Protocol C4391010

A Phase 1, Open-Label, Parallel-Group, Single-Dose Study in Healthy Adult Male Participants to Investigate the Absorption, Distribution, Metabolism and Excretion of ^{14}C-PF-07220060 and to Assess the Absolute Bioavailability and Fraction Absorbed of PF-07220060 Using a ^{14}C-Microtracer Approach

[redacted]

Statistical Analysis Plan
(SAP)

Version: 1

Date: 18 Oct 2023

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APPENDICES

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 / 18 Oct 2023	Original 08 Aug 2023	N/A	N/A

2. INTRODUCTION

PF-07220060 is a selective cyclin-dependent kinase (CDK)4 inhibitor that is currently being investigated in participants with metastatic or advanced solid tumors. PF-07220060 differs from currently approved dual CDK4/6 inhibitors in that it displays greater CDK4-over-CDK6 selectivity and is therefore hypothesized to drive tumor growth inhibition through greater CDK4 selectivity, while minimizing CDK6 driven hematopoetic effects. This may translate to improved efficacy and tolerability over other CDK4/6 inhibitors.

The purpose of the study will be to investigate the metabolism and excretion following a single oral administration of [^{14}C]PF-07220060 under fasted condition in healthy male participants. The data generated from this study will be used to assess clearance mechanisms for PF-07220060 as well as identify metabolites that should be qualified to adhere to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (M3) R2 guidance. In addition, this study will characterize the fraction of dose absorbed and bioavailability of orally administered PF-07220060 under the fasted condition, in reference to an intravenous (IV) infusion of [^{14}C]PF-07220060 (given as a microtracer microdose infusion following administration of an oral unlabeled dose), and will also assess pharmacokinetic (PK) parameters of PF-07220060 following both oral and IV administration of [^{14}C]PF-07220060.

This study will also evaluate sensory and taste attributes (eg, bitterness and tongue/mouth sensation) of the PF-07220060 oral suspension to guide the future development of pediatric friendly oral formulations.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4391010.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives, Endpoints, and Estimands

The following are the objectives and endpoints in this study. Estimand framework will not be applied to this Phase 1 study in healthy participants.

Objectives	***Endpoints***
Primary:	***Primary:***
• *To characterize the rate and extent of excretion of total radioactivity following administration of a single oral dose of [^{14}C]PF-07220060.*	• *Mass Balance: Cumulative recovery (%) of radioactivity in urine and feces (adjusted for vomitus, if any), expressed as a percent of total oral radioactive dose administered (quantification by AMS).*
• *To characterize the metabolic profile for PF-07220060 and identify the circulating and excreted metabolites of PF-07220060 following administration of a single oral dose of [^{14}C]PF-07220060.*	• *Metabolic profiling/metabolite identification and determination of relative abundance of [^{14}C]PF-07220060 and its metabolites in plasma, urine and feces, if possible (Cohort 1).*
Secondary:	***Secondary:***
• *To determine the absolute oral bioavailability (F) of PF-07220060 from a single oral dose of PF-07220060 under fasted conditions followed by a single IV microdose of [^{14}C]PF-07220060.*	• *The ratio of dose-normalized plasma AUC_{inf} of oral PF-07220060 (LCMS) and IV [^{14}C]PF-07220060 (HPLC-AMS) [Cohort 2 only].*
• *To determine the fraction of PF-07220060 dose absorbed (F_a) from a single oral dose of [^{14}C]PF-07220060 under fasted conditions.*	• *F_a calculated from the ratio of total recovered radioactivity [^{14}C] in urine following single dose administration of [^{14}C]PF-07220060 orally in Cohort 1 and via IV infusion in Cohort 2 (quantification by AMS).*
• *To determine the safety and tolerability of PF-07220060, administered as a single oral dose of [^{14}C]PF-07220060 or a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060.*	• *AE monitoring, physical examination, clinical laboratory measurements, vital signs and 12-lead ECGs.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To characterize the metabolic profile and identify the circulating and excreted metabolites of PF-07220060 following administration of a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060 (as needed).*	• *Contingent metabolic profiling/metabolite identification and determination of relative abundance of [^{14}C]PF-07220060 and the metabolites of [^{14}C]PF-07220060 in plasma, urine and feces, if possible (Cohort 2).*

