Protocol C3421012

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL GROUP STUDY TO EVALUATE THE PHARMACOKINETICS OF PF-06882961 IN PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS WITH VARYING DEGREES OF RENAL IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT RENAL IMPAIRMENT

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 10 DEC 2020

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

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 10 Dec 2020	Original 13 Oct 2020	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3421012. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***
Primary:	***Primary:***
• *To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.*	• *Plasma: C_{max}, AUC_{inf}, AUC_{last}, fu, as data permit*
Secondary:	***Secondary:***
• *To compare additional PK parameters of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.*	• *Plasma: $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}$/F, T_{max}, $t_{1/2}$, as data permit*
• *To evaluate the safety and tolerability of a single oral dose of PF-06882961 in T2DM participants with varying degrees of renal impairment and in participants with normal renal function.*	• *Incidence and severity of treatment-emergent AEs, clinical laboratory abnormalities, vital signs (blood pressure and pulse rate), ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).*

Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To compare urine PK parameters of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.*	• *Urine: CL_r, Ae_{24}, Ae_{24}%*
• *To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with T2DM and normal renal function relative to healthy participants with normal renal function.*	• *Plasma: C_{max}, T_{max}, AUC_{inf}, AUC_{last}, CL/F, V_z/F, $t_{1/2}$, fu, as data permit* • *Urine: CL_r, Ae_{24}, Ae_{24}%*
• *To explore the relationship of markers of innate OATP activity in adult participants with T2DM and varying degrees of renal impairment relative to participants with normal renal function.*	• *CP-I concentration*
• *To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.*	• *Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).*

There are no estimands for this study.

2.2. Study Design

This Phase 1, open-label, single-dose, parallel group, multi-site study will assess the effect of varying degrees of renal impairment on the PK, safety and tolerability of PF-06882961 after a single oral dose of 20 mg administered in a fed state.

Approximately 40 participants will be enrolled in the study. Refer to Table 2 *below for details of study groups. Due to the potential difficulty in recruiting T2DM patients with estimated glomerular filtration rate (eGFR) <30 mL/min, the number of participants to be enrolled in this group is flexible (6 to 8 participants).*

This study will permit enrollment of 2-4 participants on dialysis, as part of the severe renal impairment group, to assist in recruitment of patients with more advanced renal impairment and to permit assessment of the PK of PF-06882961 in participants with the highest degree of renal impairment. Since PF-06882961 has a large unbound non-renal clearance and a large unbound volume of distribution, dialysis is not expected to significantly impact the clearance of PF-06882961 and therefore the dialysis clearance of PF-06882961 will not be characterized in this study. Thus, Day 1, per the schedule of activities, *will occur in dialysis patients on a day in which dialysis is* ***not*** *administered.*

Table 2. Study Groups

Group	*Disease State*	*Renal Impairment*	*No.of Participants*	*eGFR[a] (mL/min)*
1	*None (healthy)*	*None (Normal Renal Function)*	*8*	*≥90*
2	*T2DM*	*None (Normal Renal Function)*	*8*	*≥90*
3	*T2DM*	*Mild*	*8*	*60-89*
4	*T2DM*	*Moderate*	*8*	*30-59*
5	*T2DM*	*Severe*	*6-8[b]*	*<30*

a. Estimate of eGFR based on the SCr-based CKD-Epi equation. The eGFR will be multiplied by each participant's ratio of BSA/1.73 to obtain the BSA-unnormalized eGFR value. The average of the 2 unnormalized eGFR values from S1 and S2 will be used for study enrollment and group placement. ***Note:*** *participants on dialysis will be placed in Group 5 regardless of unnormalized eGFR from S1 and S2.*
b. This includes approximately 4 participants not on dialysis and 2-4 participants on dialysis.

