Protocol C1061011

A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 3-ARM, PARALLEL GROUP STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACODYNAMICS OF PF-06835919 ADMINISTERED DAILY FOR 16 WEEKS IN ADULTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND TYPE 2 DIABETES MELLITUS ON METFORMIN

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 17July2019

[redacted]

Table of Contents

1. VERSION HISTORY 4
2. INTRODUCTION 4
2.1. Study Objectives, Endpoints, and Estimands 4
2.1.1. Primary Estimand 6
2.1.2. Secondary Estimand 7
2.2. Study Design 8
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 9
3.1. Primary Endpoint(s) 9
3.2. Secondary Endpoint(s) 10
CCI
3.4. Baseline Variables 12
3.5. Safety Endpoints 13
3.5.1. Adverse Events 13
3.5.2. Laboratory Data 14
3.5.3. Vitals 14
3.5.4. ECGs 15
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 15
5. GENERAL METHODOLOGY AND CONVENTIONS 16
5.1. Hypotheses and Decision Rules 16
5.2. General Methods 16
5.3. Methods to Manage Missing Data 18
6. ANALYSES AND SUMMARIES 19
6.1. Primary Endpoint 1: Whole Liver Fat using MRI-PDFF 19
6.1.1. Main Analysis 19
6.1.2. Sensitivity/Robustness Analyses 20
6.1.3. Supplementary Analysis 1 20
6.2. Primary Endpoint 2: HbA1c 21
6.2.1. Main Analysis 21
6.2.2. Supplementary Analysis 22
6.3. Secondary Endpoints 22

6.3.1. Secondary Endpoint 1: Hs-CRP 22
6.3.2. Secondary Endpoint 2: Fasting Insulin, Glucose, and HOMA-IR 23
6.3.3. Secondary Endpoint 3: ALT 24
6.3.4. Secondary Endpoint 4: HbA1c at all time points prior to Week 16 25
CCI [redacted]
6.5. Subset Analyses 27
6.6. Baseline and Other Summaries and Analyses 28
6.7. Safety Summaries and Analyses 28
6.7.1. Adverse Events 28
6.7.2. Laboratory Data 29
6.7.3. Vital Signs 29
6.7.4. Electrocardiogram 30
7. INTERIM ANALYSES 31
8. REFERENCES 31
APPENDIX 1: CATEGORICAL CLASSES FOR ECG AND VITAL SIGNS 32
APPENDIX 2: TIER 1 ADVERSE EVENTS 32
APPENDIX 3: LIST OF ABBREVIATIONS 34

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 17 July 2019	Original 21 Mar 2019	N/A	N/A

