Protocol C4471002

A Phase 1, Open-Label, Randomized, Single Dose, 2 Sequence, 3 Period Crossover Study to Evaluate the Effect of a Low-fat and High-fat Meal on the Relative Bioavailability of PF-07284890 in Healthy Adult Participants

Statistical Analysis Plan
(SAP)

Version: 1

Date: 17 May 2022

[redacted]

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

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 17 May 2022	Original 06 Apr 2022	N/A	N/A

2. INTRODUCTION

PF-07284890 (also known as ARRY-461) is a potent, selective, highly brain-penetrant small-molecule inhibitor of BRAF V600 mutations that is currently being developed for the treatment of BRAF V600-mutant solid tumors with or without brain involvement.

The purpose of the study is to evaluate the effect of a low-fat and high-fat meal on the relative bioavailability of PF-07284890 following single dose oral administration of PF-07284890 using 2 of the 100 mg PF-07284890 tablets currently used in the first-in-patient study C4471001 (200 mg per single dose). Results from the study will be used to inform food instructions for patients in PF-07284890 first-in-patient study C4471001, Phase 1b.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4471002.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The following are the objectives and endpoints in this study. Estimand framework is not applied to this phase 1 study.

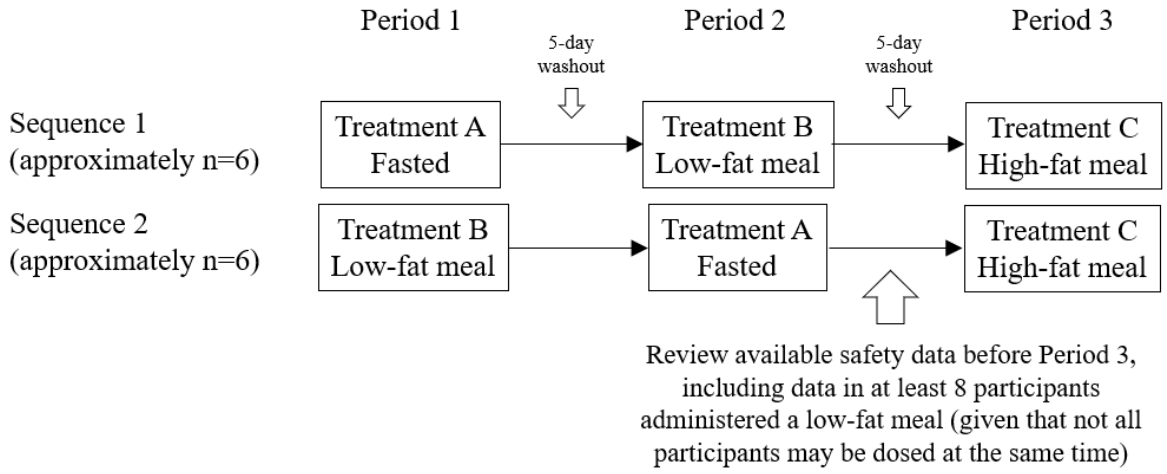
Objectives	*Endpoints*
Primary:	***Primary:***
• *To evaluate the effect of a low-fat meal on the exposures of PF-07284890 following a single oral 200-mg dose* • *To evaluate the effect of a high-fat meal on the exposures of PF-07284890 following a single oral 200-mg dose*	• *Comparison of low-fat meal with fasted PK: The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890* • *Comparison of high-fat meal with fasted PK: The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890*
Secondary:	***Secondary:***
• *To characterize the pharmacokinetic parameters of PF-07284890 following a single oral 200-mg dose*	• *T_{max}, $t_{½}$, CL/F and V_z/F (if data permit).*
• *To evaluate the safety and tolerability of PF-07284890 in healthy participants*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*
CCI [redacted]	[redacted]

2.3. Study Design

This is a Phase 1, open-label, randomized, single dose, 3-treatment, 2-sequence, 3-period crossover study to evaluate the effect of a low-fat and high-fat meal on the relative bioavailability of PF-07284890 following a single oral dose of PF-07284890 using two 100-mg tablets of PF-07284890 in healthy adult participants, males and females of non-childbearing potential. The study will consist of 3 treatments: a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Treatment A, Reference), a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under low-fat meal fed conditions (Treatment B, Test 1), and a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under high-fat meal fed conditions (Treatment C, Test 2).

