Protocol *B7981030*

A PHASE 1, RANDOMIZED, OPEN-LABEL, CROSS-OVER, SINGLE DOSE STUDY TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF PEDIATRIC RITLECITINIB (PF-06651600) CAPSULES AND SPRAY CONGEALED BEADS RELATIVE TO ADULT CAPSULES IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 2.0

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	17 November 2020	PPD	Not Applicable
2.0	27 August 2021	PPD	**Section 2.2:** Added additional other objective. **Section 8.2.2:** Added Taste Assessment Analyses

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

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None.

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This Statistical Analysis Plan for Study B7981030 is based on the Protocol Amendment 1, dated 11 August 2021. Additions include:

- Section 2.2; added an additional taste objective.
- Section 8.2.2; added descriptive stats and depiction of taste assessments for Treatment C.

2. INTRODUCTION

Ritlecitinib (PF-06651600) is a selective covalent inhibitor of JAK3 and the TEC family kinases and is currently under development for the treatment of AA, RA, vitiligo, UC, and CD. The primary objective of this study is to obtain an estimate of the bioavailability of a single oral dose of pediatric ritlecitinib (PF-06651600) capsules (3 x 10 mg capsules) relative to the 30 mg adult capsule in healthy adult participants under fasting conditions. Additionally, an alternative pediatric formulation utilizing a spray congealed beads will also be evaluated.

2.1. Study Design

The study will be conducted as a Phase 1, open-label, single dose, randomized, 3 periods, cross-over design in a single cohort of approximately 12 healthy male or female participants at a single center. Participants will be randomized into 2 sequences of treatment as described in Table 1*:*

Sequence 1 (n=6): A B C

Sequence 2 (n=6): B A C

Table 1. Study Schematics

Sequence	***Period 1***	***Washout Period***	***Period 2***	***Washout Period***	
1 (n=6)	*A*	*At least 2 days of washout between dosing*	*B*	*At least 2 days of washout between dosing*	*C*
2 (n=6))	*B*		*A*		*C*

n = number of participants.

Treatment A: ritlecitinib (PF-06651600) 30 mg intact adult capsule.

Treatment B: ritlecitinib (PF-06651600) 3 x 10 mg pediatric capsules.

Treatment C: ritlecitinib (PF-06651600) 30 mg spray congealed beads.

Since ritlecitinib (PF-06651600) is rapidly eliminated ($t_{½}$ ~2 hours), there will be at least a 48-hour washout between each dose.

Blood samples for PK analysis will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24 hours post-dose.

Participants will participate in the study up to approximately 2.5 months, including the screening and follow-up periods. Participants will be screened within 28 days of the first dose of study intervention and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Period 1 Day 1 dosing (Day -1). On Day 1 of each period, participants will receive a single dose of study intervention. Capsules and spray congealed beads will be administered with approximately 240 mL of ambient temperature water, and will be swallowed (not chewed). Participants will be fasted for at least 10 hours pre-dosing and 4 hours post-dosing.

Participants will be confined in the CRU for a total of at least 7 days (6 nights which includes admission to the CRU on Day -1) and discharged at the discretion of the investigator.

A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of the study interventions to capture any potential AE and confirm appropriate contraceptive usage.

Participants who withdraw from the study may be replaced at the discretion of the sponsor.

2.2. Study Objectives

Primary:

- *To estimate the relative BA of ritlecitinib (PF-06651600) pediatric capsules (3 x 10 mg capsule, Test) relative to adult 30 mg capsule (Reference) under fasted conditions in healthy adult participants.*

- *To estimate the relative BA of ritlecitinib (PF-06651600) administered as 30 mg spray congealed beads (Test) relative to adult 30 mg capsule (Reference) under fasted conditions in healthy adult participants.*

Secondary:

- *To evaluate the safety and tolerability of 10 mg capsules, 30 mg capsules and spray congealed beads at the 30 mg dose of ritlecitinib (PF-06651600) administered to healthy adult participants under fasted conditions.*

Other:

- *To characterize the PK of ritlecitinib (PF-06651600) administered as pediatric capsules (3 x 10 mg capsule), adult 30 mg capsule and 30 mg spray congealed beads in healthy adult participants under fasted conditions.*

- *To assess the sensory characteristics and overall palatability of spray congealed beads by 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.

