PROTOCOL C2541005

A PHASE 1B, RANDOMIZED, DOUBLE-BLIND (SPONSOR-OPEN), PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACODYNAMICS AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF PF-06865571 FOR 2 WEEKS IN ADULTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Version: 1

Date: 17MAY2018

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C2541005 is based on the protocol dated 27FEB2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C2541005. 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

Primary Objective:	**Primary Endpoint:**
• To evaluate the effect of multiple oral doses of PF-06865571 on whole liver fat, following 14 days of administration to subjects with NAFLD.	• Relative change from baseline in whole liver fat at Day 15, as assessed by MRI-PDFF.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the safety and tolerability of multiple oral doses of PF-06865571, administered for 14 days to subjects with NAFLD.	• Assessment of AEs, clinical laboratory tests, vital signs and 12-lead ECGs.
• To characterize the plasma exposure of multiple oral doses of PF-06865571, administered for 14 days to subjects with NAFLD.	• PF-06865571 C_{max}, AUC_{tau}, T_{max}, C_{min}, CL/F, and PTR on Day 14, as permitted by the data.
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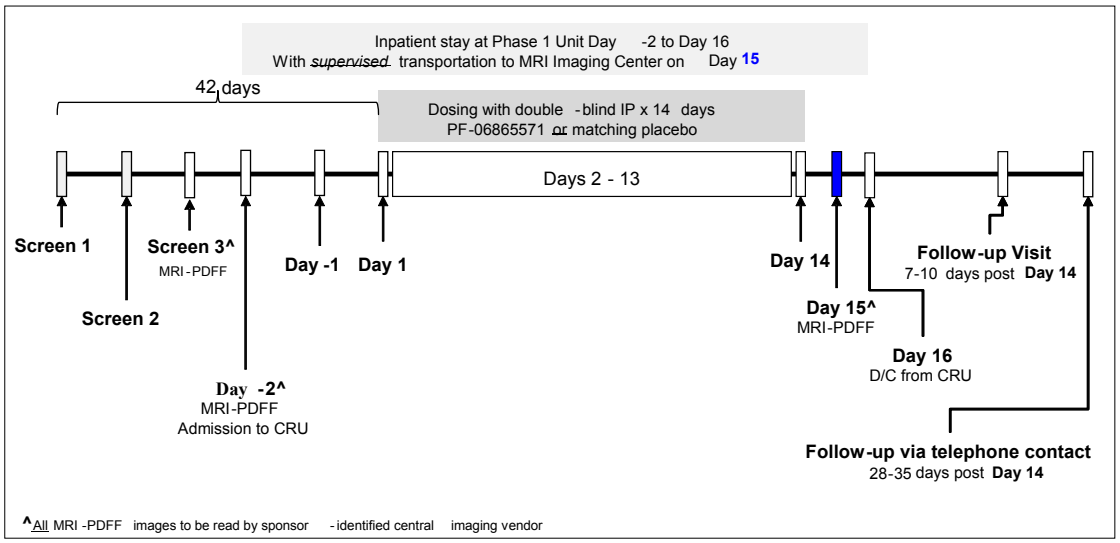
2.2. Study Design

This will be a randomized, double-blind (sponsor-open), stratified, placebo-controlled, 3-arm (placebo, plus 2 active doses of PF-06865571), parallel-group study. A total of approximately 45 subjects (15 per arm) will be randomized at approximately 4 to 6 sites to ensure a minimum of 42 subjects complete the study (assuming an approximate 5% premature withdrawal rate). Subjects may be replaced at the discretion of the principal investigator (PI) and Sponsor. Subjects will be randomized to receive PF-06865571 (2 dosing regimens) or matching placebo (1 dosing regimen) in a 1:1:1 ratio.

For a given subject, the total study duration from Screen 1 to the follow-up phone call will be up to approximately 13 weeks. Screen 1 will occur within 42 days prior to the first dose of blinded investigational product (IP, PF-06865571 or matching placebo). Eligible subjects who meet the entry criteria will progress to admission on the morning of Day -2, prior to lunch, for an 18-day (17-night) inpatient stay. While inpatient, subjects will receive blinded IP for 14 consecutive days and remain inpatient for approximately an additional 48 hours post AM dose on Day 14. Following discharge on Day 16, subjects will return for an on-site follow-up visit 7 to 10 days following the last dose of blinded IP, and a follow-up phone call (or visit, if necessary per the PI) 28 to 35 days following the last dose of blinded IP. The schematic of the study design is provided in Figure 1.