• *To determine the plasma PK parameters of a single oral dose of PF-07220060 following administration as a single oral dose of [^{14}C]PF-07220060 or a single oral dose of PF-07220060 followed by administration of a single IV microdose of [^{14}C]PF-07220060.*	• *Plasma PK parameters of PF-07220060 from LCMS analyses (Cohort 1 and Cohort 2):*
	  • *AUC_{last}, C_{max}, T_{max}.*
	  • *If data permits: AUC_{inf}, $t_{½}$, V_z/F, CL/F.*

Objectives	***Endpoints***
• *To determine plasma PK parameters of [^{14}C]PF-07220060 following administration of a single IV microdose of [^{14}C]PF-07220060.*	• *Plasma PK parameters of [^{14}C]PF-07220060 from HPLC-AMS analyses (Cohort 2):* • *AUC_{last}, C_{max}, T_{max}.* • *If data permits: AUC_{inf}, $t_{½}$, CL, V_{ss}.*
• *To determine the urine PK parameters of PF-07220060 following administration as a single oral dose of [^{14}C]PF-07220060 (if measured)*	• *Urine PK parameters of PF-07220060 from LCMS (Cohort 1):* • *CL_R, Ae, and Ae%.*
• *To determine plasma PK parameters of total radioactivity following administration of a single oral dose of [^{14}C]PF-07220060.*	• *Plasma PK parameters of total radioactivity [^{14}C] from AMS analyses (Cohort 1):* • *AUC_{last}, C_{max}, T_{max} of total radioactivity.* • *If data permit: AUC_{inf}, $t_{½}$.*
• *To determine plasma PK parameters of total radioactivity following a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060 (as needed).*	• *Plasma PK parameters of total radioactivity [^{14}C] from AMS analyses (Cohort 2):* • *AUC_{last}, C_{max}, T_{max} of total radioactivity.* • *If data permit: AUC_{inf}, $t_{½}$.*
• *To explore the impact of pharmacogenomics on absorption, distribution, metabolism and excretion of [^{14}C]-PF-07220060 and the absolute bioavailability and fraction absorbed of PF-07220060.*	• *Allelic variants of drug metabolizing enzymes and transporters*
• *To evaluate the sensory and taste attributes of the PF-07220060 oral suspension in healthy participants under fasted conditions.*	• *Taste Assessment Survey Scoring Metrics: mouthfeel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, throat burn, and overall liking.*

2.3. Study Design

This study will be a Phase 1, randomized, open-label, parallel-group, single-dose study of PF-07220060 to characterize the metabolic profile and routes of excretion for oral [^{14}C]PF-07220060 and to evaluate the absolute oral bioavailability (F) of PF-07220060 and fraction absorbed (F_a) of [^{14}C]PF-07220060, in reference to IV microtracer [^{14}C]PF-07220060 in fasted healthy male participants.

Approximately 6 healthy adult male participants will be enrolled in each of the 2 cohorts. Participants in Cohorts 1 and 2 will receive treatment regimen A and B, respectively. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary and secondary PK objective(s), additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

Blood, urine, feces, and vomitus (if any) samples will be collected according to the schedule of activities (SoA) given in the protocol to analyze the following primary endpoints.