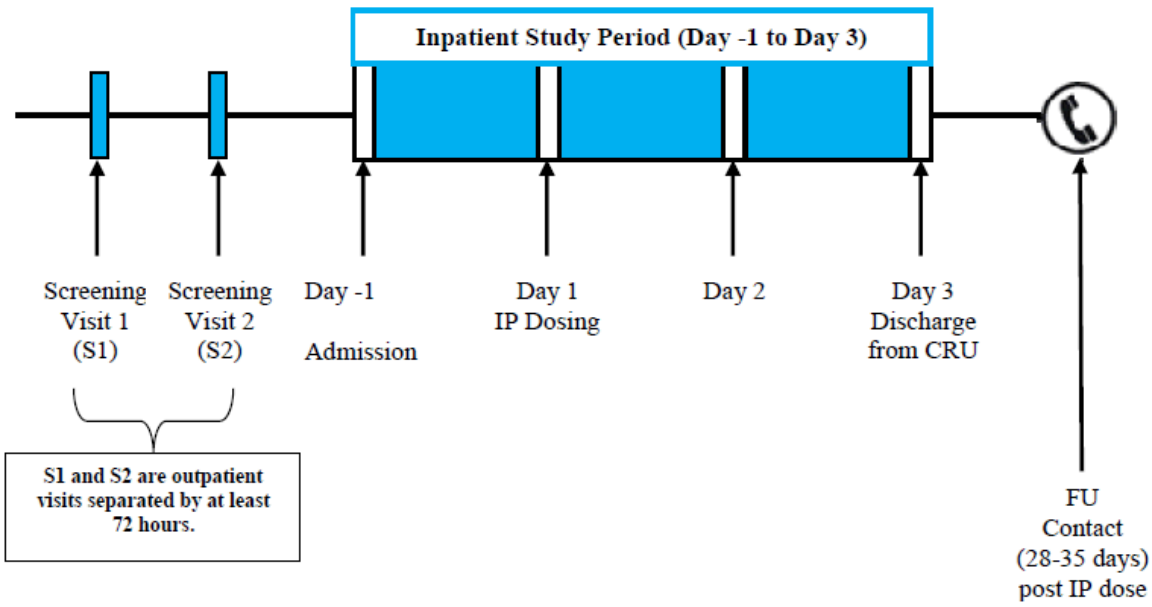
Screening will occur within 28 days of the first dose of study intervention on Day 1. All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. All participants who are not on dialysis must have stable renal function to enter the study, defined as ≤25% difference between 2 measurements of BSA-unnormalized eGFR obtained from the 2 screening visits, S1 and S2 as listed in the schedule of activities. *As indicated in* Table 2*, the estimate of eGFR will be based on the SCr-based CKD-Epi equation,* defined in Section 3.2.1.

Participants with T2DM and varying degrees of renal impairment (Groups 3-5) will be recruited and enrolled first. An average value for age and weight for these groups will be determined and participants in Groups 1-2 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 3-5. Recruitment for participants in Groups 1-2 may start when approximately 75% of total participants across Groups 3-5 (ie, approximately 17-18) have been dosed. Approval from the sponsor must be garnered ***before*** *proceeding with dosing participants in Groups 1 and 2.*

Refer to Figure 1 *for study schema.*

Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

Figure 1. Study Schema



*Screening period is ≤28 days from dosing on Day 1.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Blood samples for PK analysis of PF-06882961 will be collected according to the Schedule of Activities given in the protocol.

PK parameters will be calculated (if possible) from the concentration-time data using standard non-compartmental methods.

3.1. Primary Endpoint(s)

- PF-06882961 Plasma Pharmacokinetic parameters: C_{max}, AUC_{inf}, AUC_{last}, fu, as data permit.

The plasma PK parameters in Table 3 will be determined using standard non-compartmental methods:

Table 3. Summary of Plasma PK Parameters of PF-06882961 to be calculated

Parameter	Analysis Scale	PF-06882961 20mg
C_{max}	ln	A, D
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
fu	ln	A, D

*=if data permits. 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).

3.2. Secondary Endpoint(s)

3.2.1. Additional Plasma PK parameters of PF-06882961

- $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}/F$, T_{max}, $t_{1/2}$, as data permit

The plasma PK parameters for PF-06882961 in Table 4 will be determined using standard non-compartmental methods:

Table 4. Summary of Additional Plasma PK parameters of PF-06882961 to be calculated

Parameter	Analysis Scale	PF-06882961 20mg
CL/F*	ln	A, D
V_z/F*	ln	D
T_{max}	R	D
$t_{1/2}$*	R	D

*=if data permits. Abbreviations: A = analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Table 8 in Section 6.2.1; ln=natural-log transformed; R=raw (untransformed).

The plasma PK parameters for unbound PF-06882961 will be calculated as described in Table 5:

Table 5. Summary of Plasma PK parameters of Unbound PF-06882961 to be calculated

Parameter	Method of Determination	Analysis Scale	PF-06882961 20 mg
$AUC_{last,u}$	fu × AUC_{last}	ln	D
$AUC_{inf,u}$*	fu × AUC_{inf}	ln	D
$C_{max,u}$	fu × C_{max}	ln	D
CL_u/F*	Dose/($AUC_{inf,u}$)	ln	A, D
$V_{z,u}/F$*	Dose/($AUC_{inf,u}$ × k_{el})	ln	D

*=if data permits. Abbreviations: A = analyzed using a statistical model, D=displayed with descriptive statistics as outlined in Table 8 in Section 6.2.1; ln=natural-log transformed , R=raw (untransformed).

