Protocol C3991006

A PHASE 1, OPEN-LABEL, 2-PERIOD, FIXED SEQUENCE STUDY TO INVESTIGATE THE ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF [^{14}C]PF-07081532 AND TO ASSESS THE ABSOLUTE BIOAVAILABILITY AND FRACTION ABSORBED OF PF-07081532 IN HEALTHY MALE PARTICIPANTS USING A [^{14}C]-MICROTRACER APPROACH

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 11 Jan 2023

.

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 11 Jan 2023	Original 30 Sep 2022	N/A	N/A

2. INTRODUCTION

The purpose of the study is to assess the metabolism and extent of excretion of [^{14}C]PF-07081532 in urine and feces, following oral administration, in the fed state, in healthy male participants. This information will enable assessment of clearance mechanisms of PF-07081532 as well as identify disproportionate metabolites that should be qualified to adhere to the ICH M3 (R2) MIST guidance. In addition, this study will characterize the fraction of dose absorbed and the bioavailability of orally administered PF-07081532 in the fed state, in reference to an IV dose of [^{14}C]PF-07081532, while it will also assess PK parameters following both oral and IV administration of [^{14}C]PF-07081532.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991006.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not Applicable

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoints
Primary		
PK **Section 6.1.1**	• *To characterize the extent of excretion of total radioactivity in urine, feces, and emesis (if any) following administration of a single oral dose of [^{14}C]PF-07081532.*	• *Total recovery of radioactivity in urine, feces, and emesis (if any), and both routes combined, expressed as a percent of total oral radioactive dose administered.*
PK **Section 6.1.2**	• *To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-07081532.*	• *Metabolic profiling/identification and determination of relative abundance of [^{14}C]PF-07081532 and the metabolites of [^{14}C]PF-07081532 in plasma, urine, and feces.*
Secondary		
PK **Section 6.2.1**	• *To quantify plasma PK parameters of PF-07081532 and total radioactivity following administration of a single oral dose of [^{14}C]PF-07081532.*	• *AUC_{last}, C_{max}, T_{max}, and if data permit, AUC_{inf}, $t_{½}$, CL/F (PF-07081532 only), and Vz/F (PF-07081532 only), to describe single oral dose PK in Period 1 of:* • *Total radioactivity in plasma;* • *PF-07081532 in plasma.*
PK **Section 6.2.1**	• *To quantify plasma PK parameters of [^{14}C]PF-07081532, following administration of a single, IV, microdose of [^{14}C]PF-07081532.*	• *[^{14}C]PF-07081532 parameters to describe IV plasma PK: AUC_{last}, AUC_{last}(dn), C_{max}, C_{max}(dn), T_{max}, and if data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL, V_{ss} and MRT.*

