Protocol C3711001

A PHASE 2A, RANDOMIZED, DOUBLE BLIND (SPONSOR-OPEN), PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF PF-05221304 AND PF-06865571 CO-ADMINISTERED FOR 6 WEEKS IN ADULTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Version: Amendment 1

Date: 16-AUG-2019

[redacted]

[redacted]

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3711001 is based on the Final Protocol Amendment 1, dated 02 October 2018.

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	• A few corrections were made: 1) Section 3.5 Vitals: Changed "supine" to "seated" CCI [redacted] • Added liver enzymes to Table 3 and Table 4 • Added detail of Interim Analysis in Sections 7, 8 and 9.2. • Minor edits, clarifications, and format/style changes throughout.	• To fix some typos • To add analysis summary for liver enzymes • To update the SAP to include detail of Interim Analysis • To provide further clarity

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

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3711001. 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

The study objectives are shown below along with their corresponding endpoints.

Primary Objective(s):	***Primary Endpoint(s):***
To determine the effect of co-administration of PF-05221304 and PF-06865571 on whole liver fat compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with non-alcohlic fatty liver disease (NAFLD).	*Relative change from Baseline in whole liver fat at Day 42, as assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF).*
Secondary Objective(s):	***Secondary Endpoint(s):***
To evaluate safety and tolerability of PF-05221304 and PF-06865571 co-administration compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	*Assessment of treatment-emergent adverse events (and serious adverse events), clinical laboratory tests including lipids, vital signs, and 12-lead electrocardiograms (ECGs).*

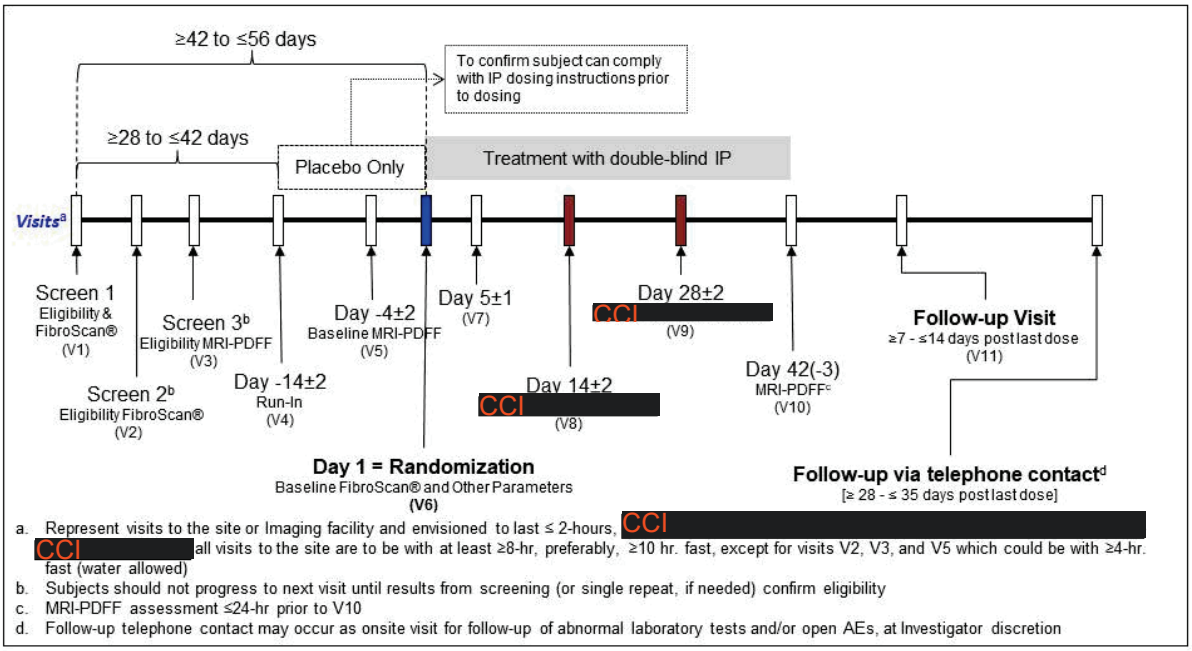
Tertiary/Exploratory Objective(s):	***Tertiary/Exploratory Endpoint(s):***
To evaluate the effect of co-administration of PF-05221304 and PF-06865571, on liver function tests (LFTs) compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	*Percent change from Baseline at all time points for:* • *Alanine aminotransferase (ALT), Aspartate aminotransferase (AST).* • *Alkaline Phosphatase.* • *Gamma-glutamyl transferase (GGT).*
To evaluate effects of co-administration of PF-05221304 and PF-06865571 on lipids compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	*Percent change from Baseline at all time points for:* • *Triglycerides.* • *Total cholesterol, HDL-C, direct LDL-C, Total cholesterol/HDL-C ratio, and non-HDL-C.*
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
To evaluate the PD effects of co-administration of PF-05221304 and PF-06865571 compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone, in adults with NAFLD.	*Analyses for PD parameters:* • *% Change from Baseline to Day 42 in Apolipoproteins (A1, B100 and C3).* CCI [redacted] *% Change from Baseline to Day 42 in plasma proprotein convertase subtilisin/kexin type 9 (PCSK9)* CCI [redacted]
CCI [redacted]	[redacted]