3.1.1. Mass Balance

Total Radioactivity *in* ***urine*** *will be reported for* ***Cohort 1 and 2*** *separately, as the percentage of the administered radioactivity excreted at each time interval and as the cumulative total percent of dose excreted in urine over time.*

Total Radioactivity *in* ***feces*** *will be reported for* ***Cohort 1*** *(and if applicable for* ***Cohort 2****), as the percentage of the administered radioactivity excreted at each time interval and as the cumulative total percent of dose excreted in feces over time.*

Total Radioactivity *in* ***vomitus*** *(if any) will be reported for* ***Cohort 1 only****, as the percentage of the administered radioactivity excreted at each time interval and the total percent of dose recovered in vomitus.*

Percent recovery of total radioactivity in urine, feces and vomitus for ***Cohort 1 only****, will be determined based on total administered dose in* ***Cohort 1****. Residual radioactivity in the oral dosing container will be required to be assessed in* ***Cohort 1*** *and documented in the study CRF.*

3.1.2. Metabolic Profiling and Metabolite Identification

Plasma, urine and fecal samples collected in Cohort 1 will be analyzed for metabolites of [^{14}C]PF-07220060. Major metabolites of PF-07220060 in plasma, urine and feces may be identified if possible. Contributions of parent and each major metabolite to total radioactivity recovered in urine and feces and to circulating radioactivity in plasma will be quantified if possible.

3.2. Secondary Endpoints

3.2.1. Absolute Oral Bioavailability

Absolute oral bioavailability (F) will be estimated as the ratio of geometric mean of dose-normalized AUC_{inf} for oral unlabeled and IV labeled PF-07220060 (from Cohort 2 only) as per the following equation:

$$F = [PF\text{-}07220060\_AUC_{po}/[^{14}C]\text{-}PF\text{-}07220060\_AUC_{iv}]*[[^{14}C]\text{-}PF\text{-}07220060\_Dose_{iv}/\ PF\text{-}07220060\_Dose_{po}]$$

3.2.2. Fraction of PF-07220060 Dose Absorbed (F_a)

Fraction of dose absorbed (F_a) will be estimated as the ratio of total radioactivity (dose normalized) excreted into the urine (from time 0 to the time of last measurable concentration) following oral and IV administration of [^{14}C]PF-07220060 microtracer doses in Cohort 1 and 2, respectively:

$$F_a = [\%^{14}C\_Urine\_PO/\%\ ^{14}C\_Urine\_IV]$$

3.2.3. Safety Data

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

- Adverse events (AE)
- Laboratory data
- Vital signs data
- ECG results

3.2.3.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 35 days after the study drug dose will be counted as treatment emergent and attributed to the treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.2.3.2. Laboratory Data

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

The baseline measurement is the predose measurement on Day -1. Changes from baseline will be defined as the change between the postdose and baseline measurements.

3.2.3.3. Vital Signs

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

The baseline measurement is the predose measurement on Day 1. Changes from baseline will be defined as the change between the postdose and baseline measurements.

3.2.3.4. 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) where RR = 60/HR (if not provided)

The baseline value is the predose ECG measurement on Day 1. Changes from baseline will be defined as the change between the postdose and baseline measurements.

3.3. Other Safety Endpoint(s)

None.

3.4. Exploratory Endpoints

3.4.1. Contingent Metabolic Profiling and Metabolic Identification

Plasma, urine and fecal samples collected in Cohort 2 will be analyzed for metabolites of [^{14}C]PF-07220060. Major metabolites of PF-07220060 in plasma, urine and feces may be identified if possible. Contributions of parent and each major metabolite to total radioactivity

recovered in urine and feces and to circulating radioactivity in plasma will be quantified if possible. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

3.4.2. Plasma PK Parameters of PF-07220060

Plasma PK parameters for PF-07220060 will be computed based on LCMS analysis of plasma samples.

