Protocol C3421002

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF MULTIPLE ESCALATING ORAL DOSES OF PF-06882961 IN ADULT SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Statistical Analysis Plan (SAP)

Version: 4

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

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[redacted]

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 22 Jun 2018	Original 22 Mar 2018	N/A	N/A
2 12 Feb 2019	Original 22 Mar 2018	Ongoing data review	• CCI [redacted] • Sections 6.4.1 & 6.4.2: Added reference to Section 7.4 for missing values. • CCI [redacted] • Section 8.4.2: Demographics and physical measurements at baseline will be summarised by treatment, rather than by Sex. • Section 8.4.8: Added that QTcB will be listed only and not summarized. • CCI [redacted]

[redacted]

			• CCI [redacted]
3 5 Mar 2019	Original 22 Mar 2018	Additional analyses required	• Defined HbA1c endpoint (Section 6.2.5.1). • CCI [redacted] • Added additional demographic table for CCI [redacted] and HbA1c (Section 8.4.2). • Added statistical analysis of HbA1c (Section 8.4.9).
4 19 Jun 2019	Original 22 Mar 2018	Ongoing data review	• CCI [redacted] • Removed certain PK endpoints and made alterations to PK reporting (Sections 6.3 and 8.2.1). • Clarification of PK exemption (Section 8). • CCI [redacted] • Added summary tables on number of AEs reported by preferred term (Section (8.4.4).

[redacted]

2. INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.GLP-1 activation of the GLP-1 receptor (GLP-1R) stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying. In addition, GLP-1 has been shown to increase satiety and suppress food intake.

PF-06882961 is an oral GLP-1R agonist that is currently being developed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

The purpose of this study is to evaluate the safety, tolerability, and PK of multiple oral doses of PF-06882961 in adult subjects with T2DM. CCI [redacted]

2.1. Study Design

This is a randomized, double-blind (sponsor-open), parallel, placebo-controlled, multiple oral dose-escalating study of PF-06882961 in subjects with T2DM on a background of metformin monotherapy.

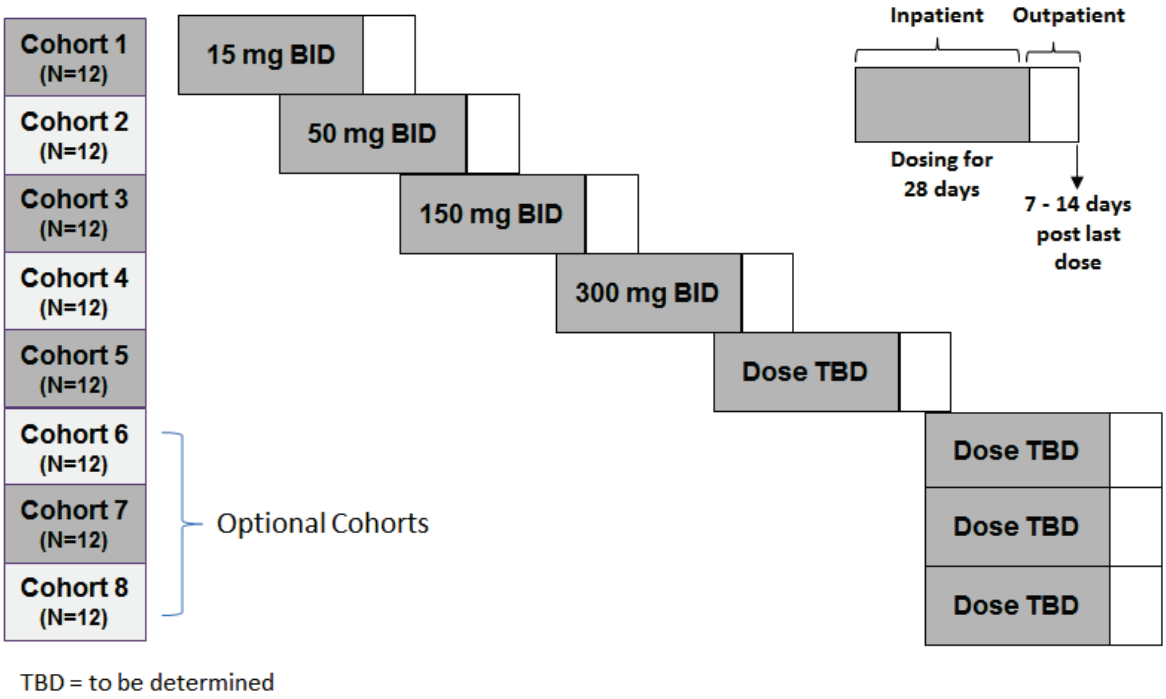
Subjects will receive oral doses of PF-06882961 or placebo in this study. A total of approximately 12 subjects (9 active and 3 placebo) will be enrolled in each cohort, for a total of approximately 60 (Cohorts 1-5) or up to approximately 96 (if including optional Cohorts 6-8) subjects randomized. The randomization ratio within a cohort will be 3:1 between PF-06882961 and placebo. The study will be conducted at approximately 2-5 clinical sites in the US.

