Protocol C3991009

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL GROUP STUDY TO COMPARE THE PHARMACOKINETICS OF PF-07081532 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 10Aug-2022

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 10 AUG2022	Original 18 May 2022	N/A	N/A

2. INTRODUCTION

PF-07081532 is an oral GLP-1R agonist that is currently being investigated as a chronic therapy to improve glycemic control in adult participants with T2DM. Based on review of the effect of hepatic impairment on human PK for compounds cleared in a similar manner to PF-07081532 (OATP-mediated hepatic uptake), impaired hepatic function is generally associated with increased drug exposures in plasma.

Therefore, t*he primary purpose of this study is to characterize the effect of varying degrees of hepatic impairment on the plasma PK of PF-07081532 following administration of a single oral dose of PF-07081532.*

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991009.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not Applicable

2.2. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***
Primary:	***Primary:***
• *To compare the PK of PF-07081532 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.*	• *Plasma: C_{max}, AUC_{inf}, AUC_{last}*, fu, $C_{max,u}$, $AUC_{inf,u}$ and $AUC_{last,u}$*, as data permit.*
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of a single oral dose of PF-07081532 when administered to adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic impairment.*	• *Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.*
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[redacted]

Objectives	*Endpoints*
CCI [redacted]	
[redacted]	[redacted]

** AUC_{last} and $AUC_{last,u}$ will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf} and $AUC_{inf,u}$.*

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2.2.1. Primary Estimand(s)

Not applicable because C3991009 is a Phase 1 study with no estimands on PK endpoints

2.2.2. Secondary Estimand(s)

Not applicable because C3991009 is a Phase 1 study with no estimands on safety endpoints

2.2.3. Additional Estimand(s)

Not applicable because C3991009 is a Phase 1 study with no estimands on safety endpoints

2.3. Study Design

This is an open-label, single-dose, parallel-group, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of PF-07081532 after a single, oral 20 mg dose administered in the fed state (standard breakfast). Safety and tolerability will be evaluated throughout the study. A total of approximately 24 participants with varying degrees of hepatic function will be dosed in the study as shown in Table 2. If recruitment of participants with severe hepatic impairment proves prohibitive, the number of participants to be enrolled in this group may be flexible (4-6 participants).

Table 2. Hepatic Function Categories Based on Child-Pugh Score

Group	*Description*	*Child-Pugh Score*	*Number of Participants*
1	*Without hepatic impairment*	*Not Applicable*	*6*[a]
2	*Mild hepatic impairment*	*Class A (5 to 6 points)*	*6*
3	*Moderate hepatic impairment*	*Class B (7 to 9 points)*	*6*
4	*Severe hepatic impairment*	*Class C (10 to 15 points)*	*6*[b]

a. Additional participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this group is aligned with the pooled averageassessed when approximately ≥75% of participants are dosed across the other 3 groups.

b. If recruitment proves to beprohibitive, study may dose 4-6 participants in this group.

Categorization of participants into Groups 2-4 will be done based on Child-Pugh scores determined at the screening visit , as described in Appendix 11 of the protocol.

Staged Enrollment of Study Groups

Participants will be dosed in a staged manner as follows:

- *Participants with moderate and severe hepatic impairment (Groups 3 and 4) will be enrolled first.*

- *Recruitment of participants with mild hepatic impairment (Group 2) will initiate when approximately 50% of the participants across Groups 3 and 4 have been dosed.*

  Sponsor approval is required before proceeding with recruitment of Group 2.

- *An average value for age and weight for the 3 hepatic impairment groups (Groups 2-4) will be determined, and participants without hepatic impairment (Group 1) will be recruited to match the average demographics (at a minimum, age and weight, and as much as practically possible gender) across the pooled Groups 2-4.*

- *Recruitment for healthy participants in Group 1 (without hepatic impairment) may start when approximately 75% of total participants across Groups 2-4 (ie, approximately 12-13 participants) have been dosed.*

  Sponsor approval is required before proceeding with recruitment of Group 1.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Baseline is defined as the last pre-dose assessment for all endpoints, unless otherwise specified.

3.1. Primary Endpoint(s)

- PF-07081532 Plasma Pharmacokinetic parameters: C_{max}, AUC_{inf}, AUC_{last}, fu, $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$ as data permit.