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 is defined as all participants randomized and treated who have at least 1 concentration in at least 1 treatment period.

5.1.2. Parameter Analysis Set

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

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

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

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 randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are assigned 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.

5.6. 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.

5.6.1. 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.

5.6.2. 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 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.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of ritlecitinib (PF-06651600) will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for ritlecitinib (PF-06651600) (if possible) from the concentration-time data using standard noncompartmental methods:

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	Ritlecitinib (PF-06651600)
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
$t_{1/2}$*	R	D
CL/F*	ln	D
Vz/F*	ln	D
T_{last}	R	D

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

6.3.2. 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 (i.e 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 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 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

Precision of the estimate of 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

8.2.1. Pharmacokinetic Analysis

To estimate the relative BA of ritlecitinib (PF-06651600) pediatric capsule (3 × 10 mg capsules) relative to adult 30 mg capsule, the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the

ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (30 mg capsule form of ritlecitinib [PF-06651600] under fasted conditions) will be the Reference treatment while Treatment B (3 × 10 mg pediatric capsules of ritlecitinib [PF-06651600] under fasted conditions) will be the Test treatment. Data from Period 3 (Treatment C) will be excluded from this analysis.

To estimate the relative BA of ritlecitinib (PF-06651600) administered as 30 mg spray congealed beads (Test) relative to adult 30 mg capsule (Reference) under fasted conditions, the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (30 mg capsule of ritlecitinib [PF-06651600] under fasted conditions) will be the Reference treatment while Treatment C (30 mg spray congealed beads of ritlecitinib [PF-06651600] under fasted conditions) will be the Test treatment.

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 3. PK Parameters to be Summarized Descriptively by Treatment

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

For AUC_{inf}, AUC_{last} and C_{max} a listing of the individual subject ratios (Test/Reference) will be provided. Box and whisker plots for individual subject 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 *ritlecitinib (PF-06651600)* concentrations will include:

- A listing of all concentrations sorted by subject 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 subject (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each subject (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 subject plots by time, the actual PK sampling time will be used.

8.2.2. Taste Assessment Analyses

The data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the taste questionnaire. The sensory attributes (overall liking, mouth feel, bitterness, sourness, saltiness, tongue/mouth burn) from the taste assessment questionnaire for Treatment C (30 mg spray congealed beads) will be listed and descriptively summarized by collection time. Radar plots for each time point, summarizing all attributes, will be generated.

8.3. Safety Analysis

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

8.3.1. Treatment and Disposition of Participants

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 Participants' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Participant discontinuations and temporary discontinuations 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 in accordance with the sponsor reporting standards.

The baseline measurement is the last predose measurement on Day 1 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. 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

Screening data will available upon request.

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

Comparison of Treatment A (intact adult capsule) and B (3 × 10 mg pediatric capsules);

```
proc mixed data=tab.pk;
        where period<3;
        class seq period trt subject;
        model l&var=seq period trt/ ddfm=KR;
        random subject(seq) /subject=subject(seq);
        lsmeans trt;
        estimate Treatment B vs Reference (A)' 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;
Treatment A: ritlecitinib (PF-06651600) 30 mg intact adult capsule (reference);
Treatment B: ritlecitinib (PF-06651600) 3 × 10 mg pediatric capsules (test);*/
```

Comparison of Treatment A (intact adult capsule) and C (spray congealed beads);
Treatment B (pediatric capsule) excluded

```
proc mixed data=tab.pk;
        where trt in (“A” “C”);
        class seq trt subject;
        model l&var=seq trt/ ddfm=KR;
        random subject(seq) /subject=subject(seq);
        lsmeans trt;
        estimate Treatment C vs Reference (A)' 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;
Treatment A: ritlecitinib (PF-06651600) 30 mg intact adult capsule (reference);
Treatment C: ritlecitinib (PF-06651600) 30 mg spray congealed beads (test); */
```