Protocol *B7451061*

A PHASE 1, RANDOMIZED, CROSSOVER STUDY TO EVALUATE RELATIVE BIOAVAILABILITY OF ABROCITINIB ORAL SUSPENSION AND EFFECT OF AN ACID-REDUCING AGENT ON THE BIOAVAILABILITY OF ABROCITINIB COMMERCIAL TABLET AND TO ASSESS THE TASTE OF ABROCITINIB ORAL FORMULATIONS IN HEALTHY ADULT PARTICIPANTS AGED 18 TO 55 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 1.0

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	June 09, 2021	PPD	Not Applicable

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

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None.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

Abrocitinib (also referred to as PF-04965842) is an orally bioavailable potent JAK1 inhibitor with good selectivity over the broader kinome being developed for the treatment of Atopic Dermatitis (AD).

The primary purpose of this study in healthy participants is to estimate the rBA of an oral suspension of abrocitinib compared to abrocitinib commercial tablet. Additionally, this study will also evaluate the effect of an acid reducing agent (ARA) on the PK of abrocitinib commercial tablet and evaluate the taste and palatability of six different oral suspensions of abrocitinib to help in guiding the selection and development of abrocitinib pediatrics formulation.

2.1. Study Design

This is a Phase 1 randomized, crossover study in healthy participants to estimate the rBA of abrocitinib oral suspension (Test formulation) compared to abrocitinib commercial tablet (Reference formulation) under fasted condition. The effect of ARA on the BA of abrocitinib and its metabolites will be evaluated by administering abrocitinib 200 mg commercial tablet with or without famotidine 40 mg as an ARA. Part B is to assess the taste and palatability of 6 different abrocitinib oral suspension formulations, to guide the selection and development of abrocitinib pediatrics oral suspension formulation.

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This study consists of 2 parts, as listed below.

Part A:

This part of the study will be an open label, randomized, single dose, crossover, 3-treatment, 6-sequence, 3-periods design. Approximately 18 healthy male and/or female participants (18-55 years) will be enrolled and randomized to 1 of 6 possible treatment sequences. Participants who discontinue from the study may be replaced at the sponsor's discretion. The replacement participant will receive the same treatment sequences as the participant who discontinued. Each randomized treatment sequence will consist of 3 treatment periods as shown in Table 1 below.

Table 1. Randomized Treatment Sequences of Part A

Sequence	*Period 1*	*Period 2*	*Period 3*
1 (n=3)	*A*	*B*	*C*
2 (n=3)	*B*	*C*	*A*
3 (n=3)	*C*	*A*	*B*
4 (n=3)	*A*	*C*	*B*
5 (n=3)	*B*	*A*	*C*
6 (n=3)	*C*	*B*	*A*

Treatment A = Abrocitinib 200 mg commercial tablet only, under fasted conditions.

Treatment B = Abrocitinib 200 mg oral suspension formulation 1, under fasted conditions.

Treatment C = Famotidine 40 mg tablet administered 2 hours prior to abrocitinib 200 mg commercial tablet under fasted conditions.

In Period 1 through Period 3 of Part A, participants will receive a single 200 mg dose of abrocitinib commercial tablet (Treatment A), a single 200 mg dose of abrocitinib oral suspension (Treatment B), or 40 mg famotidine tablet administered 120 minutes prior to a single dose of 200 mg dose of abrocitinib commercial tablet (Treatment C) after a fast of at least 10 hours before taking the study intervention, abrocitinib. There will be at least a 72-hour washout period between each dose, ie, Day 1 of each study period (study treatment administration day) is separated by 72 hours.

Part B:

Participants who complete Part A of the study are expected to proceed to Part B. Part B will be a single-blind, randomized, 6-period, cross-over study in healthy male and/or female adult participants (18-55 years). A total of 18 healthy participants will be enrolled and randomized to 1 of 6 possible treatment sequences. Participants who discontinue from the study may be replaced at the sponsor's discretion. The replacement participant will receive the same treatment sequences as the participant who discontinued. Each randomized treatment sequence will consist of 6 treatment periods (Table 2).

