Protocol C3991002

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE ESCALATING ORAL DOSES OF PF-07081532 IN ADULT PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 10-Jul-2020

[redacted]

[redacted]

TABLE OF CONTENTS

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LIST OF TABLES

CCI [redacted]

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol / Amendment	Rationale	Specific Changes
1 10-Jul-2020	Original 16-Jan-2020	N/A	N/A

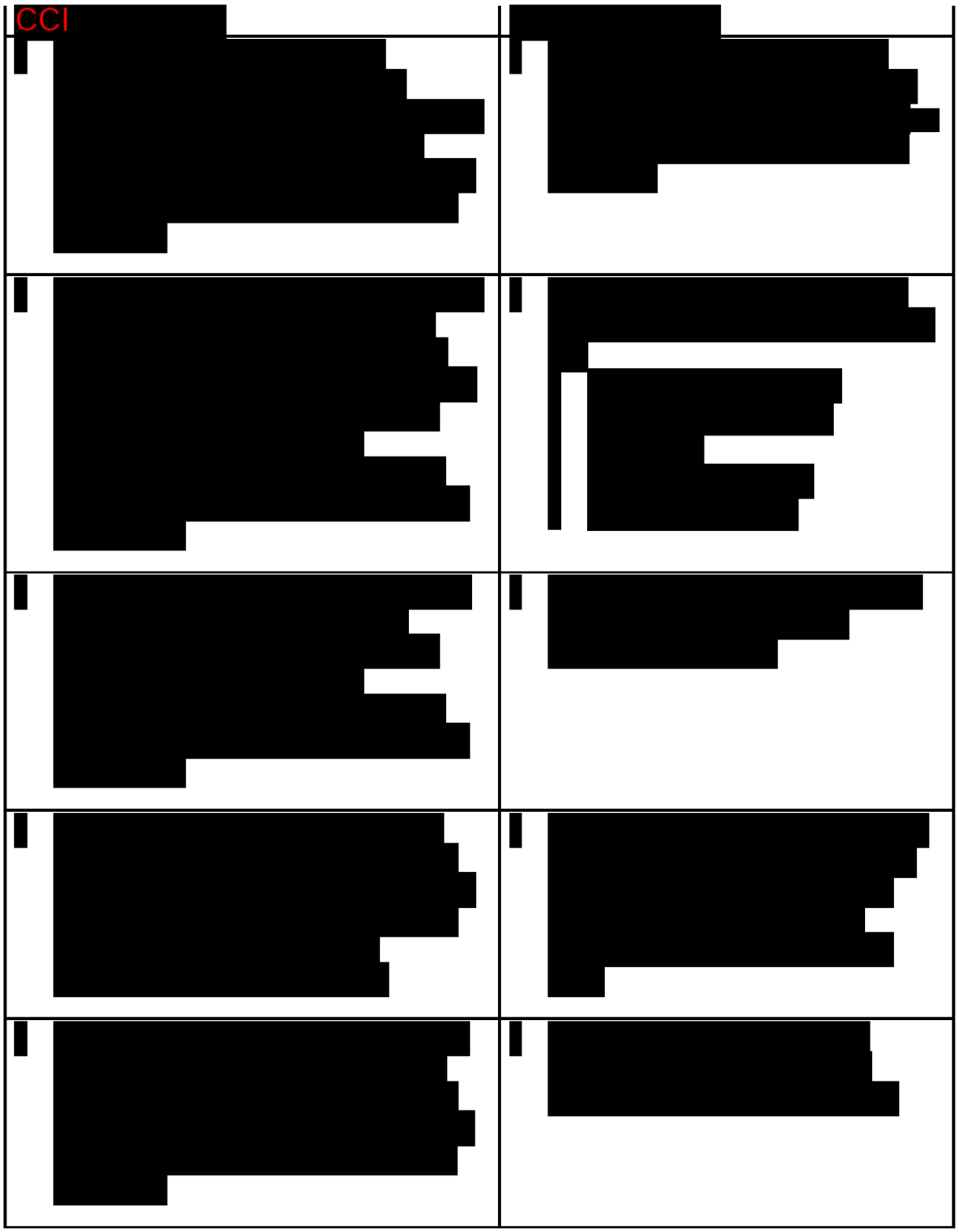
2. INTRODUCTION

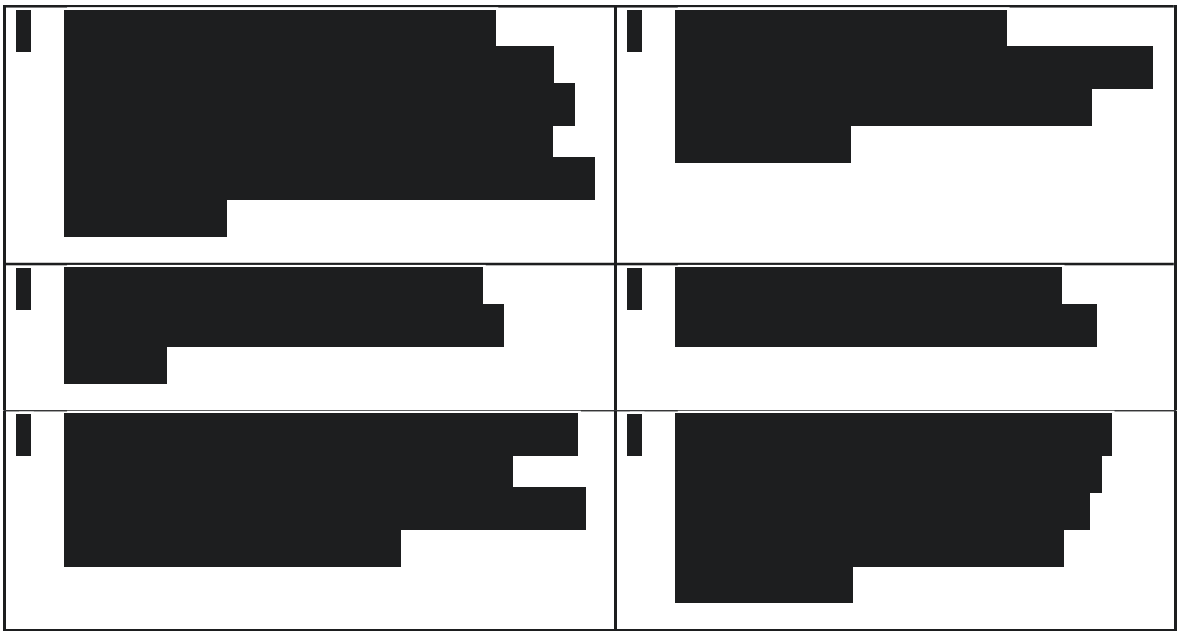
The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple oral doses of PF-07081532 in participants with inadequately controlled T2DM on metformin and optionally in non-diabetic obese participants. CCI [redacted]

This statistical analysis plan (SAP) provides the *detailed methodology for summary and statistical analyses of the data collected* in Study C3991002 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

Primary Objective:	***Primary Endpoints:***
• *To evaluate the safety and tolerability of escalating, multiple doses of PF-07081532, orally administered to adult participants with T2DM inadequately controlled by metformin and, if conducted, to non-diabetic obese participants.*	• *Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.*
Secondary Objectives:	***Secondary Endpoints:***