The plasma PK parameters will be derived (as data permits) from the concentration-time data using standard noncompartmental methods as outlined in Table 2. Actual PK sampling times will be used in the derivation of PK parameters. 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 PK Parameters Definitions

Parameter	***Definition***	***Method of Determination***
AUC_{last}[a]	*Area under the plasma concentration-time profile from time 0 to time of the last quantifiable concentration (C_{last})*	*Linear/Log trapezoidal rule*
AUC_{last}(dn)	*Dose normalized AUC_{last} in Cohort 2 only*	*AUC_{last}/Dose*
AUC_{inf}[a]	*Area under the plasma concentration-time profile from time 0 extrapolated to infinite time*	*AUC_{last} + (C_{last}*/k_{el}), where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression*
AUC_{inf}(dn)[a]	*Dose normalized area under the plasma concentration-time profile from time 0 extrapolated to infinite time, in Cohort 2 only*	*AUC_{inf}/Dose*
C_{max}	*Maximum plasma concentration*	*Observed directly from data*
C_{max}(dn)	*Dose normalized maximum plasma concentration, in Cohort 2 only*	*C_{max}/Dose*
T_{max}	*Time for C_{max}*	*Observed directly from data as time of first occurrence*
$t_{½}$[a]	*Terminal elimination half-life*	*$Log_e(2)/k_{el}$*
CL[a] (IV)	*CL: systemic clearance*	*Dose/AUC_{inf}*
V_{ss}[a] (IV)	*V_{ss}: Steady state volume of distribution following IV infusion*	*CL × [MRT-(infusion time/2)]* *where MRT is the Mean Residence Time and is calculated as $AUMC_{inf}$/AUC_{inf}* *$AUMC_{inf}$ is the area under the first moment curve from 0 time to infinity.*
CL/F[a] (oral)	*Apparent clearance following oral administration*	*Dose/AUC_{inf}*
Vz/F[a] (oral)	*Apparent volume of distrubution following oral administration*	*Dose /(AUC_{inf}*k_{el})*

Table 2. Plasma PK Parameters Definitions

Parameter	*Definition*	*Method of Determination*
F	*Absolute oral bioavailability*	*[AUCpo/^{14}CAUCiv]*[[^{14}C]-PF-07220060_Doseiv/PF-07220060_Dosepo]* *where,* *AUCpo is PF-07220060 area-under-the-plasma concentration curve following oral administration of unlabeled PF-07220060* *PF-07220060_Dosepo: Oral dose of unlabeled PF-07220060* *^{14}CAUCiv is PF-07220060 area-under-the-plasma concentration curve following IV administration of [^{14}C]PF-07220060* *[^{14}C]-PF-07220060 Doseiv: IV dose of [^{14}C]-PF-07220060* *AUC_{inf} will be used unless data do not allow estimation of AUC_{inf}, in which case, AUC_{last} will be used*

a. If data permits.

3.4.3. Plasma PK Parameters of [^{14}C]PF-07220060

*For **Cohort 2**, following a single IV microtracer dose of [^{14}C]PF-07220060 at 2 hours post oral dose, IV plasma PK parameters of [^{14}C]PF-07220060 will be derived from plasma radioactivity concentration equivalent-time profiles following chromatographic separation of [^{14}C]PF-07220060 (ie. HPLC-AMS analysis).*

Actual administered [^{14}C] doses will be used for the [^{14}C]PF-07220060 PK parameter calculations.

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

3.4.4. Urine PK Parameters of PF-07220060

The following urine PK parameters will be calculated using the outlined methods in Table 3.