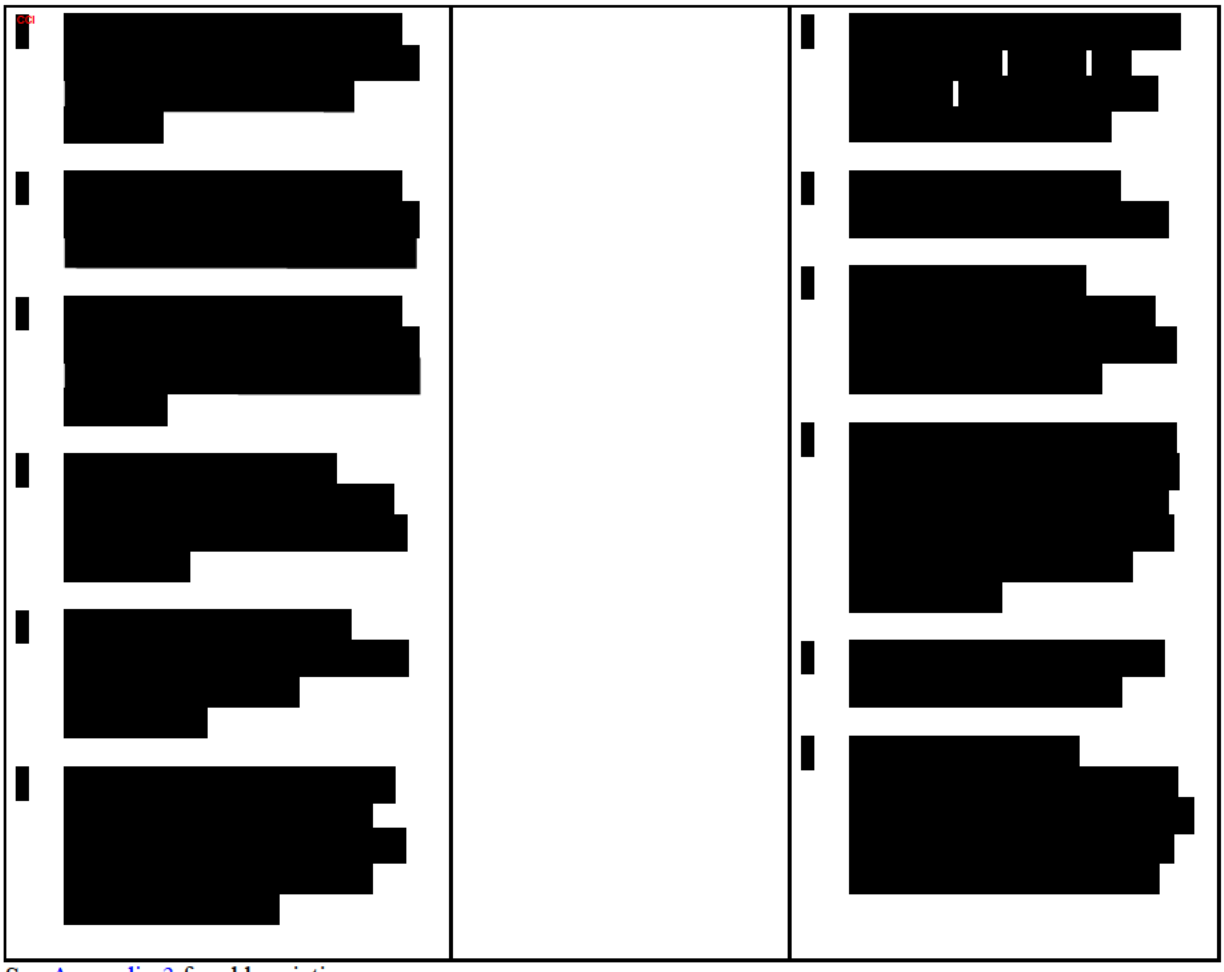
2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C1061011. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate the effect of 2 dose levels of PF-06835919 compared to placebo on **whole liver fat** measured by MRI-PDFF. • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **HbA1c.**	Estimand 1: • This estimand is intended to provide a population level estimate of the treatment effect of the IP alone relative to placebo under the scenario of no discontinuation of study intervention, without the potential confounding effects of additional prohibited medications, regardless of the participant's compliance with the IP dosing.	• %CFB in whole liver fat at 16 weeks using MRI-PDFF. • CFB in HbA1c at 16 weeks.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the **safety and tolerability** of 2 dose levels of PF-06835919 administered daily for 16 weeks. • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **hs-CRP.**	• No estimand is defined for safety and tolerability endpoints. These will be analyzed using Pfizer Data Standards, as applicable. • hs-CRP, measures of glycemic metabolism, ALT and HbA1c will be	• Assessment of AEs, including hypoglycemia AEs, clinical laboratory tests, vital signs and 12-lead ECGs. • %CFB in hs-CRP over 16 weeks.

• To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **glycemic metabolism.** • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **ALT.** • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **HbA1c.**	analyzed using Estimand 1.	• CFB in fasting insulin, glucose, and HOMA-IR over 16 weeks. • %CFB in ALT over 16 weeks. • CFB in HbA1c at all time points other than Week 16.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



See Appendix 3 for abbreviations.

2.1.1. Primary Estimand

Primary Estimand is a hypothetical estimand intended to provide a population level estimate of the treatment effect of the investigational product (IP) alone relative to placebo under the scenario of no discontinuation of study intervention, without the potential confounding effects of additional prohibited medications, regardless of the participant's compliance with the IP dosing.

Population:

The target population consists of patients with NAFLD and type 2 diabetes mellitus (T2DM) on stable doses (≥500 mg/day) of metformin monotherapy.

Variable:

In this study there are 2 co-primary endpoints:

- %CFB (change from baseline) in whole liver fat at 16 weeks using MRI-PDFF;

- CFB in HbA1c at 16 weeks.

Note: CFB or %CFB in tertiary/exploratory endpoints over 16 weeks will also be analyzed using the primary estimand.

Intercurrent Events:

a. Withdrawal from study intervention – All data collected after a participant stops taking IP will be excluded.

b. Prohibited medications – All assessments after a participant receives prohibited medications that would modulate the primary endpoints will be omitted from the analysis. Receiving a medication prohibited due to drug-drug interaction (DDI) risk will not affect this estimand. The list of concomitant medications would be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.

c. Inadequate compliance – Participants with inadequate compliance will have their primary endpoint measurements used as recorded in the analysis.

Population level summary:

The population level summary will be the mean difference in change from baseline between PF-06835919 and placebo groups for the endpoint of interest.

2.1.2. Secondary Estimand

Secondary Estimand is a treatment policy estimand intended to provide a population level estimate of the treatment effect of the IP alone relative to placebo on liver fat measured by MRI-PDFF and HbA1c at Week 16 without regard to compliance or discontinuation of study drug or administration of prohibited medication.

Population:

- The target population consists of patients with NAFLD and T2DM on stable doses (≥500 mg/day) of metformin monotherapy.

Variable(s):

The 2 co-primary endpoints will be analysed using this estimand:

- %CFB in whole liver fat at 16 weeks using MRI-PDFF;

- CFB in HbA1c at 16 weeks.

