Protocol *B7451021*

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-04965842 IN SUBJECTS WITH RENAL IMPAIRMENT AND IN HEALTHY SUBJECTS WITH NORMAL RENAL FUNCTION

Statistical Analysis Plan (SAP)

Version: 1.0

SAP Author: PPD (PPD ., Mumbai)

Date: 10-SEP-2018

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	10 Sep 2018	PPD	Not Applicable

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

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).

PF-04965842 is intended for chronic use in patients with atopic dermatitis who may have some degree of impaired renal function. Therefore, the present study is being conducted to evaluate whether renal impairment has an impact on PF-04965842 PK.

The purpose of this study is to characterize the effect of renal impairment on the plasma PK of PF-0496482 following administration of a single 200 mg oral dose. Findings from this study will be used to develop dosing recommendations so that dose and/or dosing interval may be adjusted appropriately in the presence of renal disease.

1.1. Study Design

This is a Phase 1 non-randomized, open-label, single-dose, parallel-cohort, multisite study to investigate the effect of severe renal impairment on the plasma pharmacokinetics, safety and tolerability of PF-04965842 after a single 200 mg oral dose. A staged approach, as outlined in detail below, will be followed in the study.

Subjects will be selected and categorized into normal renal function or renal impairment groups based on their estimated glomerular filtration rate (eGFR) as shown in Table 1.

Table 1. Cohort Assignment Based on estimated Glomerular Filtration Rate Ranges

Cohort	***Renal Impairment[a]***	***Estimated eGFR[b] (mL/min)***	***Number of Completer Subjects***
1	*None (Normal)*	*≥90*	*6[c]*
2	*Severe Renal Impairment*	*<30 and not requiring dialysis*	*6*
3	*Moderate Renal Impairment*	*≥30 to <60*	*6*
4	*Mild Renal Impairment*	*60 – 89*	*6*

a. Stages of renal impairment are based on Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD).

b. Estimate of eGFR based on Modification of Diet in Renal Disease (MDRD) formula. The Day -1 eGFR value will be used for group assignment.

- *Step 1: eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr, std})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay.*
- *Step 2: Convert the MDRD-derived, body surface area (BSA)-adjusted eGFR obtained above to absolute eGFR*

(mL/min) for eligibility assessment using the following equation:
eGFR (mL/min) = eGFR (mL/min/1.73 m^2) ×subject's BSA;
where, BSA =(Weight$^{0.425}$ x Height$^{0.725}$) x 0.007184.

c. *Additional subjects may be dosed to a maximum of 10 subjects to ensure mean age is ±10 years and mean body weight ± 15 kg of this cohort is in line with pooled average assessed when >=75% of subjects are dosed in cohort 2.*

Part 1*: A total of approximately 16 subjects will be enrolled in Part 1; approximately 8 subjects with severe renal impairment and approximately 8 with normal renal function. The 8 subjects from the impaired group will be recruited first. The demographics will be pooled across study sites to determine an average value for age and weight. Subsequently, the healthy subjects will be recruited later such that each subject's age is within ±10 years and weight is within ±15 kg of the mean of the pooled impaired groups. An attempt will be made to maintain a similar male/female ratio and racial make-up between groups. Care will be taken when recruiting the healthy subjects such that the entire group is not younger and of lower body weight than the impaired subjects. Approval from the sponsor must be obtained* ***before*** *proceeding with dosing healthy subjects with normal renal function (Cohort 1).*

Subjects who withdraw from the normal and severe impairment groups for non-safety related reasons and who are considered to be non-evaluable with respect to the primary objective may be replaced at the discretion of the principal investigator (PI) and the sponsor to ensure 6 completers.

Statistical Criteria to proceed to Part 2: *After statistical evaluation of results from Part 1, Part 2 will be conducted if the upper bound (UB) of the 90% CI for PF-04965842 AUC_{inf} geometric mean ratio (GMR) for the severe renal impairment group (compared to the normal group as control) is ≥3.0. If variability is unexpectedly higher than assumed, eg, if the UB of the GMR is substantially higher than 3 with a point estimate of the GMR close to 2, the data will be further evaluated to determine whether to proceed to Part 2. If the above mentioned criterion is not met, the study will stop after Part 1.*

Part 2: *Based on whether the decision criterion to proceed to Part 2 is met, approximately 8 subjects each with moderate and mild renal impairment will be enrolled. As in Part 1, renal impairment classification will be based on eGFR. Healthy subjects will not be enrolled in Part 2.*

As in Part 1, subjects who withdraw from the moderate or mild impairment group for non-safety related reasons and who are considered to be non-evaluable with respect to the primary pharmacokinetic objective may be replaced at the discretion of the PI and the sponsor to ensure 6 completers.