Table 2. Randomized Treatment Sequences of Part B

Sequence	*Period 4*	*Period 5*	*Period 6*	*Period 7*	*Period 8*	*Period 9*
1 (n=3)	*F1+ARA*	*F2+ARA*	*F3+ARA*	*F4+ARA*	*F5+ARA*	*F6+ARA*
2 (n=3)	*F6+ARA*	*F1+ARA*	*F2+ARA*	*F3+ARA*	*F4+ARA*	*F5+ARA*
3 (n=3)	*F5+ARA*	*F6+ARA*	*F1+ARA*	*F2+ARA*	*F3+ARA*	*F4+ARA*
4 (n=3)	*F4*	*F5*	*F6*	*F1*	*F2*	*F3*
5 (n=3)	*F3*	*F4*	*F5*	*F6*	*F1*	*F2*
6 (n=3)	*F2*	*F3*	*F4*	*F5*	*F6*	*F1*

F1 = Abrocitinib oral suspension formulation 1 under fasted conditions.

F2 = Abrocitinib oral suspension formulation 2 under fasted conditions.

F3 = Abrocitinib oral suspension formulation 3 under fasted conditions.

F4 = Abrocitinib oral suspension formulation 4 under fasted conditions.

F5 = Abrocitinib oral suspension formulation 5 under fasted conditions.

F6 = Abrocitinib oral suspension formulation 6 under fasted conditions.

ARA = Famotidine 40 mg under fasted condition.

For any new healthy participants joining Part B only to support the achievement of the total number of 18 healthy participants enrolled or randomized in this part of the study, screening for healthy participants will be performed within 28 days prior to the first administration of the study intervention to confirm that they meet the participant selection criteria for the study.

Abrocitinib oral suspension formulations 1 to 6 for tasting will be offered to all participants in a blinded fashion. Participants randomized to Sequence 1-3 will receive famotidine (40 mg with 240 mL of room temperature water) 120 minutes before administering a single 200 mg dose of abrocitinib oral suspension formulations 1 to 6 with participants fasting for at least 10 hours before taking abrocitinib. While participants randomized to Sequence 4-6 will receive abrocitinib oral suspension formulations 1 to 6 with participants fasting for at least 10 hours before taking abrocitinib.

For participants receiving the ARA, famotidine, a 40 mg dose of famotidine tablet will be administered 2 hours before administering the study intervention with participants fasting for at least 10 hours before taking abrocitinib.

For a participant who completes both Part A and Part B of the study, the expected duration of participation from screening in Part A to the follow-up telephone contact in Part B of the study is approximately 11 weeks. While for a participant who completes only Part A or Part B of the study, the expected duration of participation from screening to the follow-up telephone contact is approximately 10 weeks. Participants who discontinue from the study may be replaced at the sponsor's discretion. The replacement participant will receive the same treatment sequences as the participant who discontinued.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last Follow-up phone call.

2.2. Study Objectives

2.2.1. Primary Objectives

- ***Part A***
  - *Estimate the rBA of abrocitinib 200 mg oral suspension formulation 1 compared to the 1×200 mg of abrocitinib commercial tablet under fasting condition.*
  - *Evaluate the effect of a single dose of an ARA (famotidine 40 mg) on the BA of abrocitinib 1×200 mg commercial tablet under fasting conditions.*
- ***Part B***
  - *Evaluate the taste and palatability of 6 abrocitinib suspension formulations using a 200 mg dose.*

2.2.2. Secondary Objectives

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- *Determine the PK of metabolites (M1, M2 and M4) following the administration of 1×200 mg of abrocitinib commercial tablet with or without an ARA (famotidine 40 mg) in Part A.*
- *Evaluate the safety and tolerability following oral administration of each of the abrocitinib formulations in Parts A and B.*

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development. After the completion of Part A (Periods 1, 2 and 3) of the study, PK analysis of Part A will be conducted, and PK tables and figures will be generated to support ongoing registrations.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No formal inferential statistics will be applied to the safety data.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Enrolled Analysis Set

All participants who sign the ICD.

5.2. Pharmacokinetic (PK) Analysis Set

5.2.1. 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.

5.2.2. 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.

5.3. Taste Analysis Set

All participants who receive at least 1 abrocitinib oral suspension formulation for taste evaluation and complete the abrocitinib Taste Assessment Questionnaire.