Intercurrent Events:

a. Withdrawal from study intervention – All data collected regardless of a participant's withdrawal from the IP will be included in the analysis.

b. Prohibited medications – All data collected for a participant regardless of the use of prohibited medications will be used in the analysis.

c. Inadequate compliance – Participants with inadequate compliance will have their primary endpoint measurements used as recorded in the analysis.

Population level summary:

The population level summary will be the mean difference in change from baseline between PF-06835919 and placebo groups for the endpoint of interest.

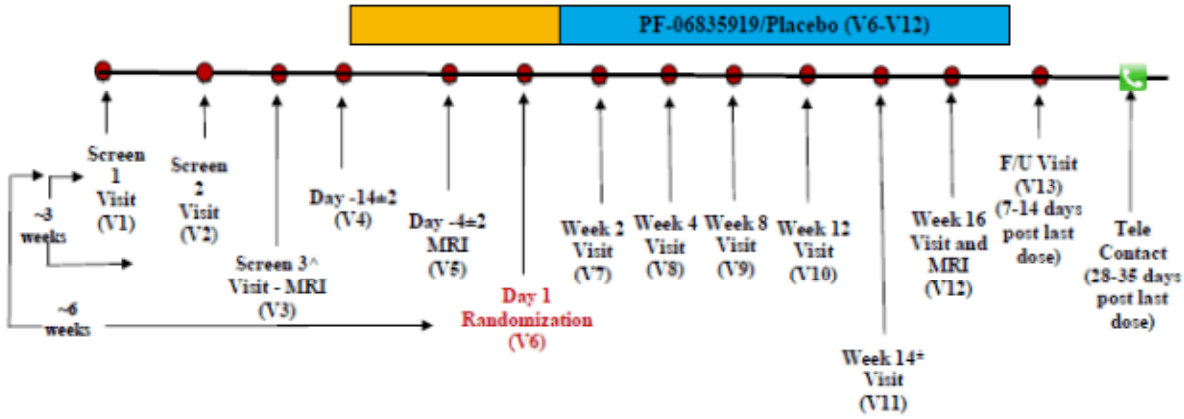
2.2. Study Design

This is a Phase 2a, placebo-controlled, randomized, double-blind, parallel-group, multicenter study to evaluate the safety, tolerability, and pharmacodynamics (PD) of PF-06835919 administered once daily (QD) for 16 weeks in adults with NAFLD and T2DM on stable doses of metformin.

A total of approximately 150 participants (50 per group) will be randomized in a ratio of 1:1:1 between PF-06835919 at 150 mg and 300 mg, and placebo to ensure a minimum of approximately 132 participants (44 per group) complete. The dropout rate for this study is presumed to be not more than approximately 12%.

For individual participants, the total duration of the study from the Screen 1 visit to the on-site follow-up visit (Visit 13) will be approximately 24 weeks. The time between Screen 1 (Visit 1) and Screen 3 (Visit 3) should be approximately 3 weeks, and approximately 6 weeks (42 days) between Screen 1 (Visit 1) and Day 1 (Visit 6), refer to **Figure 1** below.

Figure 1: C1061011 Study Design



^This visit to occur at the local, sponsor-approved imaging facility.

*This visit is only applicable to participants involved in the sub-study. Participants will return to the site for distribution of food and water diary, placement of devices, receive instructions for use, and report AEs. IP does not need to be administered at the site.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

This study has 2 co-primary endpoints:

- %CFB in whole liver fat at 16 weeks using MRI-PDFF;
- CFB in HbA1c at 16 weeks.

1. Whole Liver Fat Using MRI-PDFF

Here the %CFB at Week 16 will be the derived endpoint. Baseline will be the measurement obtained at Visit 5.

The liver fat or the whole liver PDFF is calculated from the pre-defined individual segmental PDFFs labeled Segments 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 segments is needed in order to calculate whole liver PDFF. All segments are equally weighted.

While deriving the %CFB, 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, at Week 16, only 7 segments have non-missing results, whole liver PDFF will be calculated using the 7 matching individual segmental PDFFs at ***both*** baseline and Week 16.

2. HbA1c

The CFB at Week 16 will be the derived endpoint. Baseline will be the closest planned measurement prior to first dose on Day 1 of Visit 6.

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 electrocardiogram (ECG). These will be further described in section 3.5. Additional secondary endpoints are described below.

- %CFB in high sensitivity C-reactive protein (hs-CRP) at Weeks 2, 4, 8, 12, 16 and at follow-up visits.

  Baseline is defined as the planned measurement closest ***prior to*** dosing at Visit 6 (Day 1).

- CFB in fasting insulin, glucose, and HOMA-IR (homeostatic model assessment of insulin resistance) at Weeks 2, 4, 8, 12, 16 and at follow-up visits. Baseline is defined as the planned measurement closest ***prior to*** dosing at Visit 6 (Day 1). HOMA-IR, which has no unit, will be calculated as follows from fasting plasma glucose and fasting plasma insulin at the time points collected:

  HOMA-IR = (FPI x FPG)/405

  where:

  FPI = fasting plasma insulin concentration in mIU/L;
  FPG = fasting plasma glucose concentration in mg/dL.