For the linear regression analysis assessing the relationship between CL/F, CL_u/F and CL_r and eGFR, the primary equation for eGFR will be SCr-based:

CKD-Epi equation[1]: $eGFR\ (mL/min/1.73m^2) = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 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

Additional outputs will also be produced using the following alternative equations to calculate eGFR:

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

Modification of Diet in Renal Disease (MDRD)[3]: 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
- Weight is in kg
- SCr is in mg/dl (based on the standardized assay)

3.2.2. Safety Endpoints

- *Incidence and severity of treatment-emergent AEs, clinical laboratory abnormalities, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG) parameters (heart rate, QT, QTcF, PR and QRS intervals).*

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-06882961 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 on Day 1 or before.

3.3. Other Endpoint(s)

3.3.1. Urine PK Parameters: CL_r, Ae_{24}, Ae_{24}%

Urine samples for PK analysis will be collected according to the Schedule of Activities given in the protocol. The urine PK parameters in Table 6 will be determined:

Table 6. Summary of Urine PK Parameters to be calculated

Parameter	Analysis Scale	PF-06882961 20mg
Ae_{24}	ln	D
Ae_{24}%	ln	D
CL_r	ln	A, D

Abbreviations: A = analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Section 6.3.1; R=raw (untransformed); ln=natural-log transformed

3.3.2. Coproporphyrin I (CP-I) concentration

Plasma CP-I concentrations will be collected prior to dosing on Day 1 only.

3.4. Baseline Variables

Not applicable.

3.5. Safety Endpoints

See Section 3.2.2.

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 releasing the database and classifications will be documented per standard operating procedures.

Population	**Description**
Enrolled	*All participants who sign the ICD*
Evaluable	*All participants assigned to IP and who take at least 1 dose of IP.*
Safety	*All participants assigned to IP and who take at least 1 dose of IP.*
PK Concentration Set	*The PK concentration population is defined as all participants who received at least 1 dose of PF-06882961 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-06882961 and have at least 1 of the* plasma *PK parameters of interest calculated.*
Urine PK Concentration Set	The urine PK concentration population is defined as all participants who received at least 1 dose of PF-06882961 and in whom at least 1 urine concentration value is reported.
Urine PK Parameter Set	The urine PK parameter analysis population is defined as all participants who received at least 1 dose of PF-06882961 and have at least 1 of the urine PK parameters of interest calculated.
CP-I Concentration Set	The CP-I concentration population is defined as all participants who received at least 1 dose of PF-06882961 and in whom at least 1 CP-I concentration value is reported.

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	Healthy and normal renal function	Healthy Normal
2	T2DM Normal renal function	T2DM Normal
3	T2DM Mild renal impairment	T2DM Mild RI
4	T2DM Moderate renal impairment	T2DM Moderate RI
5	T2DM Severe renal impairment	T2DM Severe RI

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 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. One-way Analysis of Variance (ANOVA)

The *ANOVA model will include all groups (i.e. both T2DM and healthy participants from the 5 groups) as a factor.*

Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and corresponding 90% CIs. Example SAS code is given in Appendix 1.

Potential differences in demographic characteristics between healthy (Group 1), T2DM normal (Group 2) and T2DM renal impairment function participants (Groups 3, 4, 5) and their impact on study conclusions will be explored based on consideration of the covariates weight, gender and age. This will be implemented by utilizing a stepwise linear regression approach, with model selection using Akaike's Information Criterion [AIC]). All the above covariates and factors will be considered (group as a factor will be restricted to always remain in the model) and if the final model selected includes at least one of these additional covariates/factors, this additional model will be reported in addition to the main ANOVA model above. Example SAS code is given in Appendix 1.

5.2.4. Linear Regression

Linear regression analysis will include eGFR as the explanatory variable, based on eGFR values obtained on Day 1 and will include only participants from the T2DM groups (Groups 2 to 5). Estimates of the slope and intercept, together with their precision (90% CIs), and the coefficient of determination will be obtained from the model. Example SAS code is given in Appendix 1.

Additionally, as an exploratory analysis, the effect of weight, gender and age will be explored as additional covariate/factors 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 and factors will be considered (eGFR will be restricted to always remain in the model) and if the final model selected includes at least one of these additional covariates/factors, 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.

In all PK data presentations (except listings) and CP-I, 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 group/analyte with ≥3 evaluable measurements. For statistical analyses (i.e. linear regression), 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 – within ~2 times the median Tmax after the dose of PF-06882961), 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

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

6.1. Primary Endpoint(s)

6.1.1. C_{max}, AUC_{inf}, AUC_{last}, fu for PF-06882961

6.1.1.1. Main Analysis

C_{max}, AUC_{inf} (if data permit), AUC_{last} and fu 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 5.3.1.