• *To characterize plasma PK of PF-07081532 following multiple doses administered orally to adult participants with T2DM inadequately controlled on metformin and, if conducted, to non-diabetic obese participants.*	• *PF-07081532 plasma PK parameters AUC_{24}, C_{max}, T_{max}, $t_{½}$ on Day 1 and following multiple, oral dose administration, as data permit.*
• *To characterize the urine PK of PF-07081532 following multiple doses administered orally to adult participants with T2DM inadequately controlled on metformin.*	• *Urine PK parameters for PF-07081532, as data permit: Ae_{24}, Ae_{24}%, and CLr following multiple, oral dose administration, as data permit.*





2.1.1. Primary Estimand(s)

Not applicable because C3991002 is a Phase 1 study with no estimands on safety endpoints

2.1.2. Secondary Estimand(s)

Not applicable because C3991002 is a Phase 1 study with no estimands on PK parameters

2.1.3. Additional Estimand(s)

Not applicable because C3991002 is a Phase 1 study with no estimands on exploratory/tertiary endpoints

2.2. Study Design

This is a randomized, double-blind (investigator- and participant-blind), sponsor-open, placebo-controlled, multiple oral dose-escalating study of PF-07081532.

There may be 2 participant populations enrolled in this study: participants enrolling with T2DM and non-diabetic obese participants. The study will be conducted in up to 3 parts, portions of which may be conducted concurrently.

