Protocol C3991007

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL-GROUP STUDY TO EVALUATE THE PHARMACOKINETICS OF PF-07081532 IN ADULT PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS WITH VARYING DEGREES OF RENAL IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT RENAL IMPAIRMENT

Statistical Analysis Plan
(SAP)

Version: 1

Date: 6-Sept-2022

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 6 Sep 2022	Original 03 Jun 2022	N/A	N/A

2. INTRODUCTION

The purpose of this study is to characterize the effect of varying degrees of renal impairment on the PK, safety and tolerability of PF-07081532. 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. CKD occurs in 20-40% of patients with diabetes and may be present at the time of diagnosis of T2DM.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991007.

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 T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal 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 T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.*	• *Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To compare additional plasma PK parameters of PF-07081532 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.*	• *Plasma: CL/F, CL_u/F, V_z/F, $V_{z,u}$/F, T_{max} and $t_{1/2}$ as data permit.*

• *To compare urine PK parameters of PF-07081532 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.*	• *Urine: CL_r, Ae_{24}, Ae_{24}%*
• CCI [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 $AUC_{inf,u}$, otherwise they will be treated as tertiary endpoints.*

2.2.1. Primary Estimand(s)

Not applicable because C3991007 is a Phase 1 study with no estimands on PK endpoints

2.2.2. Secondary Estimand(s)

Not applicable because C3991007 is a Phase 1 study with no estimands on safety endpoints

2.2.3. Additional Estimand(s)

Not applicable because C3991007 is a Phase 1 study with no estimands on other endpoints

2.3. Study Design

This is an open-label, single-dose, parallel-group study to investigate the effect of varying degrees of renal function on the PK of PF-07081532 after a single, oral 20 mg dose administered in the fed state (standard, non-high fat breakfast). Safety and tolerability will be evaluated throughout the study. A total of approximately 32 participants with T2DM and varying degrees of renal function will be dosed in the study as shown in Table 2. If recruitment of participants with eGFR <30 mL/min proves prohibitive, the number of participants to be enrolled in the group with severe impairment may be flexible (6-8 participants).

Table 2. Renal Function Categories Based on eGFR

Group	*Renal Impairment*	*eGFR[a](mL/min)[a]*	*Number of Participants*
1	*None (Normal Renal Function)*	*≥90*	*8*
2	*Mild*	*60-89*	*8*
3	*Moderate*	*30-59*	*8*
4	*Severe*	*<30*	*8[b]*

a. Note:participants on dialysis will be placed in Group 4 regardless of unnormalized eGFR value.

b. 2-4 participants on dialysis are permitted (not required). If requirement proves to be prohibitive, study may dose 6-8 participants with severe renal impairment.

Categorization of participants into Groups 2-4 will be done based on eGFR values determined at the screening visit , as described in Section 4.1 of the protocol.

Staged Enrollment of Study Groups

- *Participants will be dosed in a staged manner such that those with moderate and severe renal impairment (Groups 3 and 4) will be enrolled first.*
- *Recruitment of participants with mild renal impairment (Group 2) will initiate when approximately 50% of the participants in Groups 3 and 4 have been dosed.*

  Approval from the sponsor is required before proceeding with recruitment of Group 2.
- *An average value for age and weight for Groups 2, 3, and 4 will be determined and participants in 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.*
- *Therefore, recruitment of participants without renal impairment (Group 1) may start when approximately 75% of total participants across Groups 2-4 (ie, approximately 17-18 participants) have been dosed.*

  Approval from the sponsor 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	ln	A, D
$C_{max,u}$	ln	A, D

$AUC_{inf,u}$*	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 8. 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.

3.3. Other Endpoint(s)

3.3.1. Additional Plasma Pharmacokinetic Parameters

- Additional PF-07081532 Plasma Pharmacokinetic parameters CL/F, V_z/F, T_{max}, $t_{1/2}$ as data permit.
- Additional Unbound PF-07081532 Plasma Pharmacokinetic parameters: CL_u/F, $V_{z,u}$/F as data permit.

