Protocol *C4411010*

A PHASE 1, OPEN-LABEL, SINGLE-PERIOD, NON-RANDOMIZED STUDY TO EVALUATE THE PHARMACOKINETICS, EXCRETION, MASS BALANCE AND METABOLISM OF [^{14}C]PF-07265803 ADMINISTERED ORALLY TO HEALTHY ADULT MALE PARTICIPANTS

Statistical Analysis Plan (SAP)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	February 18, 2022	PPD	Not Applicable

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

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None.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-07265803 (formerly known as known as ARRY-371797) is a potent and selective, oral small molecule inhibitor of the α isoform of p38 MAPK. Mutations in the LMNA gene encoding nuclear lamina components cause nuclear envelope dysfunction leading to altered nuclear activity, impaired structural dynamics and aberrant cell signaling including activation of p38α MAPK signaling pathways. Structural alterations in the nuclear envelope and connected cytoskeleton resulting from LMNA mutations make cardiomyocytes highly susceptible to damage even by physiological mechanical stress, leading to a disease specific maladaptive activation of the p38α MAPK. Up-regulation of p38 MAPK has been observed in the hearts of animal models and adult patients with LMNA-related DCM compared to wild-type/healthy individuals. Inhibition of p38 MAPK in this disease setting may halt aberrant apoptosis and cardiac remodeling resulting in improved cardiac function.

2.1. Study Design

This is a Phase 1, open-label, single-period, single-center, non-randomized single oral dose study administering a liquid formulation with 400 mg of PF-07265803 containing 100 µCi of [^{14}C]PF-07265803 to healthy male participants. Participants will be screened for participation in this study within 28 days before dosing on Day 1 to confirm that they meet the inclusion/exclusion criteria specified in protocol Section 5.1.

The duration of this non-randomized Phase 1, open-label, single-center, single-dose study is approximately 7 days, with a 30-day safety follow up. The maximum period of confinement is expected to be 14 days. The minimum period of confinement is expected to be 3 days. Inpatient stay must be extended until >90% radioactive dose administered has been recovered or <1% is excreted in total (urine and feces) in any 24H period for two consecutive days. Maximum confinement will be 14 days.

The expected duration of participation from Screening to the follow-up telephone contact will be approximately 5 weeks (minimum) to 8 weeks (maximum). Approximately 6 participants will be enrolled to study intervention.

On Day-1, participants will be admitted in order to ensure that a group of 6 participants are dosed on Day 1. The study will dose 6 adult male participants in order to ensure that at least 4 participants provide evaluable data. There are no plans to replace participants who are prematurely withdrawn.

2.2. Study Objectives

2.2.1. Primary Objectives

- *To characterize rate and extent of excretion of total radioactivity in urine and feces, following a single oral dose of [^{14}C]PF-07265803 administered to healthy adult male participants.*

- *To characterize metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-07265803 to healthy adult male participants.*

2.2.2. Secondary Objective

- *To quantify plasma concentrations and pharmacokinetic parameters of PF-07265803, its known circulating metabolites (PF-07327859, PF-07327860, PF-07327890) and total radioactivity in plasma following administration of a single oral dose of [^{14}C]PF-07265803 to healthy adult male participants.*

- *To evaluate safety and tolerability of a single oral dose of [^{14}C]PF-07265803 administered to healthy adult male participants.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

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/PD modeling, and/or supporting clinical development.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. PK Concentration Analysis Set

The PK concentration population for PF-07265803 is defined as all participants who receive at least 1 dose of PF-07265803 and who have at least 1 measurable concentration of PF-07265803 (Or its known circulating metabolites PF-07327859, PF-07327860, PF-07327890). The PK concentration population for ^{14}C is defined as all participants dosed with [^{14}C]PF-07265803, who have at least one ^{14}C measurement.

5.1.2. PK Parameter Analysis Set

The PK parameter analysis population for PF-07265803 is defined as all participants treated who have at least 1 of the PF- 07265803(Or its known circulating metabolites PF-07327859, PF-07327860, PF-07327890) PK parameters of interest. The PK parameter analysis population for ^{14}C analysis is defined as all participants treated who have at least one of the ^{14}C parameters of interest. The PK concentration and PK parameter analysis sets may differ.

5.1.3. Extent of Excretion Analysis Set

Extent of excretion population is defined as all participants who have received 1 dose of [^{14}C]PF-07265803 and who have evaluable total radioactivity concentration (urinary and fecal) data and who had no protocol deviations or AEs (such as vomiting of the dose, diarrhoea or severe constipation) that may have affected the extent of excretion analysis.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All participants assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

This is a nonrandomized study. All subjects will receive the same treatment.