***Part A**: adult participants with T2DM inadequately controlled on metformin who will receive PF-07081532 or placebo daily for 28 days. Up to 5 such cohorts will be enrolled, with approximately 10 participants (8 PF-07081532: 2 placebo) per cohort. For individual participants in Part A, the duration of the study from the Screening visit to the on-site follow-up visit will be approximately 10 weeks of which approximately 33 days will be inpatient at the CRU.*

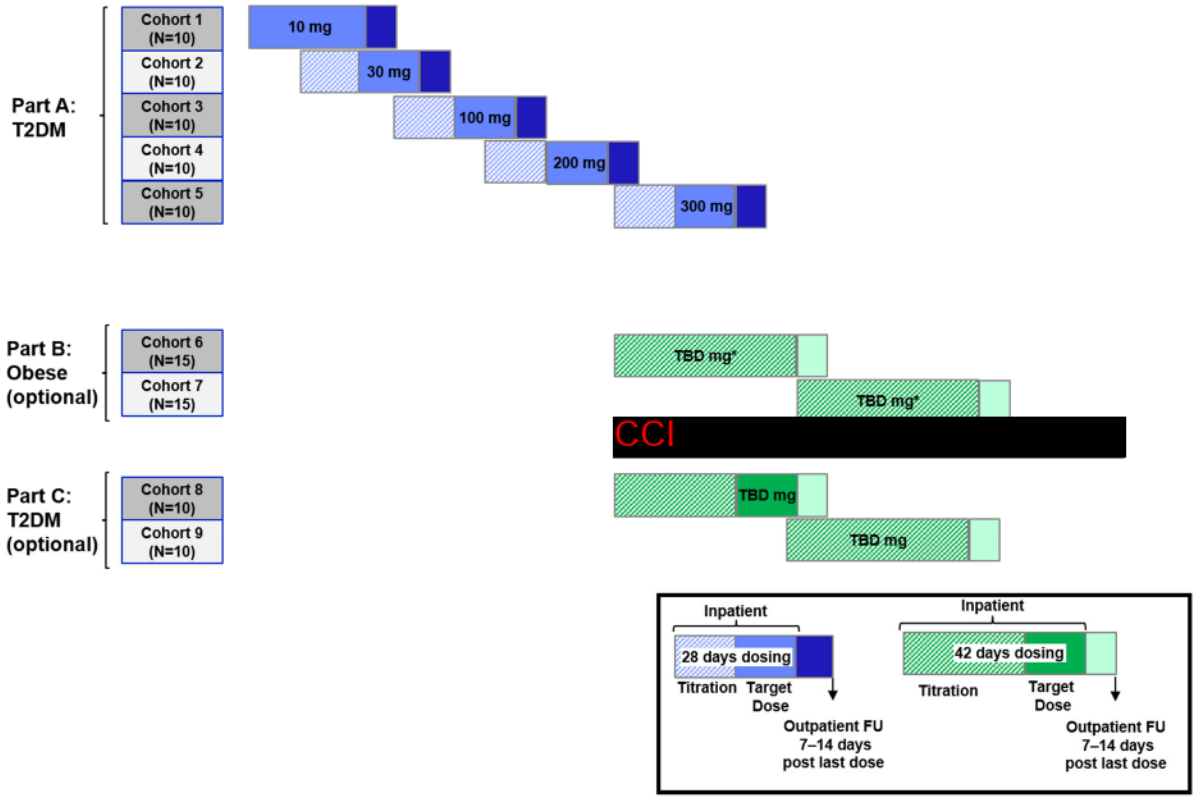
***Part B (optional)**: obese (non diabetic) adult participants who will receive PF-07081532 or placebo daily for 42 days. This is an optional study part for which up to 2 cohorts may be enrolled with approximately 15 obese participants (12 PF-07081532: 3 placebo) per cohort.* CCI [redacted] *For individual participants in Part B, the duration of the study from the Screening visit to the on-site follow-up visit will be approximately 12 weeks of which approximately 48 days will be inpatient at the CRU.*

***Part C (optional)**: adult participants with T2DM inadequately controlled on metformin who will receive PF-07081532 or placebo daily for 42 days. Up to 2 cohorts of 10 participants (8 PF-07081532: 2 placebo per cohort) may be enrolled if judged necessary to meet the study objectives. For individual participants in Part C, the duration of the study from the Screening visit to the on-site follow-up visit will be approximately 12 weeks of which approximately 47 days will be inpatient at the CRU.*

In all study parts, participants will initially return to the clinical research unit (CRU) 7 to 14 days after the last administration of IP for an on-site follow-up visit. A further follow-up contact with participants will be conducted at least 28 days and up to 35 days after the last administration of IP; this contact may be done via a phone call.