5.4. Pharmacodynamic Analysis Set

None.

5.5. Safety Analysis Set

All participants randomly 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.

5.6. Other Analysis Sets

None.

5.7. Treatment Misallocations

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

If a subject 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, PK and taste analyses, where applicable.

5.8. 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.

5.8.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 of the protocol.

5.8.2. 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

An adverse event will be considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time (28 days) will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. 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;*
- *ECG results.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-04965842 and its metabolites (M1, M2 and M4) will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-04965842 and its metabolites (M1, M2 and M4) (if possible) from the concentration-time data using standard noncompartmental methods:

Table 3. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-04965842	M1	M2	M4
AUC_{inf}*	ln	A, D	A, D	A, D	A, D
AUC_{last}	ln	A, D	A, D	A, D	A, D
AUC_{24}	ln	D	D	D	D
C_{max}	ln	A, D	A, D	A, D	A, D
T_{max}	R	D	D	D	D
$t_{1/2}$*	R	D	D	D	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 (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 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.

The safety data will be presented for Part A, Part B and Part A+B (combined).

8.2. Statistical Analyses

Actual PK sampling times will be used in the derivation of PK parameters.

PK parameters in Table 3 will be summarized descriptively by analyte and by treatment, as applicable, in accordance with Pfizer Data Standards. Concentrations will be listed and summarized descriptively by analyte, nominal PK sampling time and treatment. Individual participant and median profiles of the plasma concentration-time data will be plotted by treatment using nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales.

For the rBA portion of Part A, natural log transformed Abrocitinib AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect 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% 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. Treatment A (abrocitinib tablet) is the Reference Treatment while Treatment B (abrocitinib suspension) and Treatment C (abrocitinib tablet + famotidine) are the Test Treatments. After the completion of Part A (Periods 1, 2 and 3) of the study, PK analysis of Part A will be conducted, and PK tables and figures will be generated to support ongoing registrations.

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.

For the taste assessment in Part B of the study, the data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire. The taste analysis set will be used for presenting this data. *The sensory attributes (overall liking, mouthfeel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn) from the taste questionnaires will be listed and descriptively summarized by prototype formulation, and question across participants. Summary statistics (mean and 90% CI) will be calculated for the various questions. Radar plots for each of 4 time points, summarizing all attributes for each treatment will be generated. Boxplots of each attribute will be plotted against the time points.*

The patient-centric sampling will be performed in this study, but the results of analyzing this data will not be included in the CSR. Instead, a separate internal bioanalytical report will be issued to document data and conclusions from this analysis.

Table 4. PK Parameters to be Summarized Descriptively by analyte and Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, AUC_{24}, C_{max}	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.

For AUC_{inf}, AUC_{last}, AUC_{24} and C_{max} a listing of the individual subject ratios (Test/Reference) will be provided.

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by treatment 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 and its metabolites (M1, M2 and M4) concentrations will include:

- A listing of all concentrations sorted by subject ID, period 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.

8.3. Safety Analysis

All safety analyses will be performed on the safety population. A set of summary tables split by treatment and by Part A, Part B and Part (A+B) will be produced to evaluate any potential risk associated with the safety and toleration of administering study treatments.

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, taste, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

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 Subjects' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Subject 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.

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8.3.5. Laboratory Data

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

8.3.6. Vital Signs Data

Supine blood pressure, pulse rate and oral temperature will be measured as per the schedule of activities mentioned in the protocol.

The vital signs data will be listed in accordance with the sponsor reporting standards.

8.3.7. ECG Data

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

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

The screening data with the exception of demography and lab data will not be brought in-house, and therefore will not be listed.

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9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

For Part A and rBA:

An example of the PROC MIXED code is provided below:

```
proc mixed data=tab.pk;
        class seq period trt subject;
        model l&var=seq period trt/ ddfm=KR;
        random subject(seq) /subject=subject(seq);
        lsmeans trt;
        estimate 'Test B vs Reference A' trt -1  1  0/cl alpha=0.1;
        estimate 'Test C vs Reference A' trt -1  0  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 = Abrocitinib tablet (Reference);
B = Abrocitinib suspension (Test);
C = Abrocitinib tablet + famotidine (Test)  */;
```

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