Figure 1. Design of Study C2541005



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Relative change from baseline in whole liver fat at Day 15, as assessed by MRI-PDFF. The relative change will be expressed in % unit, [100*(relative change – 1)]. Baseline is defined as the planned measurement collected closest ***prior to*** dosing on Day 1.

The liver fat or the whole liver PDFF is calculated from the pre-defined individual segmental PDFFs labeled Segment I, II, III, IVa, IVb, V, VI, VII and VIII as follows:

Whole Liver PDFF= PDFFs for (Segment I + Segment II + Segment III + Segment IVa + Segment IVb + Segment V + Segment VI + Segment VII + Segment VIII) / (number of segments assessed).

A minimum of 5 non-missing common segments is needed in order to calculate whole liver PDFF. All segments are equally weighted.

While deriving the relative change from baseline, the same segments are to be used at both baseline and post-baseline time points in the calculation of whole liver PDFF. For example, if at baseline PDFFs from all segments are available but, on Day 15, only 7 segments have non-missing results, whole liver PDFF will be calculated using the matching individual segmental PDFFs at ***both*** baseline and Day 15.

3.2. Secondary Endpoint(s)

- The secondary endpoints include the standard safety endpoints, namely, adverse events (AEs), clinical laboratory tests, vital signs (including blood pressure and pulse rate), and 12-lead electrocardiograms (ECG). These will be further described in Section 3.5.

- PF-06865571 C_{max}, AUC_{tau}, T_{max}, C_{min}, CL/F, and PTR on Day 14, as permitted by the data,

  The PK parameters for PF-06865571 will be derived from the concentration-time profiles as data permit. The various PK parameters to be assessed in this study, their definition and method of determination are outlined in Table 2. Actual PK sampling times will be used in the derivation of PK parameters.

Table 2. Definition of Steady State (Day 14) Plasma PK Parameters for PF 06865571

Parameter	Definition	Method of Determination
AUC_{tau}	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval	Linear/Log trapezoidal method
C_{max}	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
CL/F	Apparent clearance	Dose/AUC_{tau}
C_{min}	Minimum plasma concentration during the dosing interval	Observed directly from data
PTR	Peak-to-trough ratio	C_{max}/C_{min}

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3.4. Baseline Variables

Baseline variables are those collected on Day 1 prior to dosing or before Day 1. The demographic data of age, race, weight, and body mass index will be summarized by sex at birth and treatment in accordance with the sponsor reporting standards. Ethnicity will not be summarized. The number and proportion of subjects enrolled in each study site will also be presented.

In this study subjects will be stratified at randomization based on the presence or absence of Type 2 Diabetes Mellitus (T2DM) and by the MRI-PDFF liver fat categories obtained during Visit 3 (Screen 3) listed below:

- Screening liver fat ≥6% and <10%;
- Screening liver fat ≥10%.

Both of these stratification variables will be used as covariates in the efficacy analysis. For baseline diabetic status, data will be obtained from the case report forms (CRFs). Even though baseline liver fat was used as a binary variable for stratification purposes, it will be used as a continuous covariate in the efficacy analysis in order to maximize the utility of information. If there is substantial imbalance in the number of subjects enrolled in each site then study site will be considered to be included as a potential covariate. If included as a covariate sites enrolling less than 6 subjects will be pooled.

3.5. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- AEs;
- Laboratory data;
- Vital signs data;
- ECG results.

3.5.1. Adverse Events

For serious adverse events (SAEs), the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving IP, through and including 28 calendar days after the last administration of the IP.

Similarly,the time period for collecting AEs ("active collection period") for each subject begins from the time the subject provides informed consent. The AEs occurring following start of the double-blind randomized treatment will be counted as treatment emergent. The AEs occurring prior to the double-blind randomized treatment intake will be listed.

The 3-Tier approach will not be used to summarize the AEs due to the small sample size.

3.5.2. Laboratory Data

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 is defined as the result closest ***prior to*** dosing on Day 1.

3.5.3. Vitals

Supine blood pressure and pulse rate measurements will be taken at time points detailed in the Schedule of Activities given in the protocol.

Baseline is defined as the result closest ***prior to*** dosing on Day 1. The following vital signs endpoints will be determined for each subject:

- The maximum decrease and increase from baseline over all measurements taken post dose for systolic and diastolic blood pressures.