The study will be conducted in the US. Where more than 1 site participates in a given cohort, an attempt will be made to have at least 1 participant randomized to placebo per participating site, which will be facilitated through block randomization. Participants who discontinue prior to completion of the study may be replaced, at the discretion of the principal investigator (PI) and sponsor.

Figure 1. Sample Study Design



This schema is for illustrative purposes only*. Dose levels represent PF-07081532 or matching placebo. Dose levels provided here may be adjusted based on emerging data. Doses for Parts B and C, if conducted, will be determined based on emerging data.*

Some cohorts may have titration schedules of less than, or more CCI [redacted].

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The safety endpoints which will be measured during the study constitute the primary endpoints. 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) for Parts A, B and C:

- *Adverse events;*
- *Laboratory data;*

- *Vital signs data;*
- *ECG results.*

3.1.1. 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 during follow-up (ie post-dose non treatment period)) will be counted as treatment emergent and attributed to the previous treatment taken.

3.1.1.1. Hypoglycemia Monitoring and Reporting

Hypoglycemia AEs will be recorded in the Case Report Form (CRF) on a specific page. Details of when these will be recorded are given in the protocol Section 8.2.4.2.

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 participant 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.

3.1.2. Safety Laboratory Tests

Safety laboratory tests as described in Section 10.2 Appendix 2 of the protocol will be performed at times defined in the schedule of activities.

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

3.1.3. Vital Signs

Single supine blood pressure and pulse rate measurements will be taken at Screening, 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.

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).

3.1.4. Electrocardiograms

A single 12-lead ECG will be obtained on all participants at screening, 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 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)

3.2. Secondary Endpoint(s)

Blood and urine samples for PK analysis of PF-07081532 will be taken according to the Schedule of Activities given in the protocol.

Plasma and urine PF-07081532 PK parameters following single or multiple dose administration of PF-07081532 will be derived using standard noncompartmental methods, as data permit, for each treatment and day (as appropriate), from the concentration time profiles as follows:

Table 2. PF-07081532 PK Parameters

Parameter	Analysis Scale	PF-07081532
AUC_{24}	ln	D
CCI		
C_{max}	ln	D
CCI		
T_{max}	R	D
$t_{1/2}$*	R	D
CCI		
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.

CCI

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CCI

[redacted]

CCI [redacted]

[redacted]

3.4. Baseline Variables

Baseline for all parameters discussed in section 5 and 6 will be defined as the values assessed on Day -1 or Day 1 0H (ie pre-dose).

When three assessements are performed at baseline, the baseline will be the average of the three values CCI [redacted]

3.5. Safety Endpoints

See section 3.1.

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.

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated. If a participant 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 CCI analyses, where applicable.

Participants 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 (eg medication errors) will be compiled and reviewed to identify major and minor deviations prior to database closure.

Population	Description
Enrolled	*All participants who sign the ICD.*
Randomly assigned to investigational product	*All participants randomly assigned to investigational product regardless of whether or not the investigational product was administered.*
Evaluable	*All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.*
Safety	*All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.*
PF-07081532 *PK Concentration Set*	*The* PF-07081532 *PK concentration population is defined as all randomized participants who received at least 1 dose of PF-07081532 and in whom at least 1 plasma concentration value is reported.*
PF-07081532 *PK Parameter Set*	*The* PF-07081532 *PK parameter population is defined as all randomized participants who received at least 1 dose of PF-07081532 and in whom at least 1 parameter value is reported.*
[redacted]	CCI [redacted]
[redacted]	[redacted]

Population	Description
[redacted]	CCI [redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Not applicable

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Not applicable

5.2.2. Analyses for Continuous Endpoints

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

5.2.3. Analyses for Categorical Endpoints

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

5.2.4. Longitudinal Analysis using Mixed Model Repeated Measures (MMRM) model

MMRM models will include the change from baseline of the relevant endpoints as specified in Section 6 as the dependent variable and will include treatment, baseline, day, baseline*day interaction and the day*treatment interaction, with day fitted as a repeated effect, and participant as a random effect.