- %CFB in ALT at Weeks 2, 4, 8, 12, 16 and at follow-up visits

  Baseline is defined as the planned measurement closest ***prior to*** dosing at Visit 6 (Day 1).

- CFB in HbA1c at Weeks 2, 4, 8, 12 and at follow-up visits

  Baseline is defined as the planned measurement closest ***prior to*** dosing at Visit 6 (Day 1).

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

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, gender, height, weight, and body mass index will be summarized by treatment and also overall in accordance with the sponsor reporting standards. Ethnicity will not be summarized. The number and proportion of participants enrolled in each study site may be presented.

This study is conducted in participants with NAFLD and T2DM. Baseline values of the markers for these 2 diseases, namely whole liver fat using MRI-PDFF and HbA1c may be used as covariates in efficacy and PD analyses. If there is substantial imbalance in the number of participants enrolled in each site then study site may be considered to be included as a potential covariate. If included as a covariate sites enrolling less than 6 participants will be pooled. The assessment of imbalance will be made following randomization of all participants but prior to DBR.

[redacted]

[redacted]

[redacted]

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 participant provides informed consent, which is obtained prior to the participant's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving IP, through and including a minimum of 28 calendar days after the last administration of the investigational product.

Similarly, the time period for collecting AEs ("active collection period") for each participant begins from the time the participant 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 but during the single-blind placebo administration will be listed and summarized as baseline symptoms. For baseline symptoms all causality summary tables as well as incidence and severity tables by System Organ Class and Preferred Terms will be provided.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.7.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan. (List is also provided in Appendix 2.)

Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 5% in any treatment group.

Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

Hypoglycemia Monitoring

Hypoglycemia AEs will be recorded in the Case Report Form (CRF) as a separate page. The hypoglycemia CRF page should be completed if there is any glucose reading <=70 mg/dL or if participants experience symptoms of hypoglycemia in the absence of a glucose reading. Any glucose >70 mg/dL (even in the presence of typical hypoglycemic symptoms) will not

be considered as hypoglycemia AE ('No Hypoglycemic Adverse Event'box in the hypoglycemia CRF will be checked).

For programming purposes, hypoglycemic AEs should be reported as a separate listing based on the first 4 categories defined by the ADA, which are:

a. 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.
b. 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.
c. Asymptomatic Hypoglycemia: If (1 – Did the subject have symptoms of hypoglycemia?) No and (2 – Was the blood glucose measured?) Yes and result<=70 mg/dL on the CRF, but hypoglycemia is not classified as severe.
d. 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.

In the above categories Severe Hypoglycemia (a) and Documented Symptomatic Hypoglycemia (b) will be treated as Tier 1 events and Asymptomatic Hypoglycemia and Probable Symptomatic Hypoglycemia (d) will be treated as Tier 2 events.

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 be made regardless of whether each participant'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 at Visit 6 (Day 1). Results from only the planned study visits will be considered for baseline assessment.

3.5.3. Vitals

Seated blood pressure and pulse rate measurements will be taken at time points detailed in the Schedule of Activities (SOA) given in the protocol. The average of the triplicate values at any time point will be used as the measurement.

Baseline is defined as the measurement closest ***prior to*** dosing at Visit 6 (Day 1). Results from only the planned study visits will be considered for baseline assessment. The following vital signs endpoints will be determined for each participant:

- The maximum increase and decrease 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 participant 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 participant does not show a decrease, the minimum increase should be taken.

3.5.4. ECGs

Single 12-lead ECGs will be obtained on all participants at times detailed in the SOA given in the protocol. Baseline is defined as the measurement closest ***prior to*** dosing at Visit 6 (Day 1). Results from only the planned study visits will be considered for baseline assessment.

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:

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

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 participant.

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 participant does not show an increase. In such an instance, the minimum decrease should be taken preserving the sign of change.

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.

Population	Description
Pre-randomization	All participants entering the placebo run-in phase.
Randomly assigned to Treatment	Defined according to Full Analysis Set
Safety	All participants randomly assigned to treatment and who take at

Population	Description
	least 1 dose of treatment. Participants will be analyzed according to the dose they actually received.

Defined Population for Analysis	Description
Full Analysis Set	All participants randomly assigned to treatment and who take at least 1 dose of treatment.
CCI [redacted]	[redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

The final primary analysis will be performed after database release following last participant's last visit.

5.1. Hypotheses and Decision Rules

The following null hypotheses will be tested for each endpoint.

1. 300 mg/d PF-06835919 is equal in effect to placebo.
2. 150 mg/d PF-06835919 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/d PF-06835919 is different from the effect of placebo.
2. The effect of 150 mg/d PF-06835919 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% (2-sided). No adjustment for multiple comparisons will be made.

If 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.

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 visit, where appropriate.