- The maximum increase and decrease from baseline over all measurements taken post dose for pulse rate.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post dose 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 largest negative value of the changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

3.5.4. ECGs

Triplicate 12-lead ECGs will be obtained on all subjects at times detailed in the Schedule of Activities given in the protocol. Average of the triplicate will be utilized in all analysis. Baseline is defined as the result closest ***prior to*** dosing on Day 1.

The QT, QTcF, heart rate, QRS and PR will be recorded at each assessment time. If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \qquad \text{where RR = 60/HR (if RR is not provided)}$$

The maximum absolute value (post dose) and the maximum increase from baseline for QTcF, heart rate, PR and QRS, will be determined by study day for each subject.

The maximum increase from baseline will be calculated by firstly subtracting the baseline value from each post dose 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 preserving the sign of change.

3.5.5. Non-Standard Safety Assessments

Serum creatinine (Scr) and serum cystatin C will be collected as part of the safety panel. From Scr estimated glomerular filtration rate (eGFR) will be calculated, if not supplied, using the modification of diet in renal disease (MDRD) equation provided below.

MDRD Formula:

$$GFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$$

GFR will be estimated from the cystatin C using the CKD-Epi-Cystatin C equation provided below:

- For serum cystatin C (Scys) ≤0.8 mg/L:

  $$eGFR\ (mL/min/1.73\ m^2) = 133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

- For serum cystatin C (Scys) >0.8 mg/L:

  $$eGFR\ (mL/min/1.73\ m^2) = 133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

Baseline is defined as the result closest ***prior to*** dosing on Day 1.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects 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.

4.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects who received at least 1 dose of randomized treatment; subjects are assigned to the randomized treatment regardless of what treatment was received. This would be the primary analysis population for all efficacy analyses.

4.2. Per Protocol Analysis Set

This will not be used in the current study.

4.3. Safety Analysis Set

All subjects who receive at least 1 dose of IP post-randomization will be included in the safety analyses and listings. All safety endpoints will be analyzed by the treatment that the subjects actually receive (for the majority of the study duration) regardless of which treatment group they are randomized. A randomized but not treated subject will be excluded from the safety analyses. A treated but not randomized subject will be reported under the treatment actually received.

For AE reporting all subjects providing informed consent regardless of their randomization status will be included.

4.4. Other Analysis Sets

The PK concentration population will be defined as all randomized subjects who received at least 1 dose of PF-06865571 and in whom at least 1 plasma PK concentration value is reported. The PK parameter analysis population will be defined as all randomized subjects who received at least 1 dose of PF-06865571 and who have at least 1 of the PK parameters of interest calculated.

5. GENERAL METHODOLOGY AND CONVENTIONS

The analysis will be performed after database release following last subject last visit.

5.1. Hypotheses and Decision Rules

The following null hypotheses will be tested for each endpoint:

1. 300 mg PF-06865571 Q12H is equal in effect to placebo.
2. 50 mg PF-06865571 Q12H is equal in effect to placebo.

The alternative hypotheses corresponding to the above null hypotheses will be the following 2-sided hypotheses:

1. The effect of 300 mg PF-06865571 Q12H is different from the effect of placebo.
2. The effect of 50 mg PF-06865571 Q12H is different from the effect of placebo.

The Type I error rate (α-level) used with the decision rule for the primary objective is 10% (1-sided). No adjustment for multiple comparisons will be made.

Interim analyses may be performed to assess efficacy and/or safety after at least 50% of the planned subjects, ie, approximately 21 subjects, complete the study. Interim analysis results may be used for internal business decisions regarding future study planning or stopping for futility. As such no adjustment in the Type I error rate is proposed.

5.2. General Methods

Descriptive Statistics

Descriptive statistics, including the sample size, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. Some measures will be summarized using graphical representations by treatment and study day of visit, where appropriate.

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Analysis of Covariance (ANCOVA)

The ANCOVA model will be used with continuous endpoints for landmark (single time point) analyses. The model will include treatment group as fixed effect, baseline value of the endpoint being analyzed, baseline whole liver PDFF and baseline diabetes status as covariates. If there is substantial imbalance in the number of subjects enrolled in each site then study site and interaction of study site with treatment will be considered to be included as potential covariates for the analysis of primary endpoint only. If included as a covariate, sites enrolling less than 6 subjects will be pooled. The number of covariates may be reduced to improve model fit. Estimates of treatment effects will be assessed using LSMs and CIs. Estimates of the mean differences between each active dose and placebo, and the corresponding 80% CI will be obtained from the model. Comparison of each PF-06865571 dose with the placebo will be performed at a Type I error rate of 10% (1-sided). If there are major deviations from the statistical assumptions underlying this model then alternative transformations (eg, log) or non-parametric analyses may be presented. Justification for any alternative to the planned analysis will be given in the study report.