Table 3 Urine PK Parameters Definitions

Parameter	***Definition***	***Method of Determination***
Total ^{14}C_Urine_PO	*Total cumulative radioactivity excreted into urine from time 0 to the time of last measurable concentration following oral administration of [^{14}C]PF-07220060 (**Cohort 1** only)*	*Directly from observed [^{14}C] data*
Total ^{14}C_Urine_IV	*Total cumulative radioactivity excreted into urine from time 0 to the time of last measurable concentration following intravenously administered [^{14}C]PF-07220060 microtracer dose (**Cohort 2** only)*	*Directly from observed [^{14}C] data*
% ^{14}C_Urine_PO	*% of radioactivity in the urine following oral administration expressed as a percent of the radioactive dose administered (**Cohort 1** only)*	*(Total ^{14}C_Urine_PO/[^{14}C] Dose$_{po}$) *100 where, [^{14}C] Dose$_{po}$ is orally administered dose of [^{14}C]PF-07220060*
% ^{14}C_Urine_IV	*% of radioactivity in the urine following IV administration expressed as a percent of the radioactive dose administered (**Cohort 2** only)*	*(Total ^{14}C _Urine_IV/[^{14}C] Dose$_{iv}$) *100 where, [^{14}C] Dose$_{iv}$ is [^{14}C] intravenously administered dose of [^{14}C]PF-07220060*
F_a	*Fraction Absorbed*	*[Total ^{14}C_Urine_PO/Total ^{14}C_Urine_IV]*[^{14}Cdoseiv/^{14}Cdosepo]*
Ae (PF-07220060 PO in Cohort 1)	*Amount of unchanged drug excreted in urine*	*Sum of [PF-07220060 urine concentration* sample volume] for each collection interval*
Ae% (PF-07220060 PO in Cohort 1)	*Percent of dose recovered unchanged in urine*	*Ae/Dose*100*
CLr (PF-07220060 PO in Cohort 1)	*Renal clearance (oral)*	*Aet/AUCt where Aet is the amount of unchanged drug excreted in urine from 0 time until time t following oral dose of PF-07220060*

3.4.5. Plasma PK Parameters of Total Radioactivity [^{14}C]

*For **Cohort 1**, following a single oral administration of a microtracer dose of [^{14}C]PF-07220060, oral PK parameters for total [^{14}C] radioactivity will be derived from the concentration equivalent-time profiles, where appropriate.* PK parameters for total radioactivity [^{14}C] will be computed based on AMS analysis.

For **Cohort 2**, following a single oral administration of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060, PK parameters for total [^{14}C] radioactivity will be derived from the concentration equivalent-time profiles, where

appropriate. PK parameters for total radioactivity [^{14}C] will be computed based on AMS analysis.

Actual administered [^{14}C] doses will be used for the total [^{14}C] PK parameter calculations.

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

3.4.6. Allelic Variants of Drug Metabolizing Enzymes and Transporters

A 4-mL blood PGx sample for DNA isolation will be collected into plastic K_2EDTA tubes, as defined in the SoA given in the protocol. The DNA sample will be analyzed for the purpose of assessing the impact of allelic variants of genes encoding drug metabolizing enzymes and transporters including, but not limited to, CYP3A and UGT2B7 on the ADME of the PF-07220060.

3.4.7. Taste Assessment Data

The data collected for taste assessment using the sponsor-provided taste questionnaire will be numerically derived by measuring the length (using a scale with gradation of at least 0.1 centimeter) of the “x” marked by the participant relative to the “good trait.” The data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the Oral Solution or Suspension Palatability Questionnaire.

3.5. Baseline Variables

Baseline characteristics will be collected according to the SoA as specified in the protocol.

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.

For purposes of analysis, the following analysis sets are defined:

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.*
Mass balance analysis set	*In Cohort 1, the mass balance population analysis set will be defined by evaluable participants who have received 1 dose of [^{14}C]PF-07220060 and who have completed total radioactivity concentration (urinary and fecal) data and who had no protocol deviations that may have affected the mass balance analysis.*