Dose titration will be incorporated to enhance tolerability to PF-06882961. Doses and dose titration schemes in the escalation sequence may be modified or repeated as guided by emerging safety, and PK data. The size of the dose increment and titration rate may be reduced or increased as the study progresses dependent upon emerging PK, safety and tolerability data, but dose increments from one cohort to the succeeding cohort will not be greater than approximately semi-logarithmic. Doses and dosing durations for Cohort 5 and optional Cohorts 6-8 will be provided to investigators in writing prior to initiation of dosing in these cohorts.

Subjects will be admitted to the clinical research unit (CRU) on or before Day -2 and may be discharged at PI discretion following completion of all assessments on Day 30. A Follow-up visit and a Follow-up contact (may be a phone call) will occur 35-42 days and 56-63 days following the first dose of IP on Day 1, respectively. Subjects who discontinue prior to completion of the study may be replaced, at the discretion of the PI and Sponsor.

The formulations administered in this study will be PF-06882961 CCI [redacted] *tablets, or matching placebo. A Sample study design overview is shown in Figure 1, however, treatment sequences, actual doses, target exposures, formulation, fasting state, titration, and dose increments may be adjusted during the study based on emerging safety, tolerability, and PK data.*

Figure 1. Study Design Overview



TBD = to be determined

2.2. Study Objectives

2.2.1. Primary Objective(s)

- *To evaluate the safety and tolerability of ascending, multiple, oral doses of PF-06882961, administered to adult subjects with T2DM.*

2.2.2. Secondary Objective(s)

- *To characterize plasma pharmacokinetics of PF-06882961 following Day 1 and following multiple oral doses administered to adult subjects with T2DM.*

- *To characterize the PK of PF-06882961 in urine following multiple, oral doses administered to adult subjects with T2DM.*

CCI

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Safety and pharmacokinetic (PK) data will be reviewed after each study period.

This is a third party open study, with the investigator and subject blinded to study treatment. Specific Pfizer personnel (eg, PK assay specialist, medical monitor, study clinician, clinical pharmacology lead, statistician, and pharmacokineticist) will be unblinded to subject treatments in order to permit real-time interpretation of the safety and PK data, and to provide information necessary to potentially alter the dose escalation sequence. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/study staff until the conclusion of the study. Unblinding for the study will not be performed until the final database has been locked for all cohorts. Final analysis will follow the official database release.

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. Full Analysis Set

This population of subjects is not applicable for this study. Analysis sets for PK, pharmacodynamic (PD) and safety data are defined in Section 5.2, 5.3 and 5.4, respectively.

5.2. Pharmacokinetic Analysis Set

5.2.1. Concentration Analysis Set

The PF-06882961 PK concentration population will be defined as all randomized subjects who received at least 1 dose of PF-06882961 and in whom at least 1 plasma PK concentration value of PF-06882961 is reported. CCI [redacted]

5.2.2. Parameter Analysis Set

The PF-06882961 PK parameter analysis population will be defined as all randomized subjects who received at least 1 dose of PF-06882961 and who have at least 1 of the PK parameters of interest for PF-06882961 calculated. PK samples from placebo samples will not be routinely analyzed. CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

5.4. Safety Analysis Set

All subjects who received at least 1 dose of study medication will be included in the safety analyses and listings.

5.5. Other Analysis Sets

None.

5.6. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and PD analyses, where applicable.

5.7. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg, 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.

5.7.1. Deviations Assessed Prior to Randomization

At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.7.2. Deviations Assessed Post-Randomization

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

In this section, the safety endpoints that will be measured during the study are detailed. Where applicable, details of the endpoints to be derived and definition of baseline are also provided.