Non-parametric Analysis

If the data have many outliers even after the log-transformation the following non-parametric analysis will be performed instead of the linear model. An outlier will be defined as any datapoint falling outside of 3.5 x standard deviations ± the median. Additional evaluative statistics will be conducted to explore the nature of the outliers in order to determine the appropriateness of a parametric analysis.

For group medians 80% CIs will be presented. In addition the 80% CIs will also be presented for differences in group medians from placebo group median. The method of McGill, Tukey, and Larson[1] will be employed to calculate the CI for the difference in treatment group medians.

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5.3. Methods to Manage Missing Data

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In all pharmacokinetic 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.)

In summary tables and plots of the median values at each time point, 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.

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint: Whole Liver PDFF

6.1.1. Primary Analysis

- **Analysis endpoint**: Whole liver PDFF.
- **Analysis time points**: Day 15.
- **Analysis population**: Full Analysis set
- **Analysis methodology**: Natural log-transformed individual relative change (RC) from baseline to Day 15 in whole liver PDFF will be analyzed using the ANCOVA. Log-transformed baseline will be the covariate. The model will include natural log-transformed baseline whole liver PDFF and diabetes status. If there is substantial imbalance in the number of subjects enrolled in each site then study site and interaction of study site with treatment will be considered to be included as potential covariates.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and Day 15 visit will be presented for each treatment arm.
- %CBL: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm at Day 15. The LSMs and their 80% CI will be exponentiated to provide estimates of the RC which will be converted to percent change as follows:

  Percent change = 100* (RC - 1).

  The LSMs of the percent change from baseline with the 80% CIs for each treatment group and the LSMs of the percent change from placebo with the 80%CIs for each of the PF-06865571 groups and the 2-sided p-values will be presented.

Figures

- Whole liver PDFF - Bar chart of the model-derived least square means for all treatment groups including the placebo group with 80%CI will be provided for Day 15 with treatment group on the X-axis.
- Whole liver PDFF - Bar chart of the placebo-adjusted least square means with 80%CI for the two PF-06865571 treatment groups will be provided for Day 15 with dose on the X-axis.

- Whole liver PDFF - Box and whisker plots for individual percent change from baseline versus treatment will be presented and overlaid with arithmetic means.

6.1.2. Sensitivity/Robustness Analyses

- **Analysis endpoint**: Whole liver PDFF.
- **Analysis time points**: Day 15.
- **Analysis population**: Full Analysis set.
- **Analysis methodology**: %CBL to Day 15 in whole liver PDFF will be analyzed using the ANCOVA. The model will include baseline whole liver PDFF and diabetes status. If there is substantial imbalance in the number of subjects enrolled in each site then study site and interaction of study site with treatment will be considered to be included as potential covariates.

Reporting results:

The LSMs, 80% CI for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 80% CI and the 2-sided p-values will be presented for whole liver PDFF.

6.2. Secondary Endpoint(s)

The analyses of safety endpoints will be described in Section 6.6.

Presentations for PF-06865571 concentrations will include:

- A listing of all concentrations sorted by dose, subject ID, day and nominal time post dose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by dose, day, and nominal time post dose, 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 LLQ.
- A median plot of steady state (Day 14) plasma concentrations by dose will be provided.
- The PK parameters listed in Section 3.2 will be summarized descriptively by dose.

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6.4. Subset Analyses

For the primary endpoint subset analysis by the whole liver PDFF stratification categories provided below may be considered.

- Screening liver fat ≥6% and <10%;
- Screening liver fat ≥10%.

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6.5. Baseline and Other Summaries and Analyses

A breakdown of demographic data will be provided for age, race, weight, and body mass index. Each will be summarized by sex at birth and treatment in accordance with the sponsor reporting standards. Baseline summary of parameters of interest, namely, fasting glucose, CCI [redacted] waist circumference, AST, ALT, alkaline phosphatase, GGT and whole liver PDFF will be presented for each treatment group and overall. Baseline summary [redacted]

[redacted]

of stratification factors, namely, diabetes status (presence or absence) and MRI-PDFF categories (≥6% and <10% or ≥10%) will be provided. The number and proportion of subjects enrolled in each study site will also be presented.