An unstructured covariance matrix will be used to estimate the variances and covariance within participant 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. Missing values will be imputed as part of the MMRM model assumptions.

The Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each treatment and day. 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.

5.2.5. Bayesian Emax Model

A Bayesian dose-response Emax model will be CCI [redacted] and applied to the change from baseline (CFB) to Day 28 (Part A) and (as sensitivity analysis) Day 42 (Part C) CCI [redacted] A four-parameter Emax model will include sustained dose for at least 5 days (ie after completing titration phase) as a continuous variable and baseline CCI [redacted] as a covariate. The change from baseline will be assumed to be normally distributed with mean of '*Pred*' and standard deviation of '*Sigma*' as defined below:

CFB = Normal(*Pred*, *Sigma*)

Where:

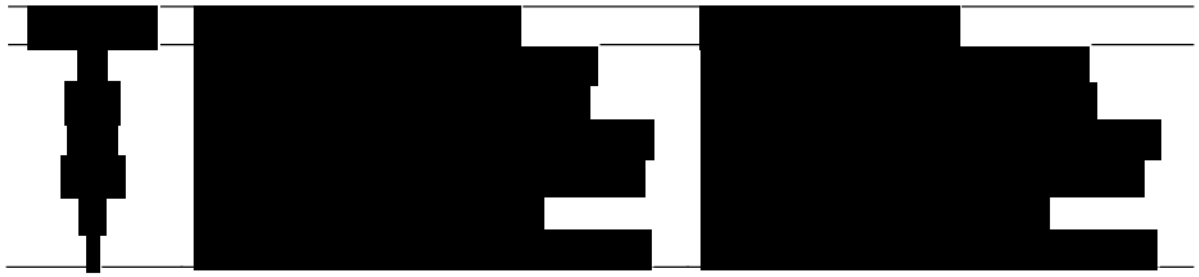
$$Pred = E_0 + \frac{E_{max} \times dose^{Hill}}{ED_{50}{}^{Hill} + dose^{Hill}} + \beta_1 \times Base$$

$$\tau = \frac{1}{Sigma^2}$$

Informative and vague priors will be included as specified in Table 4.

Details around the derivation of these priors are provided in Appendix 2.2.1. The selections of the informative priors (Prior List 1) were based on historical data and/or credible ranges for the parameters and are primarily used to aid model convergence. The vague priors (Prior List 2) are less informative and as such provide a sensitivity analysis to the informative priors.

CCI [redacted]



This analysis will be conducted by the study statistician in OpenBUGS or ClinDR. QC of the analysis will be conducted by an independent statistician using the same and different starting values to test convergence of the chains, and the .txt outputs will be provided to the programming team for inclusion in the final CSR table formats.

Markov chain Monte Carlo (MCMC) methods will be used as a means of sampling from the posterior distribution of interest from the Emax model. MCMC algorithms, using Gibbs sampling, will enable calculation of the posterior distribution of the treatment differences to placebo with incorporation of the priors above.

Three chains will be run, with three diverse sets of initial values. 525,000 samples will be generated for the informative priors and 1,025,000 for vague priors and the first 25,000 will be discarded to allow for burn-in. A thin of 10 will also be originally used for the informative priors and a thin of 20 for the vague priors, resulting in 50,000 samples for summarizing the posterior nodes of interest.

If there is evidence that the chain has not converged by the end of the first 25,000 samples, the burn-in should be increased until the chains are consistent with convergence. If the MCMC error of any of the nodes of direct interest (ie, PredMeans, Diff, Prob.C1, Prob.C2) is greater than 5% of the posterior standard deviation of that node then, assuming convergence has occurred, the number of samples post burn-in may be increased so that this MCMC Error criterion is met. All other nodes monitored should be an equivalent rule, but with a 10% margin.

Model diagnostics will be examined, including trace plots, Brooks-Gelman-Rubin diagnostic plot and autocorrelation plots. If these result in concerns over model convergence, the model may be re-run with small changes such as different initial values or an increased number of samples/thinning. The final trace plots, Brooks-Gelman-Rubin diagnostic plot and autocorrelation plots will not be output for inclusion in the study report.

The posterior means, standard deviations, and 90% credible intervals (5^{th} and 95^{th} percentiles of the relevant posterior distribution) will be derived for each steady-state dose and for each steady-state dose contrast relative to placebo.