5.6. Protocol Deviations

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

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

5.6.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 of the protocol.

5.6.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

An adverse event will be considered a Treatment-emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that starts on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time (28 days) will be flagged as TEAEs. The algorithm will not consider any event that started prior to the first dose date. Any event occurring following start of treatment or increasing in severity will be counted as treatment emergent.

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.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Plasma PK Parameters

Blood samples will be collected according to the Schedule of Activities given in the protocol. Plasma samples will be analyzed for concentrations of PF-07265803 and its known circulating metabolites PF-07327859, PF-07327860, PF-07327890 and total radioactivity.

PK parameters will be determined from concentration-time data for plasma. The following parameters will be determined using standard noncompartmental methods:

Table 1. Noncompartmental PK Parameters of Plasma

Parameter	Analysis Scale	Plasma *PF-07265803 (and known circulating metabolites PF-07327859, PF-07327860, PF-07327890)*	Plasma Radioactivity
AUC_{inf}*	ln	D	D
AUC_{last}	ln	D	D
C_{max}	ln	D	D
T_{max}	R	D	D
$t_{1/2}$*	R	D	D
CL/F*,†	ln	D	D
V_Z/F*,†	ln	D	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits, †=where appropriate.

6.3.2. Mass Balance

Mass Balance: cumulative recovery of urinary, fecal, and total excretion of radioactivity over time expressed as percentage of total radioactive dose administered.

6.3.3. Metabolic Profiling and Metabolite Identification

Plasma, urine and fecal samples will be analyzed for metabolites and/or chiral inversion of PF-07265803. Major metabolites and/or stereoisomers of PF-07265803 in plasma, urine, and feces following oral dose of [^{14}C] PF-07265803 will be identified.

Contributions of each major metabolite to total radioactivity recovered and to circulating radioactivity in plasma will be approximated. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

6.3.4. PD Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

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

7.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample).

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular group with ≥3 evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

The PK and radioactivity data will be summarized using descriptive statistics.

8.2. Statistical Analyses

8.2.1. Pharmacokinetic Analysis

The PK parameters detailed in Section 6.3 will be listed and summarized for subjects in the appropriate analysis sets (as defined in Section 5.1.2). Missing values will be handled as detailed in Section 7.

PK parameters will be summarized as specified in the table below. All parameters will be presented in the same table using separate columns for plasma PK, plasma radioactivity.

Table 2. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, CL/F* and V_Z/F*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

- For PF-07265803 only.

Box and whisker plots for individual subject parameters (AUC_{inf}, AUC_{last} and C_{max}) be presented and overlaid with geometric means.

Supporting data from the estimation of t½ and AUC_{inf} will be listed: 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 PK and total radioactivity (plasma) concentrations will include:

- A listing of all concentrations sorted by subject id and nominal time postdose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv) and the number of concentrations above the lower limit of quantification.

- A plot of median PK and radioactivity concentrations against nominal time postdose (based on the summary of concentrations by time postdose), where the median concentration-time profiles for plasma PK, and plasma radioactivity will be presented together on the same plot.

- A log-linear plot of the median concentrations against nominal times postdose, as described above.

- Plots of individual concentrations against actual time postdose, where profiles for plasma PK, and plasma radioactivity, will be presented together on the same plot.

- Log-linear plots of individual concentrations against nominal times postdose, as described above.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

8.2.2. Mass Balance

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 and/or feces.

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

Individual participant and median data profiles will be graphically presented for the cumulative recovery of radioactivity in urine, feces and their combination. The total recovery of radioactivity in urine, feces and their combination will be listed and summarized using descriptive statistics. Where possible, the rate of excretion of radioactivity will be estimated.

8.3. Safety Analysis

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s).

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

8.3.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Subject discontinuation due to adverse events will be detailed and summarized.

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

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

8.3.5. Laboratory Data

Laboratory data will be listed in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

The baseline measurement is the last predose measurement.

Blood pressure and pulse rate will be measured as per the schedule of activities mentioned in the protocol.

For each planned timepoint, baseline values and change from baseline values will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

8.3.7. ECG Data

The baseline measurement is the predose measurement.

Absolute value and changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be listed by treatment and time.

These data will be listed in accordance with the sponsor reporting standards.

8.3.8. Other Safety Data

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

8.3.9. Concomitant Treatments

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

8.3.10. COVID-19 Specific Assessments

Participants will be tested for SARS-COVID-19 infection by PCR at screening and at the time of being admitted to the clinic for confinement. Additional testing may be required by local regulations or by the Principal Investigator.

This data will be provided in listings.

8.3.11. Screening and Other Special Purpose Data

If the screening data is brought in-house, then will be listed.

9. REFERENCES

None.

10. APPENDICES