The plasma PK parameters for PF-07081532 in Table 5 will be determined using standard non-compartmental methods:

Table 5. Summary of Additional Plasma PK Parameters of PF-07081532 to be calculated

Parameter	Analysis Scale	PF-07081532 20mg
CL/F*	ln	D
CL_u/F*	ln	D
V_z/F*	ln	D
$V_{z,u}$/F*	ln	D
T_{max}	R	D
$t_{1/2}$*	R	D

*=if data permits. Abbreviations: D = displayed with descriptive statistics as outlined in Table 8 in Section 6.3.1, ln = natural-log transformed, R = raw (untransformed).

The plasma PK parameters for unbound PF-07081532 will be calculated as described in Table 6:

Table 6. Summary of Additional Plasma PK parameters of Unbound PF-07081532 to be calculated

Parameter	Method of Determination	Analysis Scale	PF-07081532 20mg
CL_u/F*	Dose/($AUC_{inf,u}$)	ln	D
$V_{z,u}$/F*	Dose/($AUC_{inf,u} \times k_{el}$)	ln	D

*=if data permits. Abbreviations: D = displayed with descriptive statistics as outlined in Table 8 in Section 6.3.1, ln = natural-log transformed, R = raw (untransformed).

3.3.2. Urine Pharmacokinetic Parameters

- PF-07081532 Urine Pharmacokinetic parameters CL_r, Ae_{24}, Ae_{24}%

The urine PK parameters for PF-07081532 in Table 7 will be determined using standard non-compartmental methods:

Table 7. Summary of Urine PK Parameters of PF-07081532 to be calculated

Parameter	Analysis Scale	PF-07081532 20mg
CL_r	ln	A, D
Ae_{24}	ln	D
Ae_{24}%	ln	D

Abbreviations: D = displayed with descriptive statistics as outlined in Table 8 in Section 6.3.1, ln = natural-log transformed, R = raw (untransformed).

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[redacted]

3.3.4. eGFR

For reporting purposes, eGFR will be calculated using the 2021 CKD-Scys formula[1]:

2021 CKD-EPI Scr-Scys Combined	***Scr*** *(mg/dL)*	***Scys*** *(mg/L)*	***Recommended eGFR Equation***
Female	*if ≤0.7*	*if ≤0.8*	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	*if ≤0.7*	*if >0.8*	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	*if >0.7*	*if ≤0.8*	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	*if >0.7*	*if >0.8*	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	*if ≤0.9*	*if ≤0.8*	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	*if ≤0.9*	*if >0.8*	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	*if >0.9*	*if ≤0.8*	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	*if >0.9*	*if >0.8*	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

The alternative equations outlined below may be used for exploratory analyses.

CKD-EPI Scr only equation[2]:

$eGFR\ (mL/min/1.73m^2) = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:

- SCr is serum creatinine in mg/dL (based on the standardized assay)
- κ is 0.7 for females and 0.9 for males
- α is -0.329 for females and -0.411 for males
- min indicates the minimum of SCr /κ or 1
- max indicates the maximum of SCr /κ or 1

- Age is in years

Cockcroft-Gault equation[3]:

eGFR (ml/min/1.73 m^{2}) =[(140-Age) × Weight × 0.85 if female]/(72 × SCr) where:

- Age is in years
- Weight is in kg
- SCr is in mg/dl (based on the standardized assay)

Modification of Diet in Renal Disease (MDRD)[4]:

eGFR (ml/min/1.73 m^{2}) = 175 × $(SCr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if black)

where:

- Age is in years
- SCr is in mg/dl (based on the standardized assay)

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.*

Participant Analysis Set	*Description*
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.*
CCI [redacted]	[redacted]

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 renal function	Without Renal Impairment
2	Mild renal impairment	Mild Renal Impairment
3	Moderate renal impairment	Moderate Renal Impairment
4	Severe renal impairment	Severe Renal 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 renal impairment group as a factor.

Estimates of the adjusted means and 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% CI for the ratios.

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.

Example SAS code is given in Appendix 1.

5.2.4. Linear Regression PK Parameters versus Renal Function

Linear regression may be used to characterize the potential relationship between appropriate PK parameters (eg, CL/F, CL_U/F and CL_r) for PF-07081532 and renal function (eGFR). This will be modelled with e*GFR* (Day 1) as a continuous explanatory variable with each PK parameter modelled separately. *Estimates of the statistical slope and intercept, together with their precision (90% CI), and the coefficient of* determination (i.e. R-squared and adj-R-squared) *will 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

Additionally, as an exploratory analysis, body weight, gender and age may be explored as an additional covariate in the models, as appropriate. This will be implemented by utilizing a stepwise linear regression approach, with model selection using Akaike's Information Criterion [AIC]). All the above covariates will be considered (renal function will be restricted to always remain in the model) and if the final model selected includes at least one of these additional covariates, this additional model will be reported in addition to the main linear regression above. Example SAS code is given in Appendix 1.