Participant Analysis Set	***Description***
	Participants who vomit [redacted] hours post oral dosing will not be excluded from this population. Participants who vomit within [redacted] hours post oral dose may be removed from the analysis at the discretion of the pharmacokineticist if the event occurs soon after dosing or the resulting mass balance data is deemed anomalous for any other reason.
PK Concentration	*The PK concentration population for PF-07220060 is defined as all participants dosed with PF-07220060 (in both Cohort 1 and 2), who have at least one PF-07220060 concentration.* *The PK concentration population for [^{14}C] is defined as all participants dosed with [^{14}C]PF-07220060 (in both Cohort 1 and 2), who have at least one [^{14}C] measurement.* *The PK concentration population for [^{14}C]PF-07220060 is defined as all participants dosed with [^{14}C]PF-07220060 in Cohort 2, who have at least one [^{14}C]PF-07220060 plasma concentration measurement.*
PK Parameter	*The PK parameter population for PF-07220060 is defined as all participants dosed with PF-07220060 (in both Cohort 1 or 2), who have at least one estimated PF-07220060 PK parameter of interest.* *The PK parameter population for total [^{14}C] is defined as all participants dosed with [^{14}C]PF-07220060 (in both Cohort 1 or 2), who have at least one total [^{14}C] PK parameters of interest.* *The PK parameter population for [^{14}C]PF-07220060 is defined as all participants dosed with [^{14}C]PF-07220060 in Cohort 2, who have at least one [^{14}C]PF-07220060 PK parameter of interest.*
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. 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 one 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 as 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 or pharmacokineticist.

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 treatment with ≥3 evaluable measurements. PK parameter 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 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

For the analysis of safety endpoints, the standard rules for imputation according to CaPS will be applied.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Mass Balance

*Individual participant and median data profiles for total radioactivity will be graphically presented for the cumulative recovery of radioactivity in urine, feces and their combination over time in **Cohort 1 only**. Vomitus, if any, will be collected in full during the [redacted] hours after oral dosing in **Cohort 1** and will be required to be prospectively tested for recovered radioactivity. For emesis that occurs after [redacted] hours up to [redacted] hours post dose, samples will be collected in full and stored for potential reflex testing for recovered radioactivity. These participants will not necessarily be excluded from analysis. The total recovery of radioactivity in urine, feces (and vomitus, if any) and their combination will be listed and summarized for **Cohort 1 only**.*

6.1.2. Metabolic Profiling and Metabolite Identification

Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

6.2. Secondary Endpoints

6.2.1. Absolute Oral Bioavailability

Natural log transformed AUC_{inf}(dn) (if data permit) and AUC_{last}(dn) from Cohort 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant variable as a random effect. Estimates of the adjusted (least squares) mean differences (Test/Reference) and the corresponding 90% confidence interval in log-scale 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 mean (Test/Reference) and 90% confidence interval for the ratio. IV [^{14}C]PF-07220060 will be considered the Reference formulation and unlabeled oral PF-07220060 will be considered the Test formulation.

6.2.2. Fraction of PF-07220060 Dose Absorbed (F_a)

The ratio (Test/Reference) of the geometric means of % Total ^{14}C in Urine will be estimated. Total ^{14}C_Urine_IV is the Reference and Total ^{14}C_Urine_PO is the Test.

A distribution-free method (nonparametric method, Hodges-Lehmann point estimate) may be conducted if extreme values are encountered in the PK parameters.

Cumulative urine ^{14}C amounts, percent ^{14}C dose as well as F_a (calculated using urine ^{14}C data, as described above) will be listed by treatment (Oral in Cohort 1 and IV in Cohort 2) and summarized using descriptive statistics. Individual and summary profiles of urine ^{14}C will be graphically presented.

In most circumstances, F_a estimation based on the urine method provides reliable F_a estimates. Total radioactivity following oral and IV administration will be generated from

different people in separate cohorts, where physiological variability may lead to a less robust estimation of F_a. Different F_a calculation methods have been compared in detail and alternative F_a calculation methods for this study may be investigated as needed based on emerging data.

6.2.3. Safety Endpoints

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 by treatment, where appropriate.

6.2.3.1. Adverse Events

Adverse events will be reported in accordance with the CaPS and listed by treatment, where appropriate.