Approximately 12 healthy participants will be randomly assigned to study intervention such that approximately 6 participants will be enrolled to each sequence. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator.

Figure 1. C4471002 Study Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are the ratios of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890 under the fed conditions (low-fat meal or high-fat meal), relative to the PK parameters under the fasted conditions.

3.2. Secondary Endpoints

The secondary endpoints are the plasma PK parameters of PF-07284890, which will be derived (as data permit) from the concentration-time data using standard noncompartmental methods of analysis as outlined in Table 2. *Actual PK sampling times will be used in the derivation of PF-07284890 PK parameters when available. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.*

Table 2. Plasma PF-07284890 PK Parameters Definitions

Parameter	***Definition***	***Method of Determination***
*AUC_{inf}**	*Area under the plasma concentration-time curve from time zero extrapolated to infinity*	*AUC_{last} + (C_{last}*/k_{el}), where C_{last}* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis*
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).*	*Linear/Log trapezoidal method.*
C_{max}	*Maximum observed plasma concentration*	*Observed directly from data*
T_{max}	*Time to reach C_{max}*	*Observed directly from data as time of first occurrence*
*$t_{½}$**	*Terminal elimination half-life*	*$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.*
*CL/F**	*Apparent clearance*	*$Dose/AUC_{inf}$*
*V_z/F**	*Apparent volume of distribution for extravascular dosing*	*$Dose/(AUC_{inf} \bullet k_{el})$*

**If data permit.*

Safety data are also considered as secondary endpoints and are discussed in Section 3.5.

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3.4. Baseline Variables

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.5. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- adverse events (AE)

- laboratory data
- vital signs data
- electrocardiogram (ECG) results

3.5.1. Adverse Events

Any events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur in a non-treatment period (ie washout or follow-up period) within the lag time of 28 days will be counted as treatment emergent and attributed to the previous treatment taken. Similarly, the time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

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 not take into account whether each participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For each period, the baseline measurement is the predose measurement on Day -1.

3.5.3. Vital Signs

Supine blood pressure (BP), pulse rate (PR) and temperature will be measured at times specified in the SoA given in the protocol. Respiratory rate (RR) will be measured if the PR is outside of normal range.

For each period, the baseline measurement is the predose measurement on Day 1.

3.5.4. Electrocardiograms

QT interval, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

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

For each period, the baseline value is the average of the triplicate ECG measurements collected before dose administration on Day 1.

The maximum absolute value (postdose) and the maximum increase from baseline for QTcF, PR and QRS, over all measurements taken postdose, will be determined.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of

these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the clinical study report (CSR) in order to place the >500 ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose ECG measurement and the predose baseline ECG value on Day 1.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. 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.*
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.*
PK Concentration Population	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value can be reported.*
PK Parameter Analysis Population	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest can be reported.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

Methods to handle missing PK data are described below.

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.).

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.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

PK 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 dose with ≥3 evaluable measurements.

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 from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

The primary endpoints are the ratios of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890 under the fed conditions (low-fat meal or high-fat meal), relative to the PK parameters under the fasted condition.

Using data from Treatments A and B, *natural log transformed 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% CI for the ratios. Treatment A (PF-07284890 under fasted condition) is the Reference treatment and Treatment B (PF-07284890 administered under fed condition, low-fat meal) is the Test treatment.*

Using data from Treatments A and C, natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with treatment and sequence as a fixed effect 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% CI for the ratios. Treatment A (PF-07284890 under fasted condition) is the Reference treatment and Treatment C (PF-07284890 administered under fed condition, high-fat meal) is 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.