Statistical Model Diagnostics

The presence of outliers will be investigated for this analysis. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A listing will be presented of any participants meeting these criteria. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, QQ plot and summary of fit statistics. The residual plots will not be included in the clinical study report.

If there are outliers or major deviations from normality then the effect of these on the conclusions will 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.

Example OpenBUGS code to fit this model, extract residuals and the process for this analysis is provided in Appendix 3.1.

5.2.6. Emax Model with baseline interaction

A 3-parameter dose-response Emax model with a baseline interaction will be CCI [redacted] and applied to the change from baseline (CFB) to Day 28 (Part A) and (as sensitivity analysis) Day 42 (Part C) CCI [redacted] The Emax model will include steady-state

dose as a continuous variable and baseline [redacted] as an interaction with Emax. The change from baseline will be assumed to be normally distributed with mean of '*Pred*' and standard deviation of '*Sigma*' as defined below:

CFB = Normal(*Pred*, *Sigma*)

Where:

$$Pred = E_0 + \left(\frac{Base}{B}\right)^{\beta_1} \times \frac{E_{max} \times dose}{ED_{50} + dose}$$

B is the mean overall baseline of participants included in the [redacted]. Missing values will not be imputed.

The Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each steady-state dose and day. Differences in LSMeans between each steady-state dose 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 3.2.

5.2.7. Analysis of Covariance (Raw Scale)

The ANCOVA model will include the change from baseline of the relevant endpoint as specified in Section 6 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 3.2.

5.2.8. Analysis of Covariance (Log Scale)

The ANCOVA model will include the natural logarithmic transformed of relative change from baseline of the relevant endpoint as specified in Section 6 as the dependent variable and will include treatment as a fixed effect and baseline as a covariate.

Missing values will not be imputed.

The adjusted geometric Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each treatment. Differences in adjusted geometric 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 3.2.

5.3. Methods to Manage Missing Data

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

5.3.1. Pharmacokinetic Concentrations Below the Limit of Quantification

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

5.3.2. 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/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, 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 participant receives a dose that was not assigned based on the randomized titration scheme (for example due to a down-titration), the PK data from that Day will not be included in the calculation of summary statistics but will be included in listings.

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 and will not be included in the calculation of summary statistics or statistical analyses.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6. ANALYSES AND SUMMARIES

6.1.1. Safety Analysis

- Estimand strategy: Not applicable
- Analysis set: Safety set

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-07081532.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 3.1 will be listed and summarized in accordance with sponsor reporting standards, Did you have by any chance review the PIPD in CORD -> I can endorse itTreatment and Disposition of Subjects

Applicable to Parts A, B and C – Analyses reported for each part separately.

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.

6.1.1.1. Demographic and Physical Examination Data

Applicable to Parts A, B and C – Analyses reported for each part separately.

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] and HbA1c will be produced as above.

Finally, data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data (unless noted above), duration of diabetes will be reported for randomized participants.

6.1.1.2. Discontinuation(s)

Applicable to Parts A, B and C – Analyses reported for each part separately.

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.

6.1.1.3. Adverse Events

Applicable to Parts A, B and C – Analyses reported for each part separately:

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.

6.1.1.4. Hypoglycemia

Applicable to Parts A, B and C – Analyses reported for each part separately.

Any hypoglycemic AEs will be listed in a separate table and summarized categorically by treatment as per Section 5.2.3.

6.1.1.5. Laboratory Data

Applicable to Parts A, B and C – Analyses reported for each part separately:

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.4.

6.1.1.6. Vital Signs Data

Applicable to Parts A, B and C – Analyses reported for each part separately:

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 3.4.

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 be summarized descriptively by treatment using categories as defined in Section 5.2.3. Numbers and percentages of subjects meeting the categorical criteria will also 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 3.4, 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 each Days as defined in the SoA 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.

6.1.1.7. ECG Data

Applicable to Parts A, B and C – Analyses reported for each part separately.

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 3.4.

Mean change from time-matched baseline in ECG parameters will be plotted against day. 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, Day 29 to 42 (when applicable) 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 Section 5.2.3 (for QTc these correspond to the Pfizer Guidance as referenced in Section 8). 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 5.2.2, 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 each Days as defined in the SoA 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-07081532 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.