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.*

6.2.1. Adverse Events

Any events occurring following start of treatment on Day 1 or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

6.2.1.1. Hypoglycemia Monitoring

Hypoglycemia AEs will be recorded in the Case Report Form (CRF) as a separate page. Details of when these will be recorded are given in the protocol Section 7.1.7.

For programming purposes, the hypoglycemic AE categories are based on the following:

- Severe Hypoglycemia: Severe is checked in the severity criteria of the CRF. This assessment will be made by the PI based on the protocol definition.
- Documented Symptomatic Hypoglycemia: If (1 – Did the subject have symptoms of hypoglycemia?) Yes and (2 – Was the blood glucose measured?) Yes and result<=70 mg/dL on the CRF, but hypoglycemia is not classified as severe.
- Asymptomatic Hypoglycemia: If (1) No and (2) Yes and result<=70 mg/dL on the CRF, but hypoglycemia is not classified as severe.

- Probable Symptomatic Hypoglycemia: If (1) Yes and (2) No and (2b – If blood glucose was not measured, did symptoms resolve when treated with carbohydrate or glucagon?) Yes on the CRF, but hypoglycemia is not classified as severe.

6.2.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last predose measurement on either Day -1 or Day 1, as applicable.

6.2.3. Vital Signs

Single supine blood pressure and pulse rate measurements will be taken at screening, Day 30, Follow-up and at early termination (if applicable). Triplicate supine measurements will be taken at all other times as detailed in the Schedule of Activities given in the protocol. The average of the triplicate measurements will be calculated prior to analyzing the data. Baseline will be defined as the time-matched value from the average of the triplicate recordings on Day -1.

The time-matched double difference in supine blood pressures and pulse rate measurements is calculated in the following steps: (1) subtract predose value on Day 1 from all postdose values; (2) subtract the value at 0 hours on Day -1 from all other values on Day -1; (3) take the difference between the adjusted postdose value in (1) and its time-matched value in (2).

The maximum decrease and increase from time-matched baseline over all measurements taken postdose will be calculated for supine systolic and diastolic blood pressures. The maximum increase from baseline will be calculated by first subtracting the time-matched baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken. Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the change from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

6.2.4. ECG

A single 12-lead ECG will be obtained on all subjects at screening, Day 30, follow-up and at early termination (if applicable). 12-lead ECGs will be recorded in triplicate at all other times as detailed in the Schedule of Activities given in the protocol. The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter.

ECG endpoints include heart rate, QT interval, PR interval and QRS interval. If not supplied QTcF will be derived using Fridericia's heart rate correction formula:
QTcF = QT / (RR)^(1/3), where RR = 60/HR (if RR is not provided). Baseline will be defined as the time-matched value from the average of the triplicate recordings on Day -1.

The maximum absolute value (postdose) and the maximum increase from baseline for QTcF and heart rate will be determined from Day 1 to Day 14 and Day 15 to Day 28 separately, and also over all measurements taken postdose for QTcF, heart rate, PR and QRS. The maximum increase from baseline will be calculated by first subtracting the time-matched baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

The time-matched double difference in heart rate, QT, QTcF, PR and QRS measures is calculated in the following steps: (1) subtract predose value on Day 1 from all postdose values; (2) subtract the value at 0 hours on Day -1 from all other values on Day -1; (3) take the difference between the adjusted postdose value in (1) and its time-matched value in (2).

6.2.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

6.2.5.1. Change from baseline in HbA1c

Baseline for HbA1c will be defined as the Day -1, 0H time point.

The change from baseline to Day 28 will be calculated for HbA1c.

6.3. Pharmacokinetic Endpoints

Blood and urine samples for PK analysis of PF-06882961 CCI [redacted] will be taken according to the Schedule of Activities given in the protocol.

