Protocol C4161007

A Phase 1, Randomized, Open-label, 4-period, 5-treatment, 6-sequence, Crossover, Single-Dose Study in Healthy Participants to Investigate the Effect of Tablet Formulation and Food on the Bioavailability of PF-07104091

Statistical Analysis Plan
(SAP)

Version: 1

Date: 09 Jun 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 09 Jun 2022	Original 21 Apr 2022	N/A	N/A

2. INTRODUCTION

PF-07104091 is an inhibitor of CDK2 that is currently being investigated in a Phase 1 study (C4161001) in participants with tumor types that have potential to have increased CCNE1 expression/CDK2 activity and/or loss of the Rb tumor suppressor. Specific targeting of CDK2 represents a novel approach to address additional high unmet medical need indications such as HR-positive HER2-negative BC, NSCLC, ovarian cancer, and TNBC. To date, clinical drug supplies of PF-07104091 have used an early development enabling formulation that is an CCI [redacted] *with an active pharmaceutical ingredient (API) of PF-07104091 monohydrate. As the clinical development program of PF-07104091 is preparing to move to later stages of development, requiring the scaling-up and refinement of the investigational drug supply, activities are underway to further develop and optimize the manufactured PF-07104091 drug product.*

The purpose of the study is to investigate the relative bioavailability of 4 tablet formulations of PF-07104091 and to characterize the effect of food on a PF-07104091 CCI [redacted] *The data generated from this study will be used to guide selection of the tablet manufacturing method used for the drug supply of future Phase 3 studies, to inform dose administration instructions for PF-07104091 with regards to dosing with or without food, and to provide clinical pharmacokinetics (PK) supporting information to investigate the potential for identifying an in-vitro dissolution safe space for PF-07104091 that can inform the future optimization of PF-07104091 drug products.*

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4161007.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	*Endpoints*
Primary:	***Primary:***
• *To estimate the bioavailability of a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation relative to a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation under fasted conditions in adult healthy participants.* • *To estimate the bioavailability of a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation and a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation relative to a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation under fasted conditions in adult healthy participants.*	• *Plasma AUC_{inf} and C_{max} for PF-07104091. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).*
Secondary:	***Secondary:***
• *To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation relative to fasted conditions in adult healthy participants.* • *To estimate the bioavailability of a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation relative to a single 300 mg dose of the PF-07104091* CCI [redacted] *formulation under fasted conditions in adult healthy participants.*	• *Plasma AUC_{inf} and C_{max} for PF-07104091. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).*
• *To evaluate the safety and tolerability of PF-07104091 when administered as a tablet formulation to healthy participants under fasted and fed conditions.*	• *Assessment of treatment emergent adverse events (TEAEs), clinical laboratory abnormalities, vital signs, physical*

Objectives	*Endpoints*
	examinations, and 12-lead electrocardiograms (ECGs).
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.3. Study Design

A Phase 1, randomized, open-label, 4-period, 5-treatment, 6-sequence, crossover, single-dose study in healthy participants.

Approximately 30 participants (5 participants per sequence) will be enrolled to study intervention. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective(s), additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

Each enrolled participant will receive one of the 5 treatments in each period according to the treatment schedule shown in Table 2.

Table 2. Treatment Schedule

Sequence	***Period 1***	***Washout: at least 5 days between PF-07104091 doses***	***Period 2***	***Washout: at least 5 days between PF-07104091 doses***	***Period 3***	***Washout: at least 5 days between PF-07104091 doses***	***Period 4***
1 (n=5)	*A*		*B*		*C*		*D*
2 (n=5)	*B*		*C*		*A*		*D*
3 (n=5)	*C*		*A*		*B*		*D*
4 (n=5)	*A*		*B*		*C*		*E*
5 (n=5)	*B*		*C*		*A*		*E*
6 (n=5)	*C*		*A*		*B*		*E*

Treatment A: 300 mg (2 × 125 mg and 2 × 25 mg) CCI [redacted].
Treatment B: 300 mg (2 × 125 mg and 2 × 25 mg) CCI [redacted].
Treatment C: 300 mg (4 × 75 mg) CCI [redacted].
Treatment D: 300 mg (4 × 75 mg) CCI [redacted]
Treatment E: 300 mg (4 × 75 mg) CCI [redacted]

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are plasma AUC_{inf} (if data permits), AUC_{last} and C_{max} for PF-07104091 administered under fasted conditions as CCI [redacted] and CCI [redacted]. Ratios of AUC_{inf}, AUC_{last} and C_{max} will be derived to assess treatment comparisons.

3.2. Secondary Endpoints

The secondary endpoints are plasma AUC_{inf} (if data permits), AUC_{last} and C_{max} for PF-07104091 administered as CCI [redacted], under fed and fasted conditions) and CCI [redacted], under fasted condition). Ratios of AUC_{inf}, AUC_{last} and C_{max} will be derived to assess treatment comparisons.

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

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Table 3. Plasma PF-07104091 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 and k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve*
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*	*$Log_e(2)/k_{el}$, 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.*

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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

[redacted]

- vital signs data
- ECG results

3.5.1. Adverse Events

Any events occurring following start of treatment will be considered as 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 or Day 1.