6.2. Primary Endpoint

6.3. Secondary Endpoint(s)

6.3.1. PF-07081532 PK Parameters

Applicable to Parts A, B and C – Analyses reported for each part separately.

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

To assess the pharmacokinetics of PF-07081532, the PK parameters detailed in Section 3.2 will be listed and summarized for participants in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3 along with handling of values where participants received a dose that was not assigned based on the titration scheme). Each PK parameter will be summarized by, matrix, treatment (eg differentiating different doses and dosing frequencies as required), and Study Day (Day 1, 14, 21, 28, or 42, as applicable).

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

Table 6. PF-07081532 PK Parameters to be Summarized Descriptively

Parameter	Matrix	Summary Statistics
AUC_{24}, CCI C_{max}, CCI	Plasma	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
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%.

There will be one summary table for each matrix presenting all PK parameters. The treatment subheading will include the analyte, matrix, dose information and day (Day 1, Day 14 or Day 21, Day 28 or Day 42). As per Section 5.3.3, data collected on days that participants 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-07081532, dose normalized AUC_{24} and C_{max} will be plotted against treatment (using a logarithmic scale) for Day 1, Day 28 (Parts A, B and C), and Day 42 (for Parts B and C only) separately and will include individual participant 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. A footnote will be added to the plots to indicate that geometric means are presented.

The observed accumulation ratio for AUC_{24} and C_{max} 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-07081532 concentrations will include:

- a listing of all concentrations sorted by participant ID, treatment, 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, 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 (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose), for Day 1, Day 28 and Day 42 (for Parts B & C only).
- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose), for Day 1, Day 28 and Day 42 (for Parts B & C only).
- individual concentration time plots by treatment and (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.
- 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 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-07081532 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 participant plots by time, the actual PK sampling time will be used.

CCI [redacted]

[redacted]

[redacted]

Part C: The change from baseline over time will be included in an MMRM model as

CCI

[redacted]

CCI

[redacted]

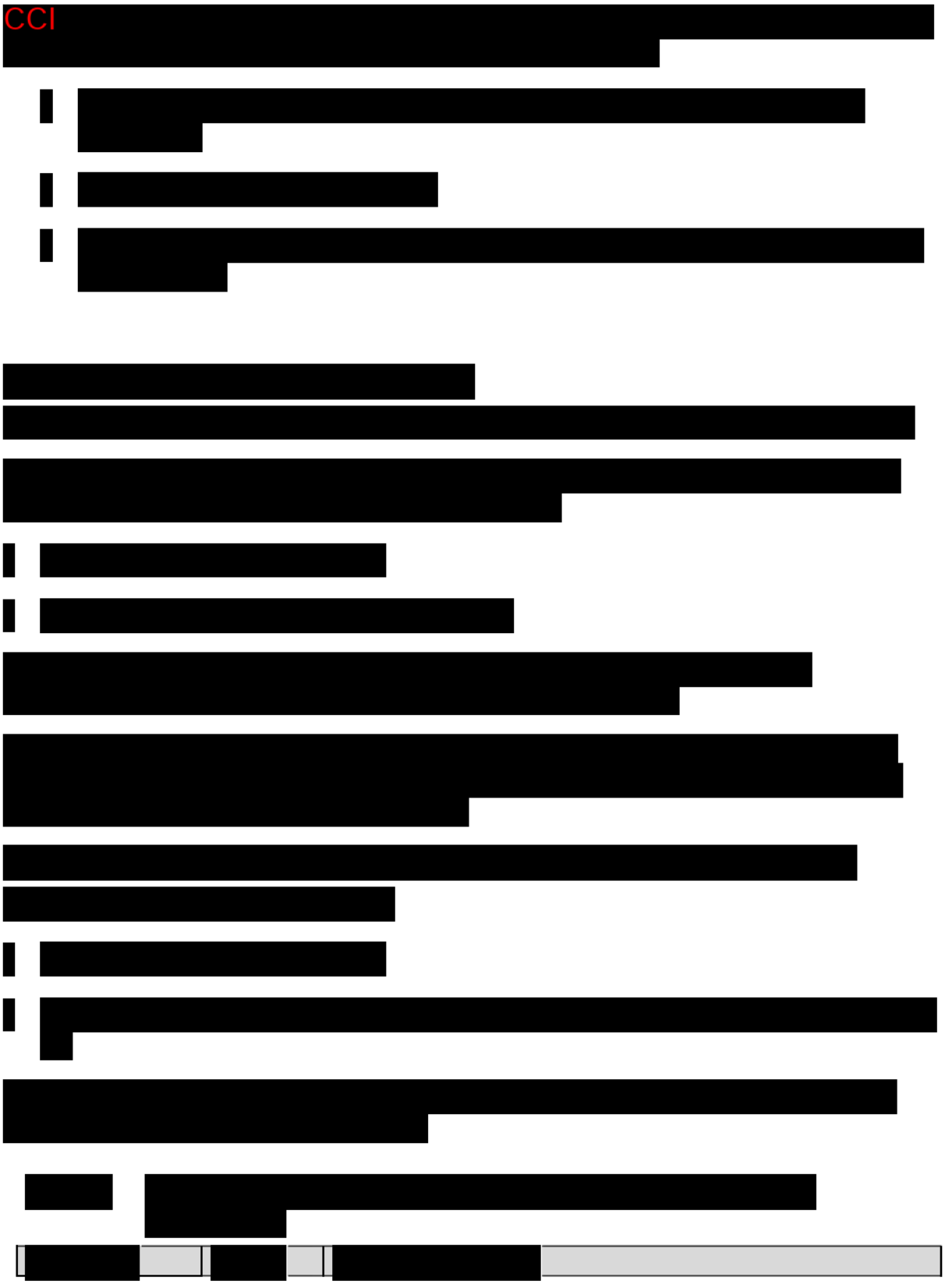
[redacted]