PK parameters for plasma PF-06882961 CCI [redacted] and PF-06882961 urine PK parameters following single and multiple dose administration of PF-06882961 will be derived using standard noncompartmental methods, as data permit for each treatment and Day (as appropriate), from the concentration time profiles in the table as follows:

Parameter	Analysis Scale	PF-06882961	CCI [redacted]
Plasma Parameters			
AUC_{24}	ln	D	D
AUC_{24}(dn)	ln	D	
AUCτ	ln	D	D
AUCτ(dn)	ln	D	

Parameter	Analysis Scale	PF-06882961	CCI [redacted]
C_{max}	ln	D	D
C_{max}(dn)	ln	D	
T_{max}	R	D	D
$t_{1/2}$*	R	D	
PTR	ln	D	
R_{ac}	ln	D	D
C_{av}	ln	D	
C_{min}	ln	D	
R_{ac}, C_{max}	ln	D	D
CL/F*	ln	D	
V_Z/F*	ln	D	
Urine Parameters			
Ae_{24}	ln	D	
Ae_{24}%	ln	D	
CL_r	ln	D	

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits.

For BID dosing, parameters will also be calculated for both dosing intervals (0-10 hr = interval 1 and 10-24 hr = interval 2) and will be displayed as C_{max1}, C_{max2}, T_{max1}, T_{max2}, $AUC_{\tau1}$, $AUC_{\tau2}$, $R_{acCmax1}$. However, R_{ac} will and $R_{ac,Cmax}$ will only be reported for the first interval (0-10 hr)... They should be presented with the same descriptive statistics as all other corresponding PK parameters.

CCI [redacted]

CCI

CCI

CCI [redacted]

[redacted]

6.6. Covariates

Full details on the covariates to be included in analyses are given in Section 8.1.3 and 8.1.4.

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 dose with ≥3 evaluable measurements.

If a subject receives a dose that was not assigned based on the randomized titration scheme (for example due to a down-titration), the data from that Day will not be included in any summary statistics but will be included in listings.

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.

CCI [redacted]

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

Unless otherwise specified for safety (Section 8.4) and other analyses (Section 8.3), the placebo groups will be pooled by frequency of dosing (QD and BID, if applicable), along with one overall pooled group. CCI [redacted]

In this section (excluding PK analyses), 'treatment' refers to the randomized treatment labels that will be provided from GRAABS or the programming plan (along with placebo as above where relevant). Otherwise, 'steady-state dose' refers to the dose that subjects received during the Day 15 to Day 28 period (only applicable to cohorts that had 2 weeks titration and a BID regimen as per Cohorts 1-5). In the case where subjects do not complete this period and/or have multiple doses during this period, the dose most received during this period will be used for analyses. An additional listing of the treatment and steady-state dose for applicable subjects will be produced (including placebo subjects from the same cohorts).

As it is unknown to what extent subjects will be unable to reach the dose targeted as per the randomized treatment, based on emerging data additional tables and/or figures may need to be produced to aid in the interpretation of the safety and tolerability of PF-06882961. For example this could include, but is not limited to, producing AE tables restricted to events occurring during Day 15 to Day 28 only. If changes are required to currently specified tables and/or figures and additional outputs are required, this would be addressed with a SAP amendment prior to database closure.

8.1. Statistical Methods

8.1.1. Summary Analyses for Continuous Data

Continuous endpoints and relevant safety endpoints will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

8.1.2. Summary Analyses for Categorical Data

Categorical endpoints and relevant safety endpoints will be presented using summary statistics: number of observations, counts and percentages.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

CCI

CCI

CCI

CCI [redacted]

8.1.6. Analysis of Covariance

The ANCOVA model will include the change from baseline of the relevant endpoint as specified in Section 8.4.9 as the dependent variable and will include treatment as a fixed effect and baseline as a covariate.

Missing values will not be imputed.

The Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each treatment. Differences in LSMeans between each treatment and placebo, together with 90% confidence intervals and standard errors, will also be obtained.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in Appendix 3.

8.2. Statistical Analyses

8.2.1. Pharmacokinetic Analysis

To assess the pharmacokinetics of PF-06882961CCI [redacted] the PK parameters detailed in Section 6.3 will be listed and summarized for subjects in the PK analysis set (as defined in Section 5.2.2). Missing values will be handled as detailed in Section 7 (along with handling of values where subjects received a dose that was not assigned based on the titration scheme). Each PK parameter will be summarized by analyte, matrix, treatment (differentiating different doses, dosing frequencies and formulations as required), and Study Day (Day 1, 14, 21 or 28 as applicable).

