Protocol *B7451092*

A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY TO ESTIMATE THE EFFECT OF MULTIPLE DOSE ABROCITINIB ON THE PHARMACOKINETICS OF SINGLE DOSES OF CAFFEINE, EFAVIRENZ, AND OMEPRAZOLE IN HEALTHY PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 1.0

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	September 27, 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

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 AD.

The purpose of the study is to evaluate the effect of abrocitinib on the in vivo PK of sensitive CYP1A2, 2B6 and 2C19 substrates, caffeine, efavirenz, and omeprazole, respectively.

2.1. Study Design

This is a Phase 1, open-label, multiple dose, single fixed-sequence, 2-period study to evaluate the effect of abrocitinib on the PK of caffeine, efavirenz and omeprazole in healthy adult participants. A total of approximately 13 healthy male and/or female participants will be enrolled in the study to obtain at least 12 evaluable participants who complete the study. Participants who withdraw from the study or are considered non-evaluable may be replaced at the discretion of the sponsor.

In Period 1, all the participants will receive single doses of probe drugs, including caffeine 100 mg, efavirenz 50 mg and omeprazole 10 mg, together on Day 1. The Day 1 of Period 2 begins on the fourth day following the start of Period 1. After 3 days of PK sampling in Period 1, Period 2 will immediately follow with no washout.

In Period 2, participants will receive abrocitinib 200 mg QD on Days 1-10. On Period 2 Day 2, participants will receive single dose of omeprazole 10 mg alone within approximately 5 minutes after administration of a 200 mg dose of abrocitinib in the morning. Participants will receive single doses of the probe drugs (caffeine 100 mg, efavirenz 50 mg and omeprazole 10 mg together) again on Day 8.

Table 1. Treatment Flow Diagram

Treatment	***Period 1***		***Period 2***				
	Day 1	*Days 2-3*	*Day 1*	*Day 2*	*Days 3-7*	*Day 8*	*Days 9-11*
Abrocitinib 200 mg QD			*X*	*X*	*X*	*X*	*X*
Caffeine 100 mg SD	*X*					*X*	
Efavirenz 50 mg SD	*X*					*X*	
Omeprazole 10 mg SD	*X*			*X*		*X*	

2.2. Study Objectives

- **Primary Objective:**
  - *To estimate effect of multiple dose abrocitinib on the PK of single, oral doses of caffeine, efavirenz and omeprazole in healthy participants.*
- **Secondary Objective:**
  - *To evaluate the safety and tolerability of abrocitinib when co administered with single doses of caffeine, efavirenz and omeprazole.*

[redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned. 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

There are no statistical hypotheses.

4.2. Statistical Decision Rules

There are no statistical decision rules.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all enrolled participants who received at least 1 dose of investigational product 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 participants who received at least 1 dose of investigational product and have at least 1 of the PK parameters of interest in at least 1 treatment period.

CCI [redacted]

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All participants who take at least 1 dose of investigational product. 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 enrolled 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.

5.6. 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.

[redacted]

[redacted]

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.*

6.2.1. Adverse Events

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.

6.2.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline is defined as the last predose measurement taken.

6.2.3. Vital Signs Data

BP, pulse rate and temperature measurements will be taken at times detailed in the Schedule of Activities given in the protocol.

Baseline is the last planned predose recording in each study period.

6.2.4. ECG Results

QT interval, QTcF, PR, RR, QRS and heart rate will be recorded at each assessment time indicated in the Schedule of Activities given in the protocol.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \qquad \text{where } RR = 60/HR \text{ (if not provided)}$$

Baseline is the last planned predose recording in each study period.

6.2.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of *caffeine, efavirenz and omeprazole* will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for *caffeine, efavirenz and omeprazole* (if possible) from the concentration-time data using standard noncompartmental methods:

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	Caffeine, Efavirenz and Omeprazole
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, CCI [redacted] *=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 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 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}, AUC_{last} [redacted]) will be analyzed using a mixed effect model with treatment as a fixed effect and subject 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. The Test and Reference treatments to estimate the treatment difference for each of the study objectives are as follows:

- *Objective 1: caffeine 100 mg (Period 1, Day 1) will be the Reference treatment; abrocitinib 200 mg + caffeine 100 mg (Period 2, Day 8) will be the Test treatment.*
- *Objective 2: efavirenz 50 mg (Period 1, Day 1) will be the Reference treatment; abrocitinib 200 mg + efavirenz 50 mg (Period 2, Day 8) will be the Test treatment.*
- *Objective 3: omeprazole 10 mg (Period 1, Day 1) will be the Reference treatment; abrocitinib 200 mg + omeprazole 10 mg (Period 2, Day 8) 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 CSR. 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}, [redacted]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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

Supporting data from the estimation of [redacted] AUC_{inf} will be listed by analyte and 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 *caffeine, efavirenz and omeprazole* concentrations will include:

- A listing of all concentrations sorted by participant 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 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

A set of summary tables will be produced to evaluate any potential risk associated with the safety and toleration of administering abrocitinib when co administered with single doses of caffeine, efavirenz and omeprazole.

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 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, 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 in accordance with the sponsor reporting standards.

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

If these data is brought in-house, then it will be listed.

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

```
proc mixed data=tab.pk;
        by analyte;
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /participant=participant;
        lsmeans trt;
        estimate 'Combined single agents alone vs Coadministration with abrocitinib ' 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 = Combined single agents alone (caffeine, efavirenz, omeprazole (Reference));
B = Coadministration (caffeine, efavirenz, omeprazole with abrocitinib (Test));
*/;
```