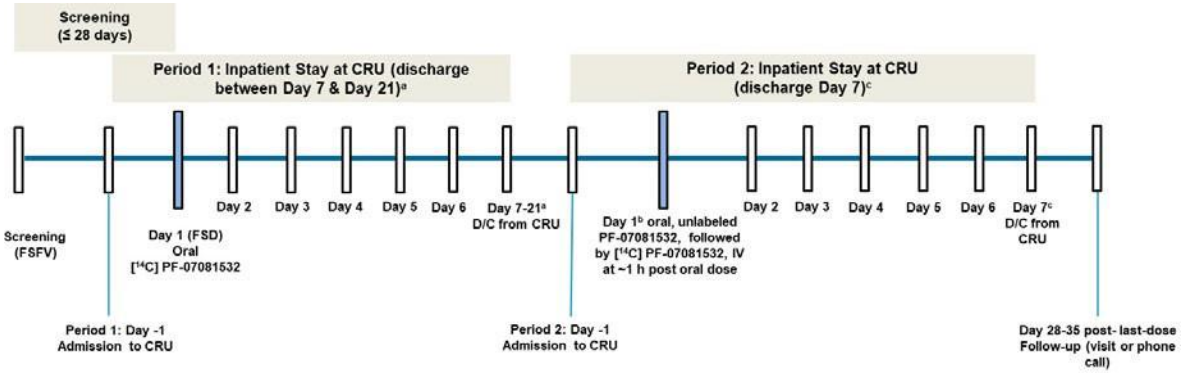
PK **Section 6.2.2**	• *To determine the absolute oral bioavailability (F) of PF-07081532 following administration of a single oral dose of PF-07081532 compared to a single IV microdose of [^{14}C]PF-07081532.*	• *F computed from plasma AUC_{inf} (if data permit, otherwise AUC_{last}) of oral unlabeled PF-07081532 in Period 2 and IV microdose of [^{14}C]PF-07081532 in Period 2.*
PK **Section 6.2.3**	• *To determine the fraction of dose absorbed (F_a) following administration of a single oral dose of [^{14}C]PF-07081532.*	• *F_a calculated from ratio of total urinary radioactivity following oral administration of [^{14}C]PF-07081532 in Period 1 and IV administration of [^{14}C]PF-07081532 in Period 2.*
Safety **Section 6.6**	• *To evaluate safety and tolerability of PF-07081532, administered as a single oral dose of [^{14}C]PF-07081532 or a single oral dose of PF-07081532 followed by administration of a single IV microdose of [^{14}C]PF-07081532.*	• *Safety endpoints including physical examinations, adverse events, clinical laboratory measurements, vital signs, and ECG.*
Tertiary/Exploratory: :		
PK **Section 6.3.1**	• *To characterize cumulative rate of excretion of total radioactivity in urine and feces over time following administration of a single oral dose of [^{14}C]PF-07081532.*	• *Cumulative recovery of radioactivity in urine and feces, and both routes combined over time as a percentage of total radioactive dose administered.*
PK **Section 6.3.2**	• *To quantify plasma PK parameters of PF-07081532, following administration of a single oral dose of (unlabeled) PF-07081532.*	• *Parameters to describe oral plasma PK following oral administration of PF-07081532 in Period 2: C_{max}, C_{max}(dn), T_{max}, AUC_{last}, AUC_{last}(dn), and if data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL/F and V_z/F.*
Other **Section 6.3.3**	CCI [redacted]	
Other **Section 6.3.4**		

There are no estimands for this study.

2.3. Study Design

C3991006 is a Phase 1, open-label, 2-period, fixed sequence study to characterize the metabolic profile and routes of excretion of oral [^{14}C]PF-07081532 and to evaluate the absolute oral bioavailability (F) and fraction absorbed (F_a) of PF-07081532 in healthy male participants.

Participants will be screened for enrollment in this study within 28 days of dosing on Day 1 of ***Period 1****, to confirm that they meet the inclusion/exclusion criteria specified in Section 5* of the protocol. *The expected duration of participation from screening to follow-up will be approximately 8 weeks (minimum) to approximately 12 weeks (maximum). The overall study design is summarized* in the schema below.



a. *See Section 4.1* of the protocol *for details on Period 1 discharge criteria.*
b. ***At least 21 days*** *of washout is required between dosing in Period 1 and Period 2.*
c. *In Period 2, participants will be discharged from the CRU on Day 7.*

Regimen in Period 1: *An oral dose of 30 mg PF-07081532 containing approximately 250 nCi [^{14}C] (ie, radiolabeled PF-07081532, [^{14}C]PF-07081532) will be administered within approximately 10 minutes of completion of a standard breakfast.*

Regimen in Period 2: *An oral dose of 30 mg unlabeled PF-07081532 will be administered followed at approximate T_{max} by an IV dose of 250 nCi [^{14}C] in 100 µg of PF-07081532 (ie, [^{14}C]PF-07081532). The [^{14}C]PF-07081532 IV dose will be administered as an infusion over approximately 15 minutes, starting at approximately 1 hour (T_{max}) after the administration of the oral unlabeled PF-07081532 dose. Oral unlabeled PF-07081532 will be administered within approximately 10 minutes of completion of a standard breakfast.*

In Period 1, a sufficient number of participants will be admitted on Day -1 to the CRU to ensure that 6 participants are dosed on Day 1. Any participants who are prematurely withdrawn (or offer non-evaluable or partially evaluable data) will be replaced to ensure 6 evaluable participants completing Period 1. In Period 2, participants who are prematurely withdrawn may be replaced at the discretion of sponsor.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Urine, feces and vomitus samples will be collected according to the Schedule of Activities given in the protocol and will be analyzed for total radioactivity.