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

6.2.3.2. Laboratory Data

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

6.2.3.3. Vital Signs

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

6.2.3.4. Electrocardiograms

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

6.3. Other Safety Summaries and Analyses Endpoint(s)

None.

6.4. Exploratory Endpoints

PK parameters will be summarized descriptively in accordance with Pfizer data standards for the PK Parameter Analysis Set, as data permit. Missing values will be handled as detailed in Section 5.3.1. Each PK parameter will be summarized and will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{inf}, AUC_{inf}(dn), AUC_{last}, AUC_{last}(dn), C_{max}, C_{max}(dn), CL, CL/F, V_{ss}, V_z/F Ae, Ae%, CLr	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

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte and group: 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 plasma PF-07220060, [^{14}C] and [^{14}C]PF-07220060 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 provided 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 (median concentration-time profiles for plasma PF-07220060, [^{14}C] and [^{14}C]PF-07220060 on the same plot per scale, based on the summary of concentrations by time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose (mean concentration-time profiles for plasma PF-07220060, [^{14}C] and [^{14}C]PF-07220060 on the same plot per scale, based on the summary of concentrations by time postdose).

- Individual concentration time plots (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots per scale for PF-07220060, [^{14}C] and [^{14}C]PF-07220060).

- 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 applicable concentration-time profiles) per scale].

6.4.1. Contingent Metabolic Profiling and Metabolic Identification

Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

6.4.2. Plasma PK Parameters of PF-07220060

Plasma PK parameters of PF-07220060, as appropriate, will be summarized descriptively in accordance with Pfizer data standards for the PK Parameter Analysis Set, as data permit. Each PF-07220060 PK parameter will be summarized by treatment and will include the set of summary statistics as specified in Table 4.

6.4.3. Plasma PK Parameters of [^{14}C]PF-07220060

Plasma PK parameters of [^{14}C]PF-07220060 for Cohort 2, as appropriate, will be summarized descriptively in accordance with Pfizer data standards for the PK Parameter Analysis Set, as data permit. Each [^{14}C]PF-07220060 PK parameter will be summarized and will include the set of summary statistics as specified in Table 4.

6.4.4. Urine PK Parameters of PF-07220060

Urine PK parameters (including Ae, Ae% and CLr in Cohort 1), will be summarized descriptively in accordance with Pfizer data standards for the PK Parameter Analysis Set, as data permit. Each urine PK parameter will be summarized and will include the set of summary statistics as specified in Table 4.

6.4.5. Plasma PK Parameters of Total Radioactivity [^{14}C]

Plasma PK parameters of total [^{14}C] radioactivity, as appropriate, will be summarized descriptively in accordance with Pfizer data standards for the PK Parameter Analysis Set, as data permit. Each total [^{14}C] radioactivity PK parameter will be summarized by treatment and will include the set of summary statistics as specified in Table 4.

6.4.6. Allelic Variants of Drug Metabolizing Enzymes and Transporters

Allelic variants of drug metabolizing enzymes and transporters will be summarized descriptively.

6.4.7. Taste Assessment Data

The sensory attributes (bitterness, tongue/mouth burn, throat burn) from the Oral Solution or Suspension Palatability Questionnaire will be listed and descriptively summarized by treatment, 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 (1, 5, 10 and 20 minutes after dosing), summarizing all attributes for each treatment will be generated. Boxplots of each attribute will be plotted against the time points.

6.5. Subset Analyses

There are no planned subset analyses.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Demographic Summaries

Demographic characteristics will be summarized for enrolled population in accordance with the CaPS.

6.6.2. 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.

6.6.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.6.4. Concomitant Medications and Nondrug Treatments

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

7. INTERIM ANALYSES

No interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development.