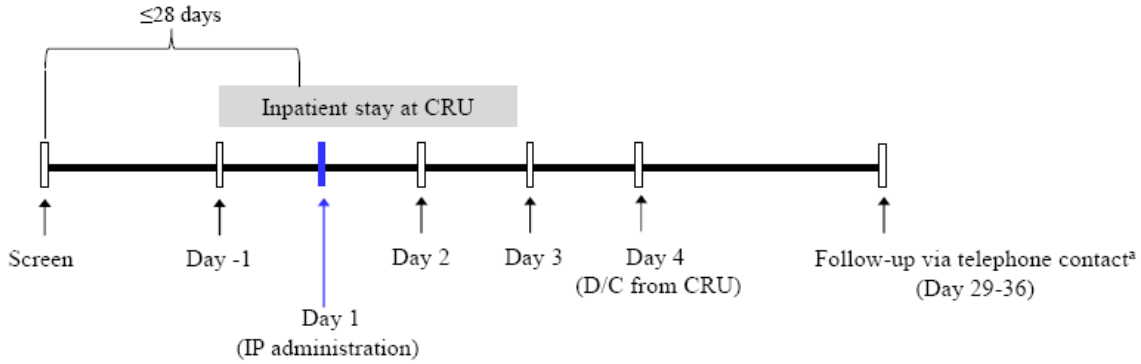
CL_{CR} will be estimated from a spot serum creatinine measurement using the following Cockcroft-Gault (C-G) equation:

$$CL_{CR}\,(mL/min) = \frac{[140 - \text{Age (years)}] \text{ x total body weight (kg) x (0.85 for females)}}{72 \text{ x serum creatinine (mg/dL)}}$$

Note that eGFR calculated by the MDRD equation will be used for categorization of degrees of renal impairment. Nevertheless, renal function will be estimated using both C-G and MDRD equations in this study.

The overall study design for both Parts 1 and 2 is summarized in below Figure 1.

Figure 1. Study Design



Abbreviations: AE = adverse event; CRU = clinical research unit; D/C = discharge; IP = investigational product.
a. Follow-up telephone contact may occur; but an onsite visit should be performed for follow-up of abnormal laboratory tests and/or ongoing AEs

2.1. Study Objectives

Primary Objectives:

- *Part 1: To evaluate the effect of severe renal impairment on the pharmacokinetics of PF-04965842 following single oral dose administration.*
- *Part 2 (if applicable): To evaluate the effect of moderate and mild renal impairment on the pharmacokinetics of PF-04965842 following single oral dose administration.*

Secondary Objective:

- *To evaluate the safety and tolerability of a single oral dose of PF-04965842 in subjects with renal impairment and in healthy subjects with normal renal function.*

Tertiary/Exploratory Objectives:

- *To compare additional plasma pharmacokinetic parameters of PF-04965842 following single oral administration in subjects with renal impairment and in healthy subjects without renal impairment.*
- CCI [redacted]
- *To determine the plasma* CCI *PK of the major circulating metabolites of PF-04965842: PF-06471658, PF-07055087* CCI .
- CCI [redacted]
- [redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. However, data will be reviewed after completion of Part 1 in order to determine whether Part 2 will proceed. Final analysis will follow the official database release. As this will be an open, nonrandomized study, there is no formal unblinding.

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 1 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) 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 Allocation

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-Allocation

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 start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Washout or 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 CCI samples for PK analysis of PF-04965842 and CCI major circulating metabolites, PF-06471658, PF-07055087 and CCI will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-04965842 and for CCI major circulating metabolites, PF-06471658, PF-07055087 and CCI (if possible) from the concentration-time data using standard non compartmental methods:

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-04965842	PF-06471658	PF-07055087	CCI
AUC_{inf}*	ln	A, D	D	D	
AUC_{last}	ln	A, D	D	D	
C_{max}	ln	A, D	D	D	
CCI					

Key: A=analyzed using statistical model, D=displayed with descriptive statistics;
ln=natural-log transformed, R=raw (untransformed);
NA=not applicable;
*=if data permits.