The plasma PK parameters in Table 3 will be derived from concentration-time profiles using standard non-compartmental analysis methods (with the exception of fu that will be directly determined by the analytical lab):

Table 3. Summary of Plasma PK Parameters of PF-07081532 to be calculated

Parameter	Analysis Scale	PF-07081532 20mg
C_{max}	ln	A, D
AUC_{inf}*	ln	A, D
AUC_{last}^{+}	ln	A, D
fu	R	A, D
$C_{max,u}$	ln	A, D

[redacted]

$AUC_{inf,u}$*	ln	A, D
$AUC_{last,u}$+	ln	A, D

*=if data permits. +AUC_{last} and $AUC_{last,u}$ will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf} and $AUC_{inf,u}$,
Abbreviations: A = analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Table 7 in Section 6.1.1.1 ; ln=natural-log transformed; R=raw (untransformed).

The plasma PK parameters for unbound PF-07081532 will be calculated as described in Table 4:

Table 4. Summary of Plasma PK parameters of Unbound PF-07081532 to be calculated

Parameter	Method of Determination
$AUC_{last,u}$+	fu × AUC_{last}
$AUC_{inf,u}$*	fu × AUC_{inf}*
$C_{max,u}$	fu × C_{max}

*=if data permits. +AUC_{last} and $AUC_{last,u}$ will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf} and $AUC_{inf,u}$,

3.2. Secondary Endpoint(s)

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:

- 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.

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, baseline will be defined as the last pre-dose measurement, unless otherwise specified.

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3.4. Baseline Variables

Not Applicable.

3.5. Safety Endpoints

See Section 3.2

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 study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Safety analysis set	*All participants assigned to study intervention and who take at least 1 dose of study intervention.*
PK Concentration Set	*The PK concentration population is defined as all participants who received at least 1 dose of PF-07081532 and in whom at least 1 plasma concentration value is reported.*
PK Parameter Set	*The PK parameter analysis population is defined as all participants who received at least 1 dose of PF-07081532 and have at least 1 of the PK parameters of interest calculated.*
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5. GENERAL METHODOLOGY AND CONVENTIONS

The following group labels (or similar) will be used for tables and figures unless otherwise stated:

Group	Description of Group	Label
1	Normal hepatic function	Without Hepatic Impairment
2	Mild hepatic impairment	Mild Hepatic Impairment
3	Moderate hepatic impairment	Moderate Hepatic Impairment
4	Severe hepatic impairment	Severe Hepatic Impairment

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

5.2.1. Analyses for Continuous Endpoints

Unless otherwise stated, continuous endpoints and relevant safety endpoints 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 endpoints and relevant safety endpoints will be presented using summary statistics: number of observations, counts and percentages.

5.2.3. One-way Analysis of Variance (ANOVA)

The *one-way analysis of variance (ANOVA)* model will include group as a factor.

Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Example SAS code is given 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.

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5.2.4. Linear Regression PK Parameters versus Hepatic Function

Linear regression will be used to analyze the potential relationship between appropriate PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max}, fu, $AUC_{inf,u}$, $AUC_{last,u}$, $C_{max,u}$) and hepatic function as a continuous explanatory variable (using either continuous serum albumin, prothrombin time or total bilirubin, each modelled separately). *Estimates of the slope and intercept, together*

[redacted]

with a 90% CI, and the coefficient of determination (i.e. R-squared and adj-R-squared) may be obtained from the model. Example SAS code is given 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. Alternative model structure may also be considered. Justification for any alternative to the planned analysis will be given in the report of the study if applicable.

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5.3. Methods to Manage Missing Data

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

5.3.1. Pharmacokinetic 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.

5.3.2. Pharmacokinetic Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median/mean 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/clinical team.

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

5.3.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a 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 analysis and 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 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 in the body), this will be footnoted in summary tables/figures and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

Data collected before baseline will only be listed, unless otherwise stated.

Unless otherwise stated, all analyses, summaries and listings will be produced by group (as outlined in Section 5) which would include all 4 groups in the same analysis/output.