3.1.1. Extent of Excretion (Period 1 Only)

Urine, feces and vomitus samples will be collected according to the Schedule of Activities given in the protocol and will be analyzed for total radioactivity.

Extent of Excretion will be determined by recovery of total radioactivity excreted in urine and feces (and emesis, if applicable). Total recovery of radioactivity in urine and feces, and both routes combined, will be calculated as a percent of total oral radioactive dose administered. The percentage of the administered radioactivity excreted at each time interval and the total percent of dose excreted in urine and feces will be reported whenever possible.

Note: the extent of Excretion analysis is summarized in this SAP for completeness only. Methods and results related to extent of Excretion will be detailed in a separate report and will be summarized within the Clinical Study Report (CSR).

3.1.2. Metabolite Endpoints

Plasma, urine and fecal samples collected in Period 1 will be analyzed for metabolites of PF-07081532. Major metabolites of PF-07081532 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.

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

Note: Methods and results related to analysis of metabolites will similarly be detailed in a separate report provided by TNO.

3.2. Secondary Endpoint(s)

3.2.1. Plasma Pharmacokinetic Parameters

Plasma samples for PK analysis will be collected according to the Schedule of Activities given in the protocol.

- *For **Period 1**, following a single oral administration of [^{14}C]PF-07081532, oral PK parameters for total [^{14}C] radioactivity will be derived from the concentration equivalent-time profiles, where appropriate. Additionally, PK parameters for PF-07081532 will be derived from the concentration-time profiles based on LC/MS/MS analysis of plasma samples.*

- *For **Period 2**, following a single oral dose of unlabeled PF-07081532, PK parameters for PF-07081532 will be derived from the concentration-time profiles based on LC/MS/MS analysis of plasma samples (note that this reflects a tertiary endpoint and as such is also listed under Section 3.3).*

- *For **Period 2**, following a single IV microdose dose of [^{14}C]PF-07081532 at 1 hour post oral dose, IV plasma PK parameters of [^{14}C]PF-07081532 will be derived from plasma radioactivity concentration-time profiles following chromatographic separation of [^{14}C]PF-07081532.*

The following plasma PK parameters will be dete1mined using standard non-compartmental methods:

Table 2. Summary of plasma PK Parameters to be calculated

Parameter	Analysis Scale	After ornl dose of [^{14}C]PF-07081532 (Period 1)		After IV dose of [^{14}C]PF-07081532 (Period 2)	After oral dose of PF-07081532 (Period 2)
		Total Radioactivity	PF-07081532	[^{14}C]PF-07081532	PF-07081532
AUC1as1	ln	D	D	D	D
AUC1as1 (dn)	ln	NC	NC	D	D
AUCinf*	ln	D	D	D	D
AUCinf*(dn)	ln	NC	NC	D	D
Cmax	ln	D	D	D	D
Cma,ldn)	ln	NC	NC	D	D
Tmax	R	D	D	D	D
t112*	R	D	D	D	D
CL*	ln	NC	NC	D	NC
V..*	ln	NC	NC	D	NC
MRT*	ln	NC	NC	D	NC
CL/F*	ln	NC	D	NC	D
Vz/F*	ln	NC	D	NC	D

*=if data permits. Abbreviations: D=displayed with descriptive statistics as outlined in Table 3 in Section 6.2.1; dn=dose nonnalized; ln=natural-log transfo1med; NC= not calculated; R=raw (untransfo1med);

Actual PK sampling times will be used in the derivation of PK parameters, defined relative to the time of the oral dose for the parameters referring to oral dosing and relative to the sta1t of the 15-minute IV infusion for the pai·ameters referring to IV dosing. Actual administered [^{14}C] doses will be used for the total [^{14}C] radioactivity and [^{14}C]PF-07081532 PK parameter calculations.