CCI

6.4. Covariates

Covariates such as weight and age may be included in the analysis of variance (ANOVA) if necessary, if the demographics of the mild and moderate cohort subjects are not within the criteria stated in the protocol (mean weight ± 15 kg of healthy group, age ± 10 years of healthy group).

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 renal 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

Following Part 1, the effect of the severe renal impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between the severe renal impairment and the normal renal function using a one-way ANOVA model based on natural log transformed data.

Following Part 2 (if conducted), the same ANOVA analysis will be performed using data from the mild and moderate renal impairment groups.

CCI [redacted]

[redacted].

8.2. Statistical Analyses

For Part 1, a one-way analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf}, AUC_{last} and C_{max} of PF-04965842 for the renal impairment cohort (Test) to the normal renal function cohort (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CI will be obtained from the model. The adjusted mean differences and 90% CI for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios.

If Part 2 is conducted, the same ANOVA analysis will be performed. Test group in this case will be subjects with moderate or mild renal impairment and the reference group will be healthy subjects with normal renal function from Part 1. Covariates such as weight and age may be included in the ANOVA if necessary, if the demographics of the mild and moderate subjects are not within the criteria stated in the protocol (mean weight ±15 kg of healthy group, age ±10 years of healthy group).

CCI [redacted]

CCI

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-04964842 and metabolites, PF-06471658, PF-07055087 and CCI will be summarized by renal function group:

Table 3. PK Parameters to be Summarized Descriptively by Cohort

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

*: as data permit; #: PF-04965842 only.

CCI *Box and whisker plots for individual subject parameters (AUC_{inf}, AUC_{last} and C_{max}) be presented by renal function cohort and overlaid with geometric means.*

Supporting data from the estimation of CCI AUC_{inf} will be listed by analyte and 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-04965842 and metabolites PF-06471658, PF-07055087 and CCI concentrations will include:

- a listing of all plasma concentrations sorted by renal 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 plasma concentrations by renal 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 plasma concentrations time plots (on both linear and semi-log scales) against nominal time postdose by renal function cohort (all renal function cohorts on the same plot per scale, based on the summary of concentrations by renal function cohort and time postdose).

- mean plasma concentrations time plots (on both linear and semi-log scales) against nominal time postdose by renal function cohort (all renal function cohorts on the same plot per scale, based on the summary of concentrations by renal function cohort and time postdose).

- individual plasma concentration time plots by renal function cohort (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each renal function cohort per scale).

- CCI [redacted]

- [redacted]

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 renal 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 renal 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 renal 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 renal function cohort.

8.3.5. Laboratory Data

Laboratory data from each planned timepoint including screening 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 planned predose measurement.

For each planned timepoint, baseline values and change from baseline values within each renal function group 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 last planned predose measurement.

For each planned timepoint, summary of shift in normality status (normal\abnormal) from baseline 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, summary of shift in normality status (normal\abnormal) from baseline 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) and physical examination data 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, urine drug screen, serum or urine pregnancy test 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 assessed at Screening.

Data for prior medication(s) and non-drug treatment(s), urine drug screen, serum or urine pregnancy test for all females of childbearing potential and tobacco use will be collected and listed at Screening or Day -1. For rest of the parameters data will not be brought in-house,

and therefore will not be listed as they will be considered the sources data at sites per protocol.

9. REFERENCES

1. FDA Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling. 05/98

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

For Part 1:

An example of the PROC MIXED code is provided below:

```
proc mixed data = tab.pk covtest alpha=0.1;
        class group;
        model l&var = group / S covb alpha=0.1 CL DDFM=KR;
        repeated/type=un subject=subjid group=group R;
        lsmeans group;
        estimate 'Severe vs Normal'    group -1 1;
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;
run;
/* Letter assignments for group within the estimate statement above are as follows;
A = Normal (Reference), B = Severe (Test);*/;
```

For Part 2:

An example of the PROC MIXED code is provided below:

```
proc mixed data = tab.pk covtest alpha=0.1;
        class group;
        model l&var = group / S covb alpha=0.1 CL DDFM=KR;
        repeated/type=un subject=subjid group=group R;
        lsmeans group;
        estimate 'Mild vs Normal'              group -1 1 0;
        estimate 'Moderate vs Normal'          group -1 0 1;
```

```
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;
run;
/* Letter assignments for group within the estimate statement above are as follows;
A = Normal (Reference), C = Moderate (Test), D = Mild (Test);*/;
```

Following Part 2:

An example of the PROC REG code is provided below:

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

Note: Similar code will be used for regression analysis with respect to eGFR.