Linear regression will be used to characterize the potential relationship between appropriate PK parameters (CL/F, CL_u/F and CL_r) for PF-06882961 and renal function (eGFR as obtained on Day 1 and defined by the SCr-based CKD-Epi equation in Section 3.2.1*),* as described in Section 5.2.4, where the PK parameter will be the dependent variable in the separate models.

Plots of PK parameters (CL/F, CL_u/F and CL_r) for PF-06882961 versus renal function (eGFR as obtained on Day 1 and defined by the SCr-based CKD-Epi equation in Section 3.2.1*) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will be 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.*

For exploratory purposes, these analyses and figures will additionally be carried out separately for each of the alternative two methods for calculating eGFR, as defined in Section 3.2.1.

A one-way analysis of variance (ANOVA) described in Section 5.2.3, that includes all 5 groups in the same model, will be used to compare the natural log transformed of C_{max}, AUC_{inf}, AUC_{last} and fu of PF-06882961 separately, for each of the T2DM renal impairment groups (Test, Groups 3, 4, 5) to the T2DM normal renal function group (Reference, Group 2). Also, the T2DM normal renal function group (Test, Group 2) will be compared to the healthy normal renal 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-06882961 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-06882961

Parameter	Summary Statistics

C_{max}, AUC_{inf} (if data permit), AUC_{last} and fu	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

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 following plot will be presented:

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

6.2. Secondary Endpoint(s)

6.2.1. Additional Plasma PK parameters of PF-06882961

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

The additional plasma PK parameters of PF-06882961 for each group will be summarized as specified in Table 8 below.

Table 8. Summary statistics to be produced for Additional Plasma PK Parameters of PF-06882961

Parameter	Summary Statistics
$C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, 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.
t½	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

The following plot will be presented:

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

The following summaries will additionally be presented for the plasma concentration data of PF-06882961 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.
- median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by group in the same plot.
- individual concentration time plots by group (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each group, with a line for each participant, per scale).

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. Safety Endpoints

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 3.2.2 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.

6.2.2.1. 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.

6.2.2.2. 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 3.2.2.

6.2.2.3. Vital Signs

Absolute values and changes from baseline in supine 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 3.2.2.

Maximum and minimum absolute values and maximum changes from baseline for supine 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.

6.2.2.4. 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 3.2.2.

Maximum absolute values and changes from baseline for QTcF interval, PR interval and QRS interval 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 timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.3. Other Endpoint(s)

6.3.1. Urine PK Parameters: CL_r, Ae_{24}, Ae_{24}%

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-06882961 for each group will be summarized as specified in Table 9 below.

Table 9. 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.

6.3.2. CP-I concentration

CP-I will be summarized descriptively by group and overall for participants in the CP-I concentration set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Linear regression will be used to characterize the potential relationship between appropriate PK parameters (AUC_{inf} [as data permit], $AUC_{inf,u}$ [as data permit], AUC_{last}, $AUC_{last,u}$, CL/F and CL_u/F) for PF-06882961 versus innate OATP activity (as measured by CP-I on Day 1) as described in Section 5.2.4, where the PK parameter will be the dependent variable in the separate models and CP-I will be the explanatory variable. This will be applied to participants from the T2DM groups only.

Plots of PK parameters vs. CP-I will be constructed separately for each PK parameter. A regression line and 90% confidence region for the PK parameters will be included in the plots and different symbols will be used to identify participants from different renal function groups.

CCI

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 (plasma and urine, separately), PD 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. Concomitant Medications and Nondrug Treatments

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

6.5.4. Other Screening Data

These data will not be recorded in the study database, and therefore will not be listed.

6.6. Safety Summaries and Analyses

See Section 6.2.2.

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/PD modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

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

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

(3) 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.

9. 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_cg age gender 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
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
Ae	Amount excreted
ANOVA	analysis of variance
AUC	area under the curve
BLQ	below the limit of quantitation
BP	blood pressure
CG	Cockcroft-Gault
CI	confidence interval
CL	Clearance
CL/F	Apparent total body clearance
C_{max}	maximum observed concentration
CP-I	Coproporphyrin I
CSR	clinical study report
CV	Coefficient of variation
ECG	Electrocardiogram
ICD	informed consent document
IP	Investigational product
LLQ	Lower limit of quantification
Ln	Natural log
MAR	missing at random
MDRD	Modification of Diet in Renal Disease
N/A	not applicable
NC	not calculated
ND	not done
NS	so sample
OATP	organic-anion-transporting polypeptide
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
T_{max}	Time to maximum observed concentration
T2DM	Type 2 Diabetis Mellitus
$t_{1/2}$	Half life
Vz/F	Apparent volume of distribution