Analysis of Covariance (ANCOVA)

The ANCOVA model will be used with continuous endpoints for landmark (single time point) analyses. Early termination data will be used with Estimand 2 and not with Estimand 1. The model will include treatment group as a fixed effect and baseline value as a covariate. If there is substantial imbalance in the number of participants enrolled in each site then study site and the interaction of study site with treatment will be considered to be included as potential covariates for the analysis of primary endpoints only. The assessment of imbalance will be made following randomization of all participants but prior to database release (DBR). If included as a covariate, sites enrolling less than 6 participants will be pooled. Estimates of treatment effects will be assessed using least square means (LSMs) and 90% Confidence Intervals (CIs). Estimates of the mean differences between each active dose and placebo at Week 16, and the corresponding 90% CI will be obtained from the model. Both comparisons of PF-06835919 doses with the placebo will be performed at a Type I error rate of 10% (2-sided). If there are major deviations from the statistical assumptions underlying this model then alternative transformations or non-parametric analyses may be presented. Justification for any alternative to the planned analysis will be given in the study report.

Mixed Model for Repeated Measurements (MMRM)

This model will be used for the analysis of endpoints with more than 1 post-baseline collection time point. All observed data collected during the post-baseline treatment period will be utilized. Early termination data will be used with Estimand 2 and not with Estimand 1. Data collected during the follow-up period will be excluded. The MMRM analysis will be performed with treatment, study day and treatment-by-study day interaction as fixed effects, baseline value as a covariate. When early termination data are utilized, the closest nominal study visit following the actual study day of early termination visit will be used in the model. Additional covariates such as, baseline whole liver PDFF, baseline HbA1c or baseline eGFR may also be considered for inclusion in the model. If there is substantial imbalance in the number of participants enrolled in each site then study site and the interaction of study site with treatment will be considered to be included as potential covariates for the analysis of primary endpoints only. The assessment of imbalance will be made following randomization of all participants but prior to DBR. Repeated measures model with unstructured correlation matrix will be utilized. Time will be fitted as a repeated effect. If this does not converge then compound symmetry structure will be considered. Additionally, the number of covariates may be reduced to improve model fit. Estimates of treatment effects will be assessed using LSMs and 90% CIs at each time point. LSM difference between each dose of PF-06835919 and placebo group along with the 90% CIs and 2-sided p-values will be provided. If there are major deviations from the statistical assumptions underlying this model then alternative transformations (e.g. 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 90% CIs will be presented. In addition the 90% CIs will also be presented for differences in group medians from placebo group median. The method of McGill, Tukey, and Larson will be employed to calculate the CIs for the difference in treatment group medians.

Exploratory Multivariate analysis

To explore correlations between endpoints and the metabolic effects of PF-06865919 multivariate analysis such as principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) with selected groups of endpoints will be conducted. These analyses will utilize CFB to Week 16 in those endpoints. Outputs will be generally graphical in nature and may not be included in the CSR.

5.3. Methods to Manage Missing Data

As the primary estimand is a hypothetical estimand all data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded. For the secondary estimand which is a treatment policy estimand all data collected regardless of a participant's withdrawal from the study medication or the use of prohibited medications will be included in the analysis.

The MMRM will provide unbiased estimates in case of missing at random (MAR). For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied. In case of biomarkers if the concentrations are above the limits of quantification such values will be truncated at the limit of quantification in all summary tables. If the concentrations are below the limits of quantification such values will be imputed by 0.5*LLQ where LLQ is the lower limit of quantification. However, in listings they will appear as reported.

CCI

[redacted]

[redacted]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint 1: Whole Liver Fat using MRI-PDFF

6.1.1. Main Analysis

- **Analysis time point:** Week 16
- **Estimand strategy:** Hypothetical
- **Analysis set:** Full Analyis Set; Participants must have a baseline and Week 16 measurements to be included.
- **Analysis methodology:** Natural log-transformed individual response ratios (RR) at Week 16 to baseline (RR = observed value at Week 16 / baseline value) in whole liver fat using MRI-PDFF will be analyzed using the ANCOVA. Log-transformed baseline will be the covariate.
- **Intercurrent events and missing data:** Data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and Week 16 visit will be presented for each treatment group.
- %CFB: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment group at Week 16. The LSMs and their 90% CIs will be exponentiated to provide estimates of the RRs which will be converted to percent change as follows:

  Percent change = 100* (RR - 1).

  The LSMs of the percent change from baseline with the 90% CIs for each treatment group and the LSMs of the percent change from placebo with the 90% CIs for each of the PF-06835919 groups and the 2-sided p-values will be presented.

Figures

- %CFB in Whole liver fat using MRI-PDFF – A bar chart of the model-derived least square mean %CFB for all treatment groups including the placebo group with 90% CIs will be provided for Week 16 with dose on the X-axis.
- %CFB in Whole liver fat using MRI-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 time point:** Week 16
- **Estimand strategy:** Hypothetical
- **Analysis set:** Full Analyis Set; Participants must have a baseline and Week 16 measurements to be included.
- **Analysis methodology:** %CFB to Week 16 in whole liver PDFF will be analyzed using the ANCOVA. The model will include baseline whole liver PDFF.
- **Intercurrent events and missing data:** Data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded.

