Protocol *B1871062*

A PHASE 1, RANDOMIZED, OPEN-LABEL, 3-PERIOD, 4-SEQUENCE, CROSSOVER, SINGLE-DOSE STUDY TO COMPARE THE BIOAVAILABILITY OF ORALLY ADMINISTERED BOSUTINIB CAPSULES AND TO ESTIMATE THE EFFECT OF FOOD ON BOSUTINIB CAPSULE

Statistical Analysis Plan
(SAP)

Version: 1.0

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[redacted]

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	October 08, 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

Bosutinib (PF-05208763, Bosulif®) is an orally active Src/Abl kinase inhibitor indicated for the treatment of adult patients with Ph+ CML.

The purpose of this study is to support the bridging of current clinical 25 mg capsule and proposed commercial 100 mg capsule in healthy participants under fed condition and to evaluate the effect of food on bosutinib plasma pharmacokinetics following administration of the proposed commercial 100 mg capsule strength. The relative bioavailability study will be conducted in the fed state since bosutinib is currently labeled to be administered with food.

2.1. Study Design

This is a Phase 1, randomized, open-label, 3-period, 4-sequence, crossover, single-dose study in approximately 28 healthy participants (7 participants per sequence). Participants will be randomized to 1 of the 4 sequences of treatment described in Table 1.

Note: "Enrolled" means a participant'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 A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.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.

Participants will remain in the study for up to 13 weeks, including the screening and follow-up periods. Participants will be screened within 28 days of the first dose of IP and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Day 1 dosing (Day -1) of each period. For Treatments A and B, following an overnight fast of at least 10 hours, on Day 1 of each period, participants will receive a high-fat and high-calorie breakfast prior to dosing which will need to be completely consumed within 20 minutes. For Treatment C, participants will be dosed after an overnight fast of at least 10 hours. Bosutinib will be administered as intact capsules with approximately 240 mL of ambient temperature water. Intact capsules will be swallowed and not chewed.

Tolerability and safety will be assessed for all treatments by monitoring AEs, ECGs, BP, pulse rate and safety laboratory data.

If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

Table 1. Study Schematics

Sequence	*Period 1*	*Washout*	*Period 2*	*Washout*	*Period 3*
1 (7 participants)	*A*	*At least 14 days between successive bosutinib doses*	*B*	*At least 14 days between successive bosutinib doses*	*C*
2 (7 participants)	*B*		*A*		*C*
3 (7 participants)	*A*		*B*		*N/A*
4 (7 participants)	*B*		*A*		*N/A*

Treatment A: 1 × 100 mg capsule under fed condition.
Treatment B: 4 × 25 mg capsules under fed condition.
Treatment C: 1 × 100 mg capsule under fasted condition.

2.2. Study Objectives

- **Primary Objectives:**
  - *To estimate the bioavailability of a single 100 mg capsule relative to four 25 mg capsules of bosutinib under fed condition in adult healthy participants.*
  - *To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single 100 mg capsule of bosutinib relative to fasted condition in adult healthy participants.*
- **Secondary Objectives:**
  - *To evaluate the plasma PK of bosutinib when administered as capsule formulation to healthy participants under fasted and fed conditions.*
  - *To evaluate the safety and tolerability of bosutinib when administered as capsule formulation to healthy participants under fasted and fed conditions.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned. 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. 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

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 subjects 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 subjects 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 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.

5.4. 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 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 and PK analyses where applicable.

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 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.

5.6.2. 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

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.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of *PF-05208763* will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for *PF-05208763* (if possible) from the concentration-time data using standard noncompartmental methods:

Table 2. PK Parameters

PK Parameter	Analysis Scale	***PF-05208763***
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
V_z/F*	ln	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.

8.2. Statistical Analyses

Natural logarithm-transformed AUC_{inf}, 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.

The following 2 comparisons will be performed:

- *Treatment B (Test) vs Treatment A (Reference).*
- *Treatment A (Test) vs Treatment C (Reference).*

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}	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.
CL/F*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
Vz/F*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

*: if data permit.

For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test-Reference) will be provided for the 2 comparisons described above. Individual participant bosutinib PK parameters for AUC_{inf}, AUC_{last} and C_{max} will be plotted by treatment and overlaid with geometric mean. Bosutinib plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median 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.

Supporting data from the estimation of t½ 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 *PF-05208763* 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].

If an individual participant has a known cause for biased estimate of a PK parameter (due for example to an event such as vomiting before all of the drug is 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. Participants who vomited at or before 2 times of median T_{max} after drug administration may be excluded from PK analysis.

8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration.

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 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 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.

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 planned predose measurement at hour 0 taken on Day 1 of each period.

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

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, HBcAb, HBsAg, HCVAb and HIV test will be assessed at Screening.

Urine drug screen, medical history, contraception check will be done at Screening, Day -1 of Period 1, Period 2 and Period 3.

Physical examination will be done at Screening or admission of Period 1 only and on Day 7 of each period.

To check exposure to SARS-CoV-2, and COVID-19 related signs and symptoms. COVID-19 questionnaires on Days 5 and 7 are only required for outpatient visits during each period.

The testing for COVID-19 pathogen by PCR will be performed on Day -1 and Day 4 of each period and other timepoints as deemed necessary to assess the safety at the discretion of the investigator. COVID-19 testing on Days 5 and 7 are only required for outpatient visits during each period. The test results per visit for each treatment will be provided in listings.

COVID-19 check temperature to be done during any visit to the CRU and at least daily during residence.

Data for prior medication(s) and non-drug treatment(s), urine drug screen, Physical examination contraception check and alcohol/tobacco use will be listed. For rest of the parameters data will not be brought in-house, and therefore will not 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;
        class seq period trt subject;
        model l&var=seq period trt/ ddfm=KR;
        random subject(seq) /subject=subject(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1  1  0 /cl alpha=0.1;
        estimate 'A vs C' 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 = Treatment A: 1 × 100 mg capsule under fed condition;
B = Treatment B: 4 × 25 mg capsules under fed condition;
C= Treatment C: 1 × 100 mg capsule under fasted condition;
*/;
```