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacodynamic (FAS) and pharmacokinetics (PK), as well as for safety (AEs and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.6. Safety Summaries and Analyses

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-06865571.

The standard safety endpoints detailed in Section 3.5 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis sets. The analyses of non-standard safety data will also utilize safety analysis set and the methods are described below.

Any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted.

6.6.1. Adverse Events

Adverse events will be summarized by treatment and in accordance with current Pfizer data standards. The AEs will be sorted alphabetically within a system organ class. Summary tables will be provided for TEAEs and AEs occurring prior to randomization will only be listed.

The 3-Tier approach will not be used to summarize the AEs due to the small sample size.

6.6.2. Laboratory Data

All planned, quantitative, standard safety laboratory data presented in Table 6 of the protocol and non-standard safety laboratory data that are not reported independently will be listed and summarized at each collection time point by treatment in accordance with the sponsor reporting standards as applicable. Baseline is as defined in Section 3.5.2.

6.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment and study day, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against study day. On each plot there will be 1 line for each treatment, all treatments on the same plot including the placebo.

For baseline subtracted supine systolic and diastolic blood pressure and pulse rate, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 90% CI) and plotted (mean, 90% CI) for each dose and day.

Maximum absolute values and maximum changes from baseline for vital signs, over all measurements taken post dose will also be tabulated by treatment using categories as defined in the Appendix. 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.

Maximum decrease and increase from baseline for supine systolic and diastolic blood pressures, and maximum increase from baseline for supine pulse rate will be summarized by treatment, according to sponsor reporting standards.

6.6.4. Electrocardiogram

Average of the triplicate measurements will be used in all analyses. Absolute values and changes from baseline in QT, heart rate, QTcF, PR, RR and QRS will be summarized by treatment and day using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against study day. On each plot there will be 1 line for each treatment, all treatments on the same plot including the placebo.

In addition for baseline subtracted QT, heart rate and QTcF, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 90% CI) and plotted (mean) for each dose and day including follow-up.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in the Appendix (for QTc these correspond to ICH E14). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Maximum absolute value (post dose) and the maximum increase from baseline for QTcF, PR and QRS will be summarized by treatment according to sponsor reporting standards.

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

6.6.5. Non-standard Safety Analysis

Serum Creatinine, Serum Cystatin C and Associated eGFRs

Absolute values and changes from baseline in serum creatinine, serum cystatin C, eGFRs obtained from serum creatinine and cystatin C will be summarized by treatment and day. Mean absolute values of all four parameters will be plotted separately against study day. On each plot there will be 1 line for each treatment, all treatments on the same plot including the placebo. Mean changes from baseline in eGFRs will also be plotted against study day.

Liver Function Tests

Raw values, change and %CBL in ALT, AST, Total Bilirubin, GGT, and alkaline phosphatase will be summarized by treatment at all relevant collection time points including follow-up. For %CBL group medians and differences in group medians from placebo with 80% CIs will be presented. Line plot of medians with 80% CIs for all treatment groups including the placebo group with study day on X-axis will be provided. Three lines corresponding to the 3 treatment groups will be overlaid on the same plot.

Body Weight

Raw values, change and %CBL in body weight will be summarized by treatment at all relevant collection time points including follow-up. For %CBL group medians and differences in group medians from placebo with 80% CIs will be presented. Line plot of medians with 80% CIs for all treatment groups including the placebo group with study day on X-axis will be provided. Three lines corresponding to the 3 treatment groups will be overlaid on the same plot.

7. INTERIM ANALYSES

Interim analyses may be performed to assess efficacy and/or safety after at least 50% of the planned subjects, ie, approximately 21 subjects, complete the study. Interim analysis results may be used for internal business decisions regarding future study planning or stopping for futility. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an internal review committee (IRC) charter. In addition, the analysis details will be documented and approved in an interim analysis SAP.

8. REFERENCES

1. *McGill, R., John W. Tukey and W. A. Larsen. 1978. "Variations of Box Plots." American Statistician 32:12-16*

9. APPENDICES

Categorical Classes for ECG and Vital Signs

Categories for QTcF

Categories for Maximum Post-dose QTc (msec)				
All subjects	≤450	450 - ≤480	480 - ≤500	>500
Categories for Maximum Increase from Baseline in QTc (msec)				
All Subjects	≤30	30 - ≤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.

Calculation of %CBL

- %CBL = 100*(Post-baseline value – Baseline value) / Baseline value.