Reporting results:

- %CFB: The LSMs, 90% CIs for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 90% CI and the 2-sided p-values will be presented.

6.1.3. Supplementary Analysis 1

- **Analysis time point:** Week 16; Early Termination visit will be included and treated as Week 16
- **Estimand strategy:** Treatment policy
- **Analysis set:** Full Analyis Set; Participants must have a baseline measurement and a post-baseline measurement to be included.
- **Analysis methodology:** Natural log-transformed individual RRs at Week 16 to baseline in whole liver fat using MRI-PDFF will be analyzed using the ANCOVA. Log-transformed baseline will be the covariate. Site may be included as a covariate.
- **Intercurrent events and missing data:** Data collected regardless of a participant's withdrawal from the study medication or the use of prohibited medications will be included in the analysis.

Reporting results:

- The LSMs and their 90% CIs will be exponentiated to provide estimates of the RRs which will be converted to percent change as follows:

  Percent change = 100* (RR - 1).

The LSMs of the percent change from baseline with the 90% CIs for each treatment group and the LSMs of the percent change from placebo with the 90% CIs for each of the PF-06835919 groups and the 2-sided p-values will be presented.

6.2. Primary Endpoint 2: HbA1c

6.2.1. Main Analysis

- **Analysis time point:** Week 16 (primary time point); model will include all relevant time points
- **Estimand strategy:** Hypothetical
- **Analysis set:** Full Analyis Set; Participants must have a baseline measurement and at least one post-baseline measurement on treatment to be included.
- **Analysis methodology:** CFB in HbA1c will be analyzed using MMRM with treatment, time and treatment by time interaction as fixed effects and baseline HbA1c value as a covariate. Time will be fitted as a repeated effect.
- **Intercurrent events and missing data:** Data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and all post-baseline time points will be presented for each treatment group.
- CFB: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment group at all post-baseline time points. The LSMs, 90% CIs for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 90% CI and the 2-sided p-values will be presented.

Figures

- HbA1c CFB – A bar chart of the model-derived least square means for all treatment groups including the placebo group with 90% CIs will be provided for Week 16 with dose on the X-axis.
- HbA1c CFB - A line plot of the model-derived LSMs for all treatment groups including the placebo group with 90% CIs will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups.
- HbA1c CFB - A line plot of the model-derived LSM differences from placebo for the two PF-06835919 treatment groups with 90% CIs will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups.

6.2.2. Supplementary Analysis

- **Analysis time point:** Week 16; model will include all relevant time points
- **Estimand strategy:** Treatment policy
- **Analysis set:** Full Analyis Set; Participants must have a baseline measurement and a post-baseline measurement to be included.
- **Analysis methodology:** CFB in HbA1c will be analyzed using MMRM with treatment, time and treatment by time interaction as fixed effects and baseline HbA1c value as a covariate. Time will be fitted as a repeated effect. Site may be included as a covariate.
- **Intercurrent events and missing data:** Data collected regardless of a participant's withdrawal from the study medication or the use of prohibited medications will be included in the analysis.

Reporting results:

- CFB: The LSMs, 90% CIs for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 90% CI and the 2-sided p-values will be presented.

6.3. Secondary Endpoints

The analyses of standard safety endpoints will be described in section 6.7. The description of analysis of other secondary endpoints is provided below.

6.3.1. Secondary Endpoint 1: Hs-CRP

- **Analysis time point:** All planned post-baseline time points
- **Estimand strategy:** Hypothetical
- **Analysis set:** Full Analyis Set; Participants must have a baseline measurement and a postbaseline measurement to be included.
- **Analysis methodology:** %CFB in hs-CRP will be analyzed using MMRM as described in section 5.2. The model will include treatment, study day and treatment-by-study day interaction as fixed effects, baseline hs-CRP and baseline whole liver PDFF as covariates. If there are major deviations from the statistical assumptions underlying the MMRM model the non-parametric analysis defined in Section 5.2 will be applied.
- **Intercurrent events and missing data:** Data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and all post-baseline visits will be presented for each treatment group.
- %CFB: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment group at all postbaseline collection time points. The LSMs, 90% CIs for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 90% CI and the 2-sided p-values will be presented. If the MMRM does not fit then medians, 90% CIs for the medians, difference between the median of each treatment group and the placebo group, and the corresponding 90% CI will be presented.

Figures

- A line plot of the model-derived LSMs for all treatment groups including the placebo group with 90% CIs will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups. If MMRM does not fit the data then this plot will not be produced.
- A line plot of medians and 90%CIs or medians±standard diviations for all treatment groups including the placebo group will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups. All planned time points including the follow-up time point will be presented.