6.2. Secondary Endpoint(s)

PK data:

The plasma concentrations of PF-07284890 will be listed and descriptively summarized by nominal PK sampling time and treatment on the PK Concentration Population. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Presentations for PF-07284890 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, SD, %CV, minimum, maximum and the number of concentrations above the LLQ.

- 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].

The PK parameters will be summarized descriptively by treatment group in accordance with Pfizer data standards on the PK Parameter Analysis Population, as data permit. A listing of the individual participant ratios (Test-Reference) and a scatterplot of the ratio of fed and fasted AUC_{inf} versus fasted AUC_{inf} will be provided. Missing values will be handled as

detailed in Section 5.3.1. Each PK parameter will be summarized by treatment group and will include the set of summary statistics as specified in Table 3.

Table 3. 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, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

Safety data:

See Section 6.5.

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[redacted]

6.4. Baseline and Other Summaries and Analyses

6.4.1. Demographic Summaries

Demographic characteristics (age, gender, ethnicity, race, weight, height and body mass index) will be summarized for enrolled population in accordance with the CaPS.

6.4.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.4.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.4.4. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported in the listings.

6.5. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.5.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.5.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.5.3. Vital Signs

Vital signs data will be listed and summarized by treatment in accordance with the CaPS.

6.5.4. Electrocardiograms

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time postdose. The frequency of uncorrected QT values above 500 ms will be tabulated.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	Mild (ms)	Moderate (ms)	Severe (ms)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, PR and QRS maximum values and maximum increases from baseline will also be tabulated by treatment using the following categories:

Safety PR and QRS Assessment

PR (ms)	Max. $\geq$300
PR (ms) increase from baseline	Baseline >200 and max. $\geq$25% increase; Baseline $\leq$200 and max. $\geq$50% increase
QRS (ms)	Max. $\geq$140
QRS (ms) increase from baseline	$\geq$50% increase

7. INTERIM ANALYSES

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, facilitating PK modeling, and/or supporting clinical development.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Available safety and PK data may be reviewed.

APPENDICES

Appendix 1. Summary of Analyses

Endpoint	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Method
Ratio of AUC_{last}, AUC_{inf}, C_{max}	PK Parameter Analysis Population	Observed data	Mixed effect ANOVA model
PK parameters	PK Parameter Analysis Population	Observed data	Descriptive statistics
PK concentrations	PK Concentration Population	Observed and imputed (Section 5.3.1) data	Descriptive statistics
Safety data	Safety analysis set	Observed and imputed (Section 5.3.2) data	Descriptive statistics

Appendix 2. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For comparison of fasted versus low-fat meal:

```
proc mixed data=tab.pk;
where trt in (“A” “B”);
        class seq period trt participant;
        model l&var=seq period trt / ddfm=KR;
        random participant(seq) / subject=participant(seq);
        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;
```

For comparison of fasted versus high-fat meal:

```
proc mixed data=tab.pk;
where trt in (“A” “C”);
        class seq trt participant;
        model l&var=seq trt / ddfm=KR;
        random participant(seq) / subject=participant(seq);
        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;

For comparison of fasted versus low-fat meal:
A = 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Reference);
B = 200 mg PF-07284890 (2 × 100 mg tablets) under low-fat meal fed conditions (Test)

For comparison of fasted versus high-fat meal:
A = 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Reference);
C = 200 mg PF-07284890 (2 × 100 mg tablets) under high-fat meal fed conditions (Test) */;

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
BLQ	below the limit of quantitation
BP	blood pressure
CAPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	confidence interval
CL/F	apparent clearance
C_{last}	predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis
C_{max}	maximum observed plasma concentration
CSR	clinical study report
%CV	coefficient of variation
ECG	electrocardiogram
HR	Heart rate
k_{el}	the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
LLQ	lower limit of quantitation
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
CCI	[redacted]
PK	pharmacokinetic(s)
PR	pulse rate
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{1/2}$	terminal elimination half-life
T_{max}	time to reach C_{max}
TEAE	treatment emergent adverse event
V_z/F	apparent volume of distribution for extravascular dosing