Plasma PK pai·ameters above will be listed and summai-ized descriptively as appropriate, by analyte (total [^{14}C], unlabeled PF-07081532, and [^{14}C]PF-07081532) and route of administration (oral or IV), as specified in Section 5.2

Absolute bioavailability (F) will additionally be calculated as the ratio of adjusted geometric means of dose-no1malized AUCinf (if data pe1mit, othe1wise AUC1ast(dn)) following oral, unlabeled, PF-07081532 and intravenous, [^{14}C]PF-07081532 which is equivalent to the following equation:

F = [PF-07081532_AUCpJPF-07081532_AUC;v]*[PF-07081532_Dose;v/PF-07081532_Dosepo]

3.2.2. Urine Pharmacokinetic Parameter

The following urine parameters will be calculated following single dose administration of a microtracer do se of [^{14}C}PF-07081532 (oral and IV administration), as data permit.

Residual [^{14}C] levels from Period 1 will be accounted for using an appropriate method, based on AMS principles and methodology.

Parameter	***Definition***	***Method of Determination***
Total [^{14}C]_Urine_PO	*Total cumulative radioactivity excreted into urine from time zero up to the time of last measurable concentration following oral administration of [^{14}C]PF-07081532 (**Period 1** only)*	*Directly from observed [^{14}C] data, calculated as sum of [^{14}C urine concentration × sample volume] for each collection interval*
*Total [^{14}C]_Urine_PO_Trunc**	*Total cumulative radioactivity excreted into urine from time zero up to Day 7 (matching duration of Period 2 urine collection up to discharge) following oral administration of [^{14}C]PF-07081532 (**Period 1** only)*	*Directly from observed [^{14}C] data, calculated as sum of [^{14}C urine concentration × sample volume] for each collection interval*
Total [^{14}C]_Urine_IV	*Total cumulative radioactivity excreted into urine from time zero up to the time of last measurable concentration following IV administered [^{14}C]PF-07081532 microdose (**Period 2** only)*	*Directly from observed [^{14}C] data, calculated as sum of [^{14}C urine concentration × sample volume] for each collection interval*
% [^{14}C]_Urine_PO	*% of radioactivity in the urine following oral administration, expressed as a percent of the radioactive dose administered (**Period 1** only)*	*(Total [^{14}C]_Urine_PO/[^{14}C] Dose$_{po}$) *100 where, [^{14}C] Dose$_{po}$ is orally administered actual dose of [^{14}C]PF-07081532*
*% [^{14}C]_Urine_PO_Trunc**	*% of radioactivity in the urine up to Day 7 (matching duration of Period 2 urine collection up to discharge) following oral administration, expressed as a percent of the radioactive dose administered (**Period 1** only)*	*(Total [^{14}C]_Urine_PO_Trunc/[^{14}C] Dose$_{po}$) *100 where, [^{14}C] Dose$_{po}$ is orally administered actual dose of [^{14}C]PF-07081532*
% [^{14}C]_Urine_IV	*% of radioactivity in the urine following IV administration expressed as a percent of the radioactive dose administered (**Period 2** only)*	*(Total ^{14}C _Urine_IV/[^{14}C] Dose$_{iv}$) *100 where, [^{14}C] Dose$_{iv}$ is [^{14}C] IV administered actual dose of [^{14}C]PF-07081532*

**_Trunc parameters may not be calculated and reported if not applicable (ie, no participant is discharged after Day 7 in Period 1).*

*F_a will be estimated as the ratio of adjusted geometric means of the % of administered radioactive dose excreted into urine following oral and IV administration of [^{14}C]PF-07081532 in **Periods 1 and 2**, respectively.*

Urine radioactivity up to Day 7 will be used for Period 1 to match the duration of Period 2 urine collection up to discharge:

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

For IV administration of [^{14}C]PF-07081532, the weight of dose administered and solution density, in conjunction with the dosing solution concentration data will be used to determine the exact dose administered, where formulas will be included in the analysis and reporting plans. This actual dose will be used for PK parameter calculations.