The parameters will include the set of summary statistics as specified in the table below:

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Matrix	Summary Statistics
AUC_{24}, $AUC_{24}(dn)$, AUC_{τ}[a], $AUC_{\tau}(dn)$[a], C_{max}[a], $C_{max}(dn)$[a], PTR, R_{ac}, C_{av}, C_{min}, $R_{ac, Cmax}$ CL/F, Vz/F	Plasma	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
[a]T_{max}	Plasma	N, median, minimum, maximum.
$t_{1/2}$	Plasma	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.
Ae_{24}, Ae_{24}%, CL_r	Urine	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

[a] For BID dosing, parameters will also be calculated for both dosing intervals (0-10 hr= interval 1 and 10-24 hr =interval 2) and will be displayed as C_{max1}, C_{max2}, T_{max1}, T_{max2}, $AUC_{\tau1}$, $AUC_{\tau2}$, $R_{acCmax1}$.

There will be one summary table for each analyte and matrix presenting all PK parameters. The treatment subheading will include the analyte, matrix, dose information and day (Day 1, Day 14, Day 21 or Day 28). As per Section 7.3, data collected on days that subjects received anything other than the assigned dose based on the titration scheme will only be listed and not summarized as part of the summary table.

To assess the relationship between the PK parameters and dose for PF-06882961, dose normalized AUC_{24} C_{max1} (BID) and C_{max} (QD) will be plotted against treatment (using a logarithmic scale) for Day 1 and Day 28 separately and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose (total daily dose for AUC_{24} and dose for C_{max}). For C_{max}, only BID cohorts will be included in this analysis. For AUC_{24}, BID and QD C CI cohorts (ie, CCI formulation excluded) will be included in the same plot and different symbols will be used to delineate dosing regimen. A footnote will be added to the plots to indicate that geometric means are presented.

Natural log transformed AUC_{24} and C_{max} will be analyzed using an MMRM approach, restricted to the BID dosing regimens only. The MMRM model will include dose, day (as a factor) and dose*day as fixed effects, with day fitted as a repeated effect, and subject as a random effect. An unstructured covariance matrix will be used to estimate the variances and covariance within subject across time points. If convergence is not obtained or model fit is not adequate then other covariance structures will be investigated as necessary. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. Example code is given in Appendix 3. The purpose of these analyses is to

obtain estimates of the intra-subject variation to assist in the planning of future studies. No treatment contrasts will be provided.

The observed accumulation ratio for AUC_{24} (QD) or $AUC_{\tau 1}$ (BID) and C_{max} (QD) or C_{max1} (BID) will be *analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation for each* dose.

Supporting data from the estimation of t½ will be listed where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); 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 PF-06882961 CCI [redacted] concentrations will include (produced separately):

- a listing of all concentrations sorted by subject ID, treatment, analyte, and matrix and nominal time postdose. 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 by treatment, analyte and nominal time postdose, 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 concentrations time plots (on both linear and semi-log scales) against nominal time postdose by analyte (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose), for Day 1 and Day 28.

- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by analyte (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose), for Day 1 and Day 28.

- individual concentration time plots by treatment and analyte (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale), paged by day (excluding times with only two points, eg, Day 21 for Cohorts 1 & 2 and Day 14 for Cohorts 3 & 4).

- individual concentration time plots by cohort (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each cohort per scale), paged by day (excluding times with only two points, eg, Day 21 for Cohorts 1 & 2 and Day 14 for Cohorts 3 & 4) and coloured by treatment.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06882961 concentration is quantifiable in the matrix.

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.

Metabolite screening may be conducted at selected dose(s) first; based on these results a decision on whether or not to analyze samples from remaining doses may be made. As part of understanding the properties of the study drug, urine samples may be used for evaluation of the bioanalytical method as well as for other internal exploratory purposes. These data would be used for internal exploratory purposes and would not be included in the CSR.

CCI

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[redacted]

CCI

CCI

CCI [redacted]

[redacted]

[redacted]

8.4. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06882961.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 6.2 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set.

8.4.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition. Frequency counts will be supplied for subject discontinuation(s) by treatment.

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

8.4.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, gender, race, and ethnicity. The physical measurement (weight, body mass index and height) at baseline will also be summarized. Each will be summarized by treatment and 'All Subjects' in accordance with the sponsor reporting standards.

An additional table summarizing the screening data of CCI [redacted] HbA1c will be produced as above.

An additional table will be produced that summarizes (as per Section 8.1.1) the overall baseline (as defined in Section 6) across all subjects for each of the following parameters:
CCI [redacted]

8.4.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

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

8.4.4. Adverse Events

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

Incidence and severity of treatment emergent adverse event (TEAE) tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment group and overall.