6.1. Primary Endpoint(s)

6.1.1. PF-07081532 PK Parameters

- Estimand strategy: Not applicable
- Analysis set: PF-07081532 Concentration and Pharmacokinetic Parameter Set

6.1.1.1. Main Analysis

C_{max}, AUC_{inf} (if data permit), AUC_{last}, fu, $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$ will be listed, summarized descriptively and analyzed by group for participants in the PK parameter set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

A one-way analysis of variance (ANOVA) described in Section 5.2.3, that includes all 4 groups in the same model, will be used to compare the natural log transformed of C_{max}, AUC_{inf}, AUC_{last}, fu, $AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$ of PF-07081532 separately, for each of the hepatic impairment groups (Test, Groups 2, 3, 4) to the healthy normal hepatic function group (Reference, Group 1).

For summary statistics and median or mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. The plasma PK parameters of PF-07081532 for each group will be summarized as specified in Table 7 below.

Table 7. Summary statistics to be produced for Plasma PK Parameters of PF-07081532

Parameter	Summary Statistics
C_{max}, AUC_{inf}*, AUC_{last}, fu, $AUC_{inf,u}$*, $AUC_{last,u}$, and $C_{max,u}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

* if data permits

The following plots will be presented:

- *Box and whisker plots for individual PK parameters (AUC_{inf}, AUC_{last}, C_{max}, f_u, $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$)) will be constructed by group and overlaid with geometric means.*

6.1.1.2. Sensitivity/Supplementary Analyses

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Plots of PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max}, f_u, $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) versus hepatic function at baseline (e.g. serum albumin, prothrombin time or total bilirubin, plotted separately) *will be constructed, with a regression line and 90% confidence region included* from the main linear regression model.

6.2. Secondary Endpoint(s)

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 3.2 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.

6.2.1. Adverse Events

Adverse events will be summarised by group and overall, in accordance with sponsor reporting standards using the safety population defined in Section 4.

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

6.2.2. Laboratory Data

Laboratory data will be listed and summarized by group and overall, in accordance with the sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.2.

6.2.3. Vital Signs

Absolute values and changes from baseline in seated systolic and diastolic blood pressure and pulse rate will be summarised by group, according to sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.2.

Maximum and minimum absolute values and maximum changes from baseline for seated vital signs will also be summarised descriptively by group 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.

6.2.4. ECG

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR interval and QRS interval will be summarised by group using sponsor reporting standards and the safety population defined in Section 4**.** Tables will be paged by parameter. Baseline is as defined in Section 3.2.

Maximum absolute values and changes from baseline for QTcF, PR and QRS will also be summarised descriptively by group 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.

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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, biological sex, race, ethnicity, weight, body mass index and height) will be summarized by group and overall, as outlined in Sections 5.2.1 and 5.2.2 as applicable.

6.5.2. Study Conduct and Participant Disposition

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

6.5.3. Study Treatment Exposure

Not applicable.

6.5.4. 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

See Section 6.2.

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 may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

None.

APPENDICES

Appendix 1. Statistical Methodology Details

An example of SAS code for ANOVA:

```
proc mixed data = tab.pk;
        class group;
        model l&var = group /residual;
        lsmeans group/diff cl alpha=0.1;
        ods output lsmeans = lsmeans&var;
        ods output diffs=diffs&var;
run;
```

An example of SAS code for the PROC REG code for linear regression analyses:

```
proc reg data=tab.pk;
        model l&var=clcr/clb alpha=0.1;
        ods output ParameterEstimates = param&var;
        ods output FitStatistics = fit&var;
        ods output ANOVA = reg&var;
run;
```

An example of SAS code for stepwise regression with model selection using AIC:

```
proc glmselect data=tab.pk analysis plot=ALL;
    model pk_p = albumin age weight/ selection=stepwise (select = AIC stop = AIC)
        include=1 hierarchy=none showpvalues;
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
Seated 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
Ae	Amount excreted
ANOVA	analysis of variance
AUC	area under the curve
BLQ	below the limit of quantitation
BP	blood pressure
CI	confidence interval
CL	Clearance
CCI [redacted]	[redacted]
C_{max}	maximum observed concentration
CCI [redacted]	[redacted]
CSR	clinical study report
CV	Coefficient of variation
ECG	Electrocardiogram
IP	Investigational Product
LLQ	Lower limit of quantitation
Ln	Natural log
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
SOA	Schedule of activities
TEAE	Treatment emergent adverse events
CCI [redacted]	[redacted]