For oral administration of [^{14}C]PF-07081532, the weight of drug powders added to each individual dosing container will be used along with specific activity and chiral potency of the drug powder to determine exact dose administered, where formulas will be included in the analysis and reporting plans. This actual dose will be used for PK parameter calculations.

3.3. Other Endpoint(s)

3.3.1. Cumulative Rate of Excretion (Period 1)

See Section 3.1.1.

3.3.2. Pharmacokinetics Parameters (Oral Unlabeled PF-07081532 - Period 2)

See Section 3.2.1.

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[redacted]

3.4. Baseline Variables

Not applicable.

3.5. Safety Endpoints

Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.

An adverse event is considered treatment emergent (TEAE) relative to a given treatment if:

[redacted]

- the event starts during the effective duration of treatment (i.e. starting on or after the dose of PF-07081532 but before this dose plus lag time)

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time is attributed to the corresponding treatment. The lag time is defined by the Pfizer Standard of 365 days post last dose of IP.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the most recent treatment taken.

A 3-tier approach for summarizing AEs will not be used due to the low number of participants planned to be recruited.

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

- adverse events,
- laboratory data,
- vital signs data,
- ECG results.

For laboratory, vital signs and ECG data, the baseline measurement is the **planned** last pre-dose measurement taken on Day -1 or Day 1 (as applicable) in 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 unblinding and 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	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to and dosing with 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.*

Participant Analysis Set	Description
Safety analysis set	*All participants assigned to study intervention and who take at least 1 dose of study intervention.*
Extent of excretion analysis set	*In Period 1, extent of excretion population will be defined by evaluable participants who have received 1 dose of [^{14}C]PF-07081532 and who have complete total radioactivity concentration (urinary and fecal) data and who had no protocol deviations that may have affected the extent of excretion analysis.*
PK concentration set	*The PK concentration population for PF-07081532 is defined as all participants dosed with PF-07081532 or [^{14}C]PF-07081532, who have at least one PF-07081532 concentration.* *The PK concentration population for [^{14}C]PF-07081532 is defined as all participants dosed with [^{14}C]PF-07081532, who have at least one [^{14}C]PF-07081532 measurement.* *The PK concentration population for total [^{14}C] is defined as all participants dosed with [^{14}C]PF-07081532, who have at least one total [^{14}C] measurement.*
PK parameter set	*The PK parameter analysis population for PF-07081532 is defined as all participants dosed with PF-07081532 or [^{14}C]PF-07081532 who have at least one of the PF-07081532 PK parameters of interest.* *The PK parameter analysis population for [^{14}C]PF-07081532 is defined as all participants dosed with [^{14}C]PF-07081532 who have at least one of the [^{14}C]PF-07081532 PK parameters of interest.* *The PK parameter analysis population for total [^{14}C] is defined as all participants dosed with [^{14}C]PF-07081532 who have at least one of the total [^{14}C] PK parameters of interest.*
Urine PK parameter analysis population	The urine PK parameter analysis population for total radioactivity excreted into urine is defined as all participants dosed who have at least one of the urine [^{14}C] parameters of interest.
CCI [redacted]	

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

For all safety outputs produced, the following treatment labels (or similar) will be used:

- [^{14}C]PF-07081532 30 mg oral
- Unlabeled PF-07081532 30 mg oral & [^{14}C]PF-07081532 100 µg IV

For all PK outputs produced, the following analyte labels (or similar) related to the above treatments will be used:

- Related to "[^{14}C]PF-07081532 30 mg oral" treatment from Period 1:
  - PF-07081532 (Period 1)
  - Total (^{14}C) (Period 1)

- Related to "Unlabeled PF-07081532 30 mg oral & [^{14}C]PF-07081532 100 µg IV" treatment from Period 2:
  - PF-07081532 (Period 2)
  - [^{14}C]PF-07081532 (Period 2)

5.2.1. Analyses for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.2.3. Mixed Model for Continuous Endpoints

A *mixed effect model with* treatment *as a fixed effect and participant as a random effect* will be used*. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% confidence interval 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 interval for the ratio*.