6.3.2. Secondary Endpoint 2: Fasting Insulin, Glucose, and HOMA-IR

- **Analysis time point:** All planned post-baseline time points
- **Estimand strategy:** Hypothetical
- **Analysis set:** Full Analyis Set; Participants must have a baseline measurement and a postbaseline measurement to be included.
- **Analysis methodology:** CFB in each endpoint will be analyzed separately using MMRM as described in section 5.2. The model will include treatment, study day and treatment-by-study day interaction as fixed effects, baseline value and baseline HbA1c as covariates. If there are major deviations from the statistical assumptions underlying the MMRM model the non-parametric analysis defined in Section 5.2 will be applied.
- **Intercurrent events and missing data:** Data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and all post-baseline visits will be presented for each treatment group.
- CFB: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment group at all postbaseline collection time points. The LSMs, 90% CIs for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 90% CI and the 2-sided p-values will be presented. If the MMRM does not fit then medians, 90% CIs for the medians, difference between the median of each treatment group and the placebo group, and the corresponding 90% CI will be presented.

Figures

- For each endpoint a separate line plot of the model-derived LSMs for all treatment groups including the placebo group with 90% CIs will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups. If MMRM does not fit the data then this plot will not be produced.

- For each endpoint a line plot of medians and 90%CIs or medians±standard diviations for all treatment groups including the placebo group will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups. All planned time points including the follow-up time point will be presented.

6.3.3. Secondary Endpoint 3: ALT

- **Analysis time point:** All planned post-baseline time points

- **Estimand strategy:** Hypothetical

- **Analysis set:** Full Analyis Set; Participants must have a baseline measurement and a postbaseline measurement to be included.

- **Analysis methodology:** %CFB in ALT will be analyzed using MMRM as described in section 5.2. The model will include treatment, study day and treatment-by-study day interaction as fixed effects, baseline ALT and baseline whole liver PDFF as covariates. If there are major deviations from the statistical assumptions underlying the MMRM model the non-parametric analysis defined in Section 5.2 will be applied.

- **Intercurrent events and missing data:** Data collected after a participant stops taking study medication or receives prohibited medications that would modulate the primary endpoints will be excluded.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and all post-baseline visits will be presented for each treatment group.
- %CFB: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment group at all postbaseline collection time points. The LSMs, 90% CIs for the LSMs, difference between the LSM of each treatment group and the placebo group, and the corresponding 90% CI and the 2-sided p-values will be presented. If the MMRM does not fit then medians, 90% CIs for the medians, difference between the median of each treatment group and the placebo group, and the corresponding 90% CI will be presented.

Figures

- A line plot of the model-derived LSMs for all treatment groups including the placebo group with 90% CIs will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups. If MMRM does not fit the data then this plot will not be produced.
- A line plot of medians and 90%CIs or medians±standard diviations for all treatment groups including the placebo group will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups. All planned time points including the follow-up time point will be presented.

6.3.4. Secondary Endpoint 4: HbA1c at all time points prior to Week 16

Note: Results for this endpoint will come from the analysis described in Section 6.2.1. The results for post-baseline measuements prior to Week 16 will be reported as secondary endpoints

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]

CCI

CCI

6.5. Subset Analyses

None planned.

6.6. Baseline and Other Summaries and Analyses

A breakdown of demographic data will be provided for age, gender, race, weight, height and body mass index summarized by treatment and overall in accordance with the sponsor reporting standards. Baseline summary (median, minimum and maximum) of primary and secondary endpoints will be presented for each treatment group and overall. Baseline summary of stratification factors, namely, number and proportion of participants in main study only and in sub-study plus main study will be provided. The number and proportion of participants enrolled in each study site by baseline stratification factors and overall will also be presented.

Participant evaluation groups will show which participants were analyzed for the 2 estimands, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for participant discontinuation(s) by treatment. If the proportion of discontinuations is more than 10% then table with participant disposition by visit will be produced. Data will be reported in accordance with the sponsor reporting standards.

6.7. 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-06835919.

No formal analyses are planned for safety data. The 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.

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.

6.7.1. 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 separately for TEAEs and baseline symptoms. For baseline symptoms limited number of tables will be provided including all causality summary tables as well as incidence and severity tables by System Organ Class and Preferred Terms.

In addition to standard safety displays, a 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. All subjects in the Safety Analysis Set will have their safety data included in the tiered analysis below.

- Tier-1 events: Displays of Tier 1 events will include proportions, risk differences, 95% CIs and p-values. The risk difference will be computed for PF-06835919 dose group versus placebo. The confidence intervals and p-values will not be adjusted for multiplicity and therefore must be considered accordingly.

- Tier-2 events: Displays of Tier 2 events will include proportions, risk differences, and 95% CIs. The risk difference will be computed for PF-06835919 dose group versus placebo. P-values will not be presented. The confidence intervals are for estimation purposes only.

- Tier-3 events: These are events that are neither tier-1 nor tier-2 events. Tier 3 events will not be explicitely tabulated and listed. They will be included with the overall AE displays described earlier in this subsection.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

Analysis of Hypoglycemia

Hypoglycemia events will also be analyzed following 3-tier approach.

6.7.2. Laboratory Data

All planned, quantitative, standard safety laboratory data presented in Appendix 2 of the protocol and non-standard safety laboratory data that are not reported independently will be listed and summarized by treatment in accordance with the sponsor reporting standards as applicable. Baseline is as defined in Section 3.5.2.