APPENDICES

Appendix 1. Summary of Analyses

Endpoint	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Method
Mass balance	Mass Balance Analysis Set	Observed data	Descriptive statistics
Metabolite identification/profiling	PK Concentration Analysis Set	Observed data	Descriptive statistics
Absolute oral bioavailability	PK Parameter Analysis Set	Observed and imputed (Section 5.3.1) data	Mixed effect model
Fraction of dose absorbed	PK Parameter Analysis Set	Observed and imputed (Section 5.3.1) data	Mixed effect model or Hodges-Lehmann point estimate
Safety data	Safety Analysis Set	Observed and imputed (Section 5.3.2) data	Descriptive statistics
PK parameters	PK Parameter Analysis Set	Observed and imputed (Section 5.3.1) data	Descriptive statistics
PK concentrations	PK Concentration Analysis Set	Observed and imputed (Section 5.3.1) data	Descriptive statistics
Taste assessment data	Safety Analysis Set, have at least 1 taste assessment performed	Observed data	Descriptive statistics

Appendix 2. SAS Code for Analyses

An example of PROC MIXED code is provided below.

For absolute oral bioavailability:

```
proc mixed data=tab.pk;
        class trt participant;
        model log&var=trt / ddfm=KR;
        random participant / subject=participant;
        lsmeans trt;
        estimate 'B vs A' 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: IV [14C]PF-07220060 (reference)
B: oral unlabeled PF-07220060 (test)
*/
```

For fraction of dose absorbed:

```
proc mixed data=tab.pk;
        class trt participant;
        model log&var=trt / ddfm=KR;
        random participant / subject=participant;
        lsmeans trt;
        estimate 'B vs A' 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: IV [14C]PF-07220060 (reference)
B: PO [14C]PF-07220060 (test)
*/
```

Appendix 3. List of Abbreviations

Abbreviation	Term
% ^{14}C_Urine_PO	% of radioactivity in the urine following oral administration expressed as a percent of the radioactive dose administered
% ^{14}C_Urine_IV	% of radioactivity in the urine following IV administration expressed as a percent of the radioactive dose administered
%CV	coefficient of variation
ADME	Absorption, Distribution, Metabolism and Excretion
AE	adverse event
Ae	total amount of excreted in the urine
Ae(%)	total amount of excreted in the urine expressed as percent of dose
AMS	accelerator mass spectrometry
AUC_{extrap}%	the percent of AUC_{inf} based on extrapolation
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{last}(dn)	dose normalized AUC_{last}
$AUMC_{inf}$	area under the first moment curve from 0 time to infinity
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CDK	cyclin-dependent kinase
CI	confidence interval
CL	systemic clearance
CL/F	apparent clearance
C_{last}	predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis
CLr	renal clearance
C_{max}	maximum plasma concentration
C_{max}(dn)	dose normalized C_{max}
CRF	case report form
CSR	clinical study report
DNA	deoxyribonucleic acid
ECG	electrocardiogram
F	absolute oral bioavailability
F_a	fraction of dose absorbed
HPLC	high performance liquid chromatography
HR	heart rate
IV	intravenous(ly)
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
k_{el}	elimination rate constant estimated from the log-linear regression analysis
LCMS	liquid chromatography mass spectrometry
LLQ	lower limit of quantitation
MRT	Mean Residence Time
ms	milliseconds
N/A	not applicable
NC	not calculated
NCA	non-compartmental analysis
ND	not done
NS	no sample

Abbreviation	Term
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PO	oral(ly)
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	goodness of fit statistic from the log-linear regression
RR	the time between the start of one QRS complex and the start of the next QRS complex
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{1/2}$	terminal plasma elimination half-life
TEAE	treatment emergent adverse event
T_{max}	time for C_{max}
Total ^{14}C_Urine_PO	total cumulative radioactivity excreted into urine from time 0 to the time of last measurable concentration following oral administration
Total ^{14}C_Urine_IV	total cumulative radioactivity excreted into urine from time 0 to the time of last measurable concentration following IV administration
V_{ss}	steady state volume of distribution following IV infusion
V_z/F	apparent volume of distribution after oral dose