Protocol *B7981069*

PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY TO ESTIMATE THE EFFECT OF MULTIPLE-DOSE RITLECITINIB (PF-06651600) ON THE PHARMACOKINETICS OF SINGLE-DOSE TOLBUTAMIDE IN HEALTHY PARTICIPANTS

Statistical Analysis Plan (SAP)

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[redacted]

[redacted]

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	September 16, 2021	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

Ritlecitinib (PF-06651600) is a selective covalent inhibitor of JAK3 and the tyrosine kinase expressed in TEC family kinases and is currently under development for the treatment of alopecia areata, rheumatoid arthritis, vitiligo, ulcerative colitis, and Crohn's disease. *Tolbutamide is a first generation sulphonylurea developed for treatment of diabetes mellitus.*

The purpose of the study is to estimate the inductive effect of multiple-dose ritlecitinib on single dose PK of tolbutamide.

2.1. Study Design

This is a Phase 1, 2-period, multiple-dose, open-label, single fixed sequence study of the effect of ritlecitinib on tolbutamide pharmacokinetics in healthy participants. A total of approximately 12 healthy male and/or female participants will be enrolled in the study to obtain at least 10 evaluable participants who complete the study. Participants who withdraw from the study may be replaced at the discretion of the sponsor.

In Period 1, participants will be dosed with a single administration of tolbutamide 500 mg tablet on Day 1. Tolbutamide PK will be assessed for 36 hours following dosing. Period 1 will be immediately followed by Period 2 with no washout. In Period 2, participants will be dosed with oral 200 mg ritlecitinib QD for 10 days followed by administration of a single dose of 500 mg tolbutamide oral tablet within approximately 5 minutes after administration of a 200-mg dose of ritlecitinib on the morning of Day 10. Tolbutamide PK in Period 2 will again be assessed at pre-dose and over 36 hours after tolbutamide dosing.

Table 1. Treatment Flow Diagram

Period	***Day****	***Treatment***
1	*1*	*Tolbutamide 500 mg (single dose)*
2	*1-9*	*Ritlecitinib 200 mg QD*
	10	*Ritlecitinib 200 mg QD + tolbutamide 500 mg (single dose)*
	11	*No treatment given*
	12	*No treatment given (discharge)*
Follow-up	*28-35 after last dose of investigational product*	*Follow-up phone contact*

***Note: Day is relative to the first day of study intervention dosing (including tolbutamide and ritlecitinib) in each period.*

Participants will have a telephone contact at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product.

2.2. Study Objectives

2.2.1. Primary Objective

- *To evaluate the effect of multiple-dose ritlecitinib (PF-06651600) on the PK of a single, oral dose of tolbutamide in healthy participants.*

2.2.2. Secondary Objective

- *To evaluate the safety and tolerability of ritlecitinib when coadministered with a single dose of tolbutamide.*

2.2.3. Exploratory Objective

- *To characterize the PK of a single oral dose of tolbutamide in healthy participants.*

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, and/or supporting clinical development.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No statistical hypothesis will be tested in this study.

4.2. Statistical Decision Rules

There are no statistical decision rules.

5. ANALYSIS SETS

5.1. Enrolled participants

"Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

5.2. Pharmacokinetic (PK) Analysis Set

5.2.1. PK Concentration

The PK Concentration population is defined as all participants treated who have at least 1 concentration in at least 1 treatment period.

5.2.2. PK Parameter Evaluable

The PK Evaluable population is defined as all participants treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.

5.3. Pharmacodynamic Analysis Set

None.

5.4. Safety Analysis Set

All participants assigned to the study intervention and who take at least 1 dose of the study intervention. Participants will be analyzed according to the intervention they actually received.

5.5. Other Analysis Sets

None.

5.6. Treatment Misallocations

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

If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, and PK analyses, where applicable.

5.7. Protocol Deviations

Participants 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.

5.7.1. Deviations Assessed Prior to Randomization

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.

5.7.2. 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 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

Vital Signs and ECG data will be databased and available upon request. Laboratory data and adverse events will be reported as per sponsor reporting standards.

6.3. PK Endpoints

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

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

PK Parameter	Analysis Scale	Tolbutamide
AUC_{last}	ln	A, D
AUC_{inf}*	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
CL/F*	ln	D
V_z/F*	ln	D
$t_{1/2}$*	R	D

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

6.3.1. PD Endpoints

None.

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 participant'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 participant discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular treatment 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 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

The interactive effect on PK parameters will be determined by constructing 90% confidence intervals around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

8.2. Statistical Analyses

Natural log-transformed parameters AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of tolbutamide will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. 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% CI for the ratios. Tolbutamide administered alone will be the Reference treatment and tolbutamide co-administered with ritlecitinib will be the Test treatment.

The tolbutamide AUC_{inf}, AUC_{last} and C_{max} will be listed and summarized descriptively by treatment.

The tolbutamide T_{max}, CL/F, V_z/F and $t_{½}$, as data permit, will be listed and summarized descriptively by treatment. Plasma concentrations will be listed and summarized descriptively by treatment and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted using actual and nominal times, respectively.

Residuals from the model 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.

Table 2. PK Parameters to be Summarized Descriptively by Treatment

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

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

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by treatment: 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 tolbutamide concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment 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 treatment 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 treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale).

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) 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

All safety analyses will be performed on the safety population. A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering tolbutamide with or without ritlecitinib. Additionally, AEs will be reported for 3 phases: tolbutamide alone, ritlecitinib alone, and tolbutamide with ritlecitinib.

8.3.1. Treatment and Disposition of Participants

Participant evaluation groups will show end of study participant disposition and will show which participants were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for participant discontinuation(s) by treatment.

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 Participants' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Participant discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

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 treatment.

8.3.5. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. The baseline measurement is the last predose measurement of Period 1.

8.3.6. Vital Signs Data

Vital Signs data will be databased and available upon request.

8.3.7. ECG Data

ECG data will be databased and available upon request.

8.3.8. COVID-19 Assessment

Participants will be tested for SARS-COVID-19 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 x 24 hours in house), or if they develop COVID-19 like symptoms. If a participant develops COVID-19 during the study, it would be reported as an AE and summarized along with other AE data.

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. Pharmacogenomics and Biomarker Data

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

8.3.11. Screening and Other Special Purpose Data

Screening data will available upon request.

9. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

```
proc mixed data=tab.pk;
        class trt participant;
        model l&var=trt/ ddfm=KR;
        random participant /participant=participant;
        lsmeans trt;
        estimate 'Test vs Reference' trt  1  -1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;


/* Letter assignments for treatments (trt) within the estimate statement above are as follows;

A = Tolbutamide co-administered with Ritlecitinib (Test) ;
B = Tolbutamide administered alone (Reference)  */;
```