The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and the Kenward-Roger degrees of freedom algorithm.
Example code is shown in Appendix 1.

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers (where studentized residuals are greater than 3 or less than -3) then the effect of these on the conclusions may 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 if applicable.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

In all PK 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.

In PK 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 (i.e. not done) or NS (i.e. 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.

Participants who experience events that may affect their PK profile (e.g. lack of compliance with dosing or vomiting) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.3.1. Plasma Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of plasma PK parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e. 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 group/analyte with ≥3 evaluable measurements.

Note: If N <3 evaluable measureemnts, only mean, median and range will be provided in summary statistics.

For statistical analyses (i.e. mixed effect model), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual participant has a known biased estimate of a plasma PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Extent of Excretion (Period 1 Only)

Radioactivity excreted in urine and/or feces will be reported as the percentage of the administered radioactivity excreted at each time interval, cumulatively through that interval and the total percent of dose recovered in urine, feces, and/or emesis (if any).

Percent recovery and cumulative recovery of total radioactivity in urine, feces and emesis (if any) will be determined based on total administered dose.

***Note:** While the total percentage of dose excreted is the primary endpoint, the percentage of the administered radioactivity excreted at each time interval and cumulatively through that interval are tertiary endpoints.*

*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 in **Period 1 only**. Emesis, if any, will be collected during 24 hours post oral dose, but these participants will not necessarily be excluded from analysis. The total recovery of radioactivity in urine, feces (and emesis, if any) and their combination will be listed and summarized for **Period 1 only**.*

Primary results of the extent of excretion (i.e., radioactivity in urine, feces, and vomitus if observed) will be detailed in a separate report provided by ICON and will be summarized within the CSR.

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 Endpoint(s)

6.2.1. Plasma PK parameters of PF-07081532 and total radioactivity in Period 1 and [^{14}C]PF-07081532 in Period 2

Plasma PK parameters of PF-07081532 (Period 1), total radioactivity (Period 1) and [^{14}C]PF-07081532(Period 2), as described in Section 3.2.1, will be listed and summarized descriptively by analyte, route of administration (IV vs. Oral) and treatment for participants in the PK analysis set (as defined in Section 4) using nominal sampling times. Missing values will be handled as detailed in Section 5.3

The relevant plasma PK parameters for each analyte, route of administration and treatment (see Section 3) will be summarized as specified in the table below:

Table 3. Summary statistics to be produced for Plasma PK Parameters

Parameter	Summary Statistics
AUC1ast, AUCinf, AUC1ast(dn), AUCini(dn), Cmax, Cmax(dn), MRT, CL/F (oral), Vz/F (oral), CL (IV) and Vss(IV)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometi·ic mean and geometi·ic cv%.
Tmax	N, median, minimum, maximum.
t112	N, arithmetic mean, median, cv%, standard deviation, mm1mum, maxnnum.

Box and whisker plots for individual participant parameters (AUCinf(dn), AUClast(dn), and Cmax(dn) be presented and overlaid with geomeu-ic means.

Suppo1ting data from the estimation oft½ and AUCinfwill be listed by analyte: tenninal phase rate constant (ke1); goodness of fit statistic from the log-linear regression (i2); the percent of AUCinf based on extrapolation (AUCextrap%); and the first, last, and number oftime points used in the estimation ofke1. These data may be included in the clinical study repo1t.