8.4.5. Hypoglycemia Monitoring and Reporting

The hypoglycemic AEs will be listed in a separate table and summarized categorically by treatment as per Section 8.1.2.

8.4.6. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 6.2.2.

8.4.7. Vital Signs Data

Absolute values and change from time-matched baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment, time post-dose and day, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.3.

Mean change from time-matched baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time post-dose and day. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure using a single line for the placebo group(s). Corresponding individual plots of change from time-matched baseline will also be produced for each treatment.

Maximum absolute values and change from time-matched baseline for vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of subjects 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.

The time-matched double differences in vital signs obtained following the Day 1 treatment, as defined in Section 6.2.3, will be summarized (N, mean, 90% confidence interval) for each treatment and time point. In addition, the time-matched double differences between each treatment and placebo will be summarized (N, mean, 90% confidence interval) for each treatment, time post-dose and day.

Mean time-matched double differences in vital signs will be plotted against time post-dose for Days 1, 14, 21 and 28 separately. On each plot there will be 1 line for each treatment and a single line for the placebo group(s). Corresponding individual plots of time-matched

double differences will also be produced for each treatment. The mean plots will similarly be produced for the time-matched double differences between each treatment and placebo.

8.4.8. ECG Data

Absolute values and change from time-matched baseline in QT interval, heart rate, QTcF interval, PR interval and QRS interval will be summarized by treatment and time postdose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.4.

Mean change from time-matched baseline in ECG parameters will be plotted against day (for Days 1, 14, 21 and 28). On each plot there will be 1 line for each treatment and a single line for the placebo group(s). Corresponding individual plots of change from time-matched baseline will also be produced for each treatment.

Maximum increase from time-matched baseline (Day 1 to Day 14, Day 15 to Day 28 and overall, produced separately) for QTcF and heart rate will be summarized by treatment, according to sponsor reporting standards.

ECG endpoints and change from time-matched baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1 (for QTc these correspond to the Pfizer Guidance as referenced in Section 9). Numbers and percentages of subjects 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.

Listings of subjects with any single post-dose value >500 msec will also be produced for QTcF.

The time-matched double differences in QT, QTcF, PR, QRS intervals and heart rate measures obtained following the Day 1 treatment, as defined in Section 6.2.4, will be summarized (N, mean, 90% confidence interval) for each treatment and time point. In addition, the differences between each treatment and placebo will be summarized (N, mean, 90% confidence interval) for each treatment, time postdose and day.

Mean time-matched double differences in ECG parameters will be plotted against time postdose for Days 1, 14, 21 and 28 separately. On each plot there will be 1 line for each treatment and a single line for the placebo group(s). Corresponding individual plots of time-matched double differences will also be produced for each treatment. The mean plots will similarly be produced for the time-matched double differences between each treatment and placebo.

The time-matched double differences in QTcF will be plotted against PF-06882961 concentration. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment.

QTcB will be listed only and not summarized.

8.4.9. Other Safety Data

The change from baseline to Day 28 for HbA1c will be included in an ANCOVA model as described in Section 8.1.6. The LSMeans and LSMean differences to placebo for each treatment (with 90% confidence intervals) will also be plotted.

Absolute values and change from baseline will be summarized descriptively by treatment and timepoint as described in Section 8.1.1.

8.4.10. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings. A separate listing restricted to metformin will also be produced.

8.4.11. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, will be obtained at Screening.

These data will be listed.

9. REFERENCES

1. Rocío Lledó-García, Norman Mazer, Mats Karlsson (2013) A semi-mechanistic model of the relationship between average glucose and HbA1c in healthy and diabetic subjects, J Pharmacokinet Pharmacodyn, 40:129-142.

2. Pfizer Guidance for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018.

3. Neal Thomas, Kevin Sweeney & Veena Somayaji (2014) Meta-Analysis of Clinical Dose–Response in a Large Drug Development Portfolio, Statistics in Biopharmaceutical Research, 6:4, 302-17.

4. Phil Woodward (2011) Bayesian Analysis Made Simple: An Excel GUI for WinBUGS. Chapman & Hall/CRC Biostatistics Series.