3.5.3. Vital Signs

Supine blood pressure (BP), pulse rate (PR), respiratory rate (RR) and temperature will be measured at times specified in the SoA given in the protocol.

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

Changes from baseline will be defined as the change between the postdose vital signs measurement on Day 3 and the predose vital signs measurement on Day 1, for each period.

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 measurement is the predose measurement on Day 1.

Changes from baseline will be defined as the change between the postdose ECG measurement on Day 3 and the predose ECG measurement on Day 1, for each period.

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/Randomly assigned to study intervention	*"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and 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. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.*
PK Concentration	*The PK concentration population is defined as all participants randomized and treated who have at least 1 PF-07104091 concentration in at least 1 treatment period.*
PK Parameter	*The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PF-07104091 PK parameters of primary interest in at least 1 treatment period.*
Safety	*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. 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 not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to dosing error or 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. For instance, if a participant has a vomiting event post dose that is within a duration of time that is 2-times the derived median T_{max} for the population for the administered treatment, then the pharmacokineticist should consider the exclusion of the PK concentration data collected following the initial vomiting event in that treatment period and the PK parameter data reported for that treatment period from the datasets used to calculate 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

For assessment of the primary objectives of the study (Periods 1, 2 and 3), natural log transformed AUC_{inf} (if data permits), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and participant within a 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. The following treatment comparisons will be performed:

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

6.2.1. PK Parameters for Secondary Objectives

For the secondary objectives of the study (where each treatment comparison occurs via fixed-sequence), 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 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. The following treatment comparisons will be performed:

- *Treatment D (Test) vs Treatment C (Reference)*
- *Treatment E (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 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.

6.2.2. Safety Data

Safety data is also considered as secondary endpoint and analyses and summaries are described in Section 6.5.

CCI [redacted]

[redacted]

6.3. Subset Analyses

There are no planned subset analyses.

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 databased and available upon request.

6.5.4. Electrocardiograms

ECG data will be databased and available upon request.

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.

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.

APPENDICES

Appendix 1. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For primary objectives:

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

```
proc mixed data=tab.pk;
        class seq period trt participant;
        model l&var=seq period trt/ ddfm=KR;
        random participant(seq) /participant=participant(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1  1  0   /cl alpha=0.1;
        estimate 'C vs A' trt -1  0  1   /cl alpha=0.1;
        estimate 'C vs B' trt  0  -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: 300 mg (2 × 125 mg and 2 × 25 mg) CCI [redacted] fasted condition.
B: 300 mg (2 × 125 mg and 2 × 25 mg) CCI [redacted] fasted
condition.
C: 300 mg (4 × 75 mg) CCI [redacted] fasted condition.
*/
```

For secondary objectives:

- **Treatment D (Test) vs Treatment C (Reference)**

```
proc mixed data=tab.pk;
where trt in (“D” “C”);
        class seq trt participant;
        model l&var=seq trt / ddfm=KR;
        random participant(seq) / subject=participant(seq);
        lsmeans trt;
        estimate 'D vs C' trt -1  1  /cl alpha=0.1;
```

[redacted]

```
        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;
C: 300 mg (4 × 75 mg) CCI [redacted] fasted condition
(Reference);
D: 300 mg (4 × 75 mg) CCI [redacted] fasted condition
(Test)
*/;
```

- **Treatment E (Test) vs Treatment C (Reference)**

```
proc mixed data=tab.pk;
where trt in ("E" "C");
        class seq trt participant;
        model l&var=seq trt / ddfm=KR;
        random participant(seq) / subject=participant(seq);
        lsmeans trt;
        estimate 'E vs C' 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;
C: 300 mg (4 × 75 mg) CCI [redacted] fasted condition
(Reference);
E: 300 mg (4 × 75 mg) CCI [redacted] fed condition  (Test)
*/;
```

Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
ANOVA	analysis of variance
API	active pharmaceutical ingredient
AUC_{extrap}%	the percentage of AUC_{inf} obtained by forward extrapolation
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
BC	breast cancer
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CCNE1	cyclin E
CDK2	cyclin-dependent kinase 2
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
DC	direct compression
CCI	[redacted]
ECG	electrocardiogram
HER2	human epidermal growth factor receptor 2
HR	heart rate; hormone-positive
IR	immediate release
k_{el}	the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
$k_{el,t(hi)}$	initial slope time point value used in the calculation of k_{el}
$k_{el,t(lo)}$	final slope time point value used in calculation of k_{el}
$k_{el,t(n)}$	number of time points used in the calculation of k_{el}
LLQ	lower limit of quantitation
MST	material-sparing tablet
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
NSCLC	non-small cell lung cancer
PK	pharmacokinetic(s)

Abbreviation	Term
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)
r^2	the goodness-of-fit statistic from the regression
Rb	retinoblastoma
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{1/2}$	terminal elimination half-life
TEAE	treatment emergent adverse event
T_{max}	time to reach C_{max}
TNBC	triple-negative breast cancer
V_z/F	apparent volume of distribution for extravascular dosing