The following summaries will additionally be presented for the plasma concenti·ation data of the analytes using the PK Concenti·ation Set (as defined in Section 4):

- a listing of all concenti·ations s01ted by paiticipant ID and nominal time post-dose for each analyte, route of adminisu-ation and ti·eatment, separately. The concenti·ation listing will also include the actual times. Deviations from the nominal time will be given in a sepai·ate listing.
- a summaiy of concenu-ations by each nominal time post-dose (produced sepai·ately for each analyte), where the set of statistics will include n, mean, median, standard deviation, coefficient of vai·iation (cv), minimum, maximum and the number of concenu-ations above the lower limit of quantification.
- median concentration time plots (on both lineai·and semi-log scales) against nominal time post-dose by analyte for PF-07081532 (Period 1) and total radioactivity (Period 1) only. The concenu-ation time plots for these analytes will be presented together on the same plot.
- median concentration time plots (on both lineai·and semi-log scales) against nominal time post-dose by analyte and route of adminisu-ation for PF-07081532 (Period 2) and [^{14}C]PF-07081532 (Period 2) only, where both have been dose-no1malized (by oral and IV dose, respectively). The dose-no1malization will be calculated by prograinming using raw concenti·ations and the actual doses administered. The concenu-ation time plots for these analytes will be presented together on the same plot.
- individual concentration time plots by analyte (on both lineai·and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each analyte per scale).

individual concenti·ation time plots by paiticipant (on both lineai·and semi-log scales) against a -07081532

[redacted]

ctual time post-dose. Concenti·ation time plots for analytes PF

(Period 1) and total radioactivity (Period 1) will be presented together on the same plot. In a separate figure, the analytes PF-07081532 (Period 2) and [^{14}C]PF-07081532 (Period 2), where both have been dose-normalized (by programming using raw concentrations and the actual doses administered), will be presented together on the same plot.

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

6.2.2. Absolute Bioavailability

All listings and analyses of absolute bioavailability will use the PK Parameter population (as defined in Section 4).

*Natural log transformed AUC_{inf}(dn) (if data permit, otherwise AUC_{last}(dn)) from **Period 2** will be analyzed using a mixed effect model* (as defined in Section 5.2.3) *with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% confidence interval 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 interval for the ratio where IV [^{14}C]PF-07081532 is the reference formulation and unlabeled oral PF-07081532 is the test formulation.*

Individual oral bioavailability (F) values (as defined in Section 3.2.1) will also be listed.

A box plot of the individual AUC_{inf}(dn) (if data permit, otherwise AUC_{last}(dn)) values used to calculate such bioavailability from Period 2 only will be produced with a separate box and whiskers for each analyte and treatment (IV vs PO), which will include the geometric means for each analyte overlaid.

The above will be conducted for AUC_{last}(dn) regardless, but will only be formally reported if AUC_{inf}(dn) data do not permit sufficient estimation of F.

6.2.3. Fraction Absorbed

All listings and analyses of absolute bioavailability will use the PK Parameter population (as defined in Section 4).

Total radioactivity excreted in urine as absolute values (Total ^{14}C_Urine_PO and Total ^{14}C_Urine_IV) and expressed as percent of [^{14}C] dose (% ^{14}C_Urine_PO and % ^{14}C_Urine_IV) as defined in Section 3.2.2 will be listed and summarized descriptively by period. Summaries will include: N; arithmetic mean; median; cv%; standard deviation; minimum; maximum; geometric mean; and geometric cv%.

Natural log transformed % [^{14}C]_Urine_PO_Trunc (if data permit) from Period 1 and % [^{14}C]_Urine_IV (if data permit) from Period 2 will be analyzed using a mixed effect

model (as defined in Section 5.2.3) *with* treatment *as a fixed effect and participant as a random effect.*

Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% confidence interval 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 interval for the ratio where IV [^{14}C]PF-07081532 is the reference formulation and oral [^{14}C]PF-07081532 is the test formulation.

The individual mean fraction absorbed (Fa) values (as defined in Section 3.2.2) will also be listed.

A box plot of the individual values of % ^{14}C_Urine_PO_Trunc and % ^{14}C_Urine_IV in Periods 1 and 2, respectively, will be produced with a separate box and whiskers for each period, which will include the geometric means for each period overlaid.

Absolute radioactivity concentration levels excreted in urine at each time interval for both periods will also be listed only.