6.7.3. Vital Signs

The average of the triplicate values at any time point will be used as the measurement. Absolute values and changes from baseline in seated systolic and diastolic blood pressure and pulse rate will be summarized by treatment and time postdose, 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 the pre-dose systolic and diastolic blood pressure and pulse rate will be plotted against study week. On each plot there will be 1 line for each treatment, all treatments on the same plot including the placebo. Corresponding individual plots of changes from baseline may be produced for each treatment if deemed necessary based on the data.

For baseline subtracted seated 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 1. 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 seated systolic and diastolic blood pressures, and maximum increase from baseline for seated pulse rate will be summarized by treatment, according to sponsor reporting standards.

Additional Analyses

- **Analysis Endpoints:** Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Pulse Rate (PR)
- **Analysis Time Points**:
  - Pre-dose values: Weeks 2, 4, 8, 12 and 16. Additionally the follow-up time point will be used for descriptive statistics only.
  - 1-2-hr post-dose: Weeks 2, 8 and 12
- **Analysis population:** Safety Analysis Set
- **Analysis methodology:** Change from baseline will be analyzed using the MMRM model or non-parametric methods. The model will include treatment, study day and treatment-by-study day interaction as fixed effects, baseline value as a covariate.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and all post-baseline visits will be presented for each treatment group.
- Change from baseline: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment group and at each post-baseline visit. Models will be fitted separately for pre-dose and 1-2-hr post dose assessment times. The LSMs, 90% CI for the LSMs, difference between the LSMs of each PF-06835919 group and the placebo group with the corresponding 90% CI and the 2-sided p-values derived from the model will be presented at the time points specified above.

Figures

- A line plot of the model-derived LSMs for all treatment groups including the placebo group with 90% CIs will be provided with time on X-axis. Separate lines will be plotted for each treatment group with 0 values at Baseline for all treatment groups.

6.7.4. Electrocardiogram

Absolute values and changes from baseline in QT, heart rate, QTcF, PR, 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 week. On each plot there will be 1 line for each treatment, all treatments on the same plot including

the placebo. Corresponding individual plots of changes from baseline may be produced for each treatment based on the data.

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 week.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in the Appendix 1 (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 QT and QTcF.

7. INTERIM ANALYSES

Interim analyses may be performed to assess efficacy or/and safety after at least 30% of the planned participants (ie, approximately 45 participants), complete their study participation through the end of the treatment phase of the study (ie, Week 16). Interim analysis results may be used for internal business decisions including, but not limited to, future study planning, stopping for futility, stopping for early success, conducting a sample size re-estimation, or adapting the study after the interim analysis. 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 IRC charter. In addition, the analysis details will be documented and approved in an interim analysis SAP.

8. REFERENCES

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

APPENDIX 1: 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
Seated pulse rate (bpm)	min. <40	max. >120

- Measurements that fulfill these criteria are to be listed in the report.

APPENDIX 2: TIER 1 ADVERSE EVENTS

Urinary tract infection
Dehydration
Electrocardiogram QT interval abnormal
Arrhythmia
Tachycardia
Renal failure
Blood creatinine increased
Blood creatinine abnormal
Blood urea increased
Blood urea abnormal
Creatinine renal clearance decreased
Glomerular filtration rate abnormal
Glomerular filtration rate decreased
Renal tubular disorder

Renal impairment
Proteinuria
Neutropenia
Genital infection fungal
Candida infection
Rash
Photosensitivity reaction
Liver function test abnormal
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Transaminases abnormal
Transaminases increased
Hypokalaemia

APPENDIX 3: LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
CCI	[redacted]
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
ApoC3	apolipoprotein C3
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CAP	controlled attenuation parameter
CFB	change from baseline
CCI	[redacted]
CI	confidence interval
CCI	[redacted]
CRF	case report form
CSR	clinical study report
DBR	Database Release
eGFR	Estimated Glomerular Filtration Rate
ECG	electrocardiogram
FAS	full analysis set
CCI	[redacted]
HbA1c	hemoglobin A1C
CCI	[redacted]
HOMA-IR	homeostatic model assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IRC	internal review committee
CCI	[redacted]
LLQ	lower limit of quantitation
LS	least-squares
LSM	least-squares mean
MAR	missing at random
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
mm Hg	millimeters of mercury
MMRM	mixed-effects model with repeated measures
MRI	magnetic resonance imaging

Abbreviation	Term
msec	millisecond
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
ND	not done
NS	no sample
PD	pharmacodynamic(s)
PDFF	proton density fat fraction
PK	pharmacokinetic(s)
QD	once daily
QRS	pulses in a heart beat
QT	Q wave to end of T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RR	Response ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOA	schedule of activities
SOP	standard operating procedure
T2DM	Type 2 Diabetes Mellitus
TEAE	treatment-emergent adverse event
CCI [redacted]	[redacted]
VCTE	vibration controlled transient elastography