CCI

[redacted]

[redacted]

CCI



CCI		

CCI [redacted]

6.5. Subset Analyses

Not applicable.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

For each part of the study, and for each endpoint defined in this statistical analysis, baseline assessment will be summarized by treatment as per Section 5.2.2 and Section 5.2.3.

CCI [redacted]

6.6.2. Study Treatment Exposure

For each part of the study, participant treatment exposure groups will be reported. Frequency counts will be supplied for participant discontinuation(s) by treatment.

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

6.6.3. Concomitant Medications and Nondrug Treatments

For each part of the study, 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 for Parts A and C.

6.6.4. Screening and Other Special Purpose Data

For each part of the study, prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, will be obtained at Screening.

These data will be listed.

CCI [redacted]

7. INTERIM ANALYSES

Not applicable because, *as this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and facilitating dose-escalation decisions. In addition, these reviews may facilitate PK* CCI *modeling and/or supporting clinical development.*

8. 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.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Not Applicable fo this study

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Not Applicable fo this study.

Appendix 2.2. Endpoint Derivations

Appendix 2.2.1. Details of Deriving Priors

CCI [redacted]

CCI

[redacted]

subjid[]	CCI	CFB[]	Base[]	Dose[]
PPD	1	0	100	0
PPD	1	-2	125	15
PPD	1	3	300	150
PPD	1	-13	200	15
PPD	1	-67	123	300
.	.	.	.	.
.	.	.	.	.

[redacted]

CCI

CCI

CCI

[redacted]

CCI

Appendix 3.2. Example SAS Code for Statistical Analyses

Appendix 3.2.1. MMRM for PK analysis:

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

CCI

CCI

[redacted]

Appendix 3.2.3. Code for the calculation of the posterior probabilities (if required):

CCI

[redacted]

Appendix 3.2.4. Traditional Emax Model with baseline interaction Model:

CCI

[redacted]

[redacted]

CCI

run;
B = average baseline of all participants in the CCI .

Appendix 3.2.5. ANCOVA for Safety analysis CCI :

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

Appendix 3.2.6. Analysis for DDI interaction (Part B):

```
      /* To compare Test PK Parameter to the Reference PK Parameter where l&var = log(&var)*/
      proc mixed data=tab.pk;
         class Day Participant;
         model l&var= Day / ddfm=KR;
         random participant;
         lsmeans Day;
         estimate 'Test vs Reference' Day -1 1 /cl alpha=0.1;
         ods 'Estimates' out=est&var;
         ods 'lsmeans' out=ls&var;
```

```
    ods 'covparms' out=cov&var;
    ods 'tests3' out=tst&var;
run;
```

Appendix 4. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee

Abbreviation	Term
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalized linear mixed-effects model with repeated measures
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
CCI	[redacted]
MNAR	missing not at random
N/A	not applicable
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level

Abbreviation	Term
[redacted]	[redacted]
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TA	therapeutic area
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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