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Appendix 3. Example SAS Code for Statistical Analyses

MMRM for PK analysis:

```
proc mixed data = input_dataset method = reml;
        class subject dose day;
        model pk_var = dose day dose*day /ddfm = kr residual;
        repeated day/ subject = subject type = un;
run;
```

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ANCOVA for Safety analysis:

```
proc mixed data = dataset method = ml;
        class treatment;
        model cfb = treatment base /residual;
        lsmeans treatment / diff cl alpha = 0.1;
run;
```

[redacted]

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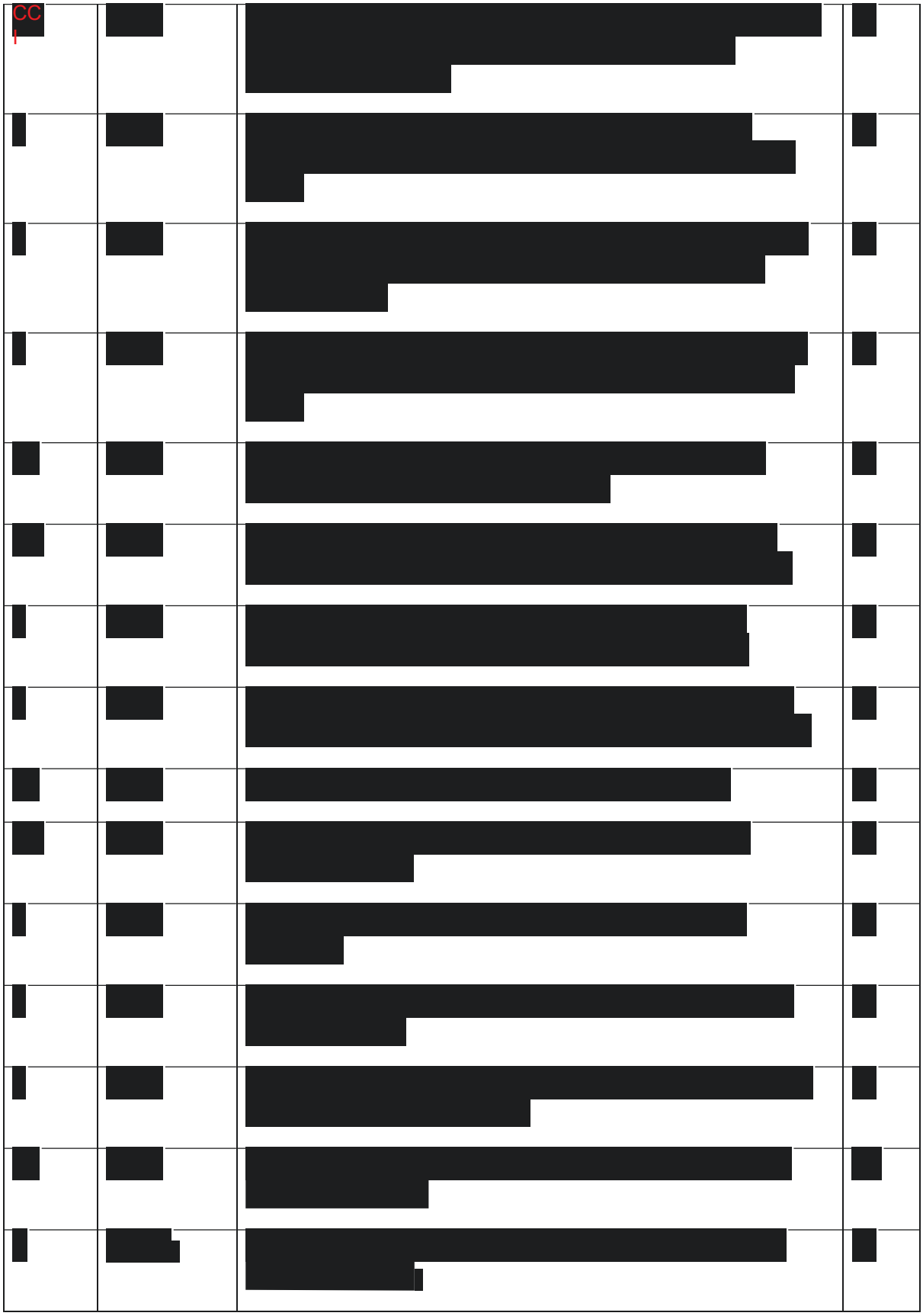

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Appendix 5. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

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
Standing pulse rate (bpm)	min. <40	max. >140