6.3. Other Endpoint(s)

6.3.1. Cumulative recovery of radioactivity excreted in Urine, Feces and Combined

Cumulative recovery of radioactivity excreted in urine, feces and both routes combined, expressed as a percentage of the administered dose of [14C]PF-07081532 up to and including each time interval, will be listed, summarized, plotted and detailed in a separate report provided by ICON and will be summarized within the CSR as part of the extent of Excretion analysis.

6.3.2. Plasma PK parameters of PF-07081532 in Period 2

Plasma PK parameters of PF-07081532 in Period 2 as described in Section 3.2.1 will be listed and summarized descriptively (as outlined in Table 3 in Section 6.2.1) for participants in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

A similar set of outputs as provided in Section 6.2.1 will be produced for the individual plasma concentration data of PF-07081532 in Period 2 PK Concentration Set (as defined in Section 4).

CCI [redacted]

CCI

[redacted]

6.3.5. Banked Biospecimens

Banked biospecimens will be collected and retained for future analyses, but will not be analyzed specifically for this study and will not be included in the CSR.

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

Data will be reported in accordance with the sponsor reporting standards.

6.5.1. Baseline Summaries

Demographics data (age, gender, race, ethnicity, weight, body mass index and height) will be summarized as outlined in Section 5.2.1 and Section 5.2.2 as applicable for all participants.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition by treatment and will show which participants were analyzed for pharmacokinetics (plasma and urine, separately), taste assessment and for safety, which may not be produced in one table. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment.

6.5.3. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be provided in listings.

6.6. Safety Summaries and Analyses

Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described.

No formal analyses are planned for safety data.

The safety endpoints detailed in Section 3.5 will be listed and summarized in accordance with sponsor reporting standards based on the safety population (as defined in Section 4), with more details provided below.

6.6.1. Adverse Events

Adverse events will be summarized by treatment and overall in accordance with sponsor reporting standards.

If applicable, subject discontinuations due to adverse events will be detailed and summarized.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment and overall in accordance with sponsor reporting standards. Baseline is as defined in Section 3.5.

6.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment in accordance with sponsor reporting standards.

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 2. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time-points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.6.4. Electrocardiograms (ECG)

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by treatment in accordance with sponsor reporting standards.

Maximum absolute values and changes from baseline for QTcF interval, PR interval and QRS interval will also be summarized descriptively by treatment using categories as defined by Appendix 2. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time-points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

In addition, listings of participants with any single post-dose value >500 msec will also be produced for QTcF.

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

Not applicable.

9. APPENDICES

Appendix 1. Example SAS Code for Mixed Model

An example of the PROC MIXED code:

```
proc mixed data=tab.pk;
        class treatment subject;
        model &var = treatment / ddfm=KR;
        random subject /subject=subject;
        lsmeans treatment/ diff cl alpha=0.1;
run;
```

Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed in the report.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
AMS	accelarated Mass Spectrometry
AUC	area under the curve
AUCinf	area under the concentration-time curve from time zero extrapolated to infinity
AUClast	area under the concentration-time curve from time zero to the last measurable concentration
BLQ	below the limit of quantitation
BP	blood pressure
C_{max}	maximum observed concentration
CL	clearance
CL/F	oral clearance
CRF	case report form
CSR	clinical study report
CRU	clinical research unit
CV	coefficient of variation
dn	dose normalized
ECG	electrocardiogram
F	oral bioavailability
Fa	fraction absorbed
LLQ	lower limit of quantitation
ICH M3 (R2) MIST	international confernec on harmonization M3 revision 2 for metabolites in safety testing
IP	investigational product
IV	intravenous
LS/MS/MS	liquid chromatography with tandem mass spectrometry
MRT	mean residence time
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PO	oral route
QTcF	corrected QT (Fridericia method)
REML	restricted maximum likelihood
SAP	statistical analysis plan
SD	standard deviation
T_{max}	time of maximum concentration
$t_{½}$	half-life
Vss	steady state volume of distribution
Vz/F	apparent volume of distribution during terminal phase