5.3. Methods to Manage Missing Data

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

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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 summary tables and statistical analyses, 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, $C_{max,u}$, $AUC_{inf,u}$ and $AUC_{last,u}$ 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 renal impairment groups (Test, Groups 2, 3, 4) to the healthy normal renal function group (Reference, Group 1).

For summary statistics, 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 8. below.

Table 8. 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 renal impairment group and overlaid with geometric means.*

6.1.1.2. Sensitivity/Supplementary Analyses

Linear regression may be used to characterize the potential relationship between appropriate PK parameters (eg, CL/F, CL_u/F and CL_r) for PF-07081532 and renal function (eGFR), calculated using the 2021 CKD-EPI Scr-Scys Combined equation given in Section 3.3.4, following the methodology described in Section 5.2.4.

Plots of PK parameters (eg, CL/F, CL_u/F and CL_r) for PF-07081532 versus renal function at baseline *(eGFR as obtained on Day 1) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify participants from different renal function groups*

6.1.1.3. Exploratory analyses of CKD-EPI, Cockcroft-Gault and MDRD formulas

Exploratory linear regression analyses similar to that described in Section 5.2.4*, (using the eGFR values determined with the 2021 CKD-EPI Scr-Scys combined equation) may be*

conducted using eGFR values determined with the 2021 CKD-EPI Scr only, the Cockcroft-Gault or the MDRD formulas as described in Section 3.3.4.

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 using 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.

6.3. Other Endpoints

6.3.1. Additional Plasma Pharmacokinetic Parameters of PF-07081532

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

CL/F, CL_u/F, V_z/F, $V_{z,u}/F$, T_{max}, $t_{1/2}$ will be listed and summarized descriptively by group in the PK parameter set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Supporting data from the estimation of $t_{1/2}$ will be listed by 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.

The additional plasma PK parameters of PF-07081532 for each group will be summarized as specified in Table 9 below.

Table 9. Summary statistics to be produced for Additional Plasma PK Parameters of PF-07081532

Parameter	Summary Statistics
CL/F, CL_u/F, V_z/F, $V_{z,u}/F$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{½}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

The following summaries will additionally be presented for the plasma concentration data of PF-07081532 using the PK Concentration Set (as defined in Section 4):

- a listing of all concentrations sorted by participant ID and nominal time post-dose for each group. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations for each nominal time post-dose (produced separately for each group), where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- *Individual participant concentration-time data (using actual times) will be plotted by renal impairment group for both total plasma PF-07081532 and unbound PF-07081532* (on both linear and semi-log scales).
- Mean and median concentration time plots against nominal time post-dose by group in the same plot (on both linear and semi-log scales).

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

6.3.2. Urine Pharmacokinetic Parameters of PF-07081532

Urine CL_r, Ae_{24}, $Ae_{24\%}$ will be listed and summarized descriptively by group for participants in the Urine PK parameter set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

The urine PK parameters of PF-07081532 for each group will be summarized as specified in Table 10 below.

Table 10. Summary statistics to be produced for Urine PK Parameters

Parameter	Summary Statistics
CL_r, Ae_{24}, $Ae_{24\%}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

The following summaries will additionally be presented:

- a listing of all urine concentrations over each time interval sorted by group, subject ID and nominal collection duration postdose.
- listing of all urine PK parameters sorted by group, subject ID and nominal collection duration postdose.

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6.3.4. 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, 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

1. Inker LA et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385:1737-49.

2 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 50(9):604-12.

3 Cockcroft D.W. and Gault M.H. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31-41.

4 Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007; 53(4):766-72.

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;
        class gender
    model pk_p = eGFR age weight gender/ 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
CL/F	Apparent total body clearance
C_{max}	maximum observed concentration
CCI	[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)
SOA	Schedule of Activities
SAP	statistical analysis plan
TEAE	Treatment emergent adverse events
T_{max}	Time to maximum observed concentration
$t_{1/2}$	Half life
Vz/F	Apparent volume of distribution