8.3.8. Physical Examination Data

The baseline measurement is the predose measurement.

For each planned timepoint, frequency count and percentage of patients with normal and abnormal physical examination will be provided using sponsor default standards.

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

CCI

[redacted]

8.3.11. Concomitant Treatments

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

8.3.12. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations (female subjects of non-childbearing potential only), urine drug screen, serum or urine B-hCG for all females of childbearing potential, alcohol/tobacco use, breath alcohol test, HepBcAb, HepBsAb, HepBsAg, HCVAb (HCV RNA reflex test in case of positive HCVAb test), HIV tests, QFT-G Test or PPD skin test (chest x-ray in case of positive QFT-G or PPD) will be obtained at Screening.

These data for alcohol/tobacco use and breath alcohol test will not be brought in-house, and therefore will not be listed. For rest of the parameters data will be provided in listings.

8.4. Other Endpoints

None.

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 'Moderate vs Normal'        group 1 0 -1;
        estimate 'Mild vs Normal'            group 0 1 -1;
        ods output Estimates = est&var;
        ods output FitStatistics = fit&var;
        ods output ModelANOVA = tst&var;
        ods output OverallANOVA = overall&var;
run;
/* Letter assignments for group within the estimate statement above are as follows;
A = Moderate (Test)
B = Mild (Test)
C = Normal (Reference);
  */;
```

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;
```