CCI [redacted]	[redacted]
To collect banked biospecimen for exploratory research, unless prohibited by local regulation or ethics committee decision.	*Collection of banked bio-specimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in Section 7.7* of the Protocol

2.2. Study Design

This is a randomized, double blind (sponsor open), placebo-controlled, 2x2 factorial, 4 arm (placebo, monotherapy of PF-05221304 , monotherapy of PF-06865571 and combination of PF-05221304 and PF-06865571), parallel group study (Figure 1).

Figure 1. C3711001 Study Design



Determination of eligibility for this study will occur via a sequential, 3 step process, starting at the first screening visit (Screen 1). Subjects identified to be eligible based on Screen 1 AND Screen 2 procedures will proceed to Screen 3 to measure liver fat by MRI-PDFF. For a given subject, this three-step eligibility assessment may take up to 6 weeks.

Once confirmed to be eligible based on results of Screen 3, subjects will progress to a Run in period (Visit 4), at which time subjects will receive single blind placebo for approximately 14 days to ensure compliance with the administration of investigational product (IP). Approximately 4 days prior to randomization, subjects will report to the imaging center (Visit 5) to have a Baseline MRI PDFF scan performed. At Visit 6 (Day 1), subjects will be

randomized to receive 1 of 4 blinded IP regimens (placebo, PF-05221304 monotherapy, PF-06865571 monotherapy, or PF-05221304 plus PF-06865571 combination) for a duration of up to 6 weeks (ie, 42 days). This study includes a total of 11 scheduled outpatient visits to the study site, including 4 visits to the imaging center, and a safety Follow up telephone contact. The total participation, from Visit 1 (Screen 1) to Follow up telephone phone call will be up to approximately 19 weeks.

Approximately 98 subjects (14 for the placebo group, 28 for each of the monotherapy groups and 28 for the combination group) will be randomized at approximately 30 sites (refer to Section 9.1 of the Protocol*).*

Subjects who are noted to have non evaluable Baseline MRI-PDFF, as determined by the sponsor identified central imaging vendor, should have their MRI-PDFF repeated once; if the images are still non evaluable on single repeat, the subject will be considered as screen failed; otherwise, there are no plans to replace subjects who are prematurely withdrawn.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Relative change from Baseline (CBL) (ie, observed value / Baseline value) in whole liver fat at Day 42, as assessed by MRI-PDFF. 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 CBL, 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 42, only 7 segments have non-missing results, whole liver PDFF will be calculated using the matching individual segmental PDFFs at ***both*** Baseline and Day 42.

3.2. Secondary Endpoints

- The secondary endpoints include the standard safety endpoints, namely, adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests including lipids,

vital signs (including blood pressure and pulse rate), and 12-lead ECGs. These will be further described in Section 3.5.

3.3. Tertiary/Exploratory **Endpoints**

- % CBL at all time points for ALT, AST, Alkaline Phosphatase, Gamma glutamyl transferase (GGT).

- % CBL at all time points for triglycerides, total cholesterol, HDL-C, direct LDL-C, total cholesterol/HDL-C ratio, and non-HDL-C

  Baseline is defined as the result closest ***prior to*** dosing on Day 1. The parameter of non-HDL-C will be calculated as follows:

  Non-HDL-C = Total cholesterol – HDL-C

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- PD Parameters:

  - % CBL to Day 42 in Apolipoproteins (A1, B100 and C3).

CCI [redacted]

[redacted]

- % CBL to Day 42 in plasma PCSK9.

[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, weight, height, and body mass index will be summarized by sex at birth and treatment in accordance with the sponsor reporting standards. In addition, the demographic data will be summarized by treatment only in accordance with the sponsor reporting standards. The number and proportion of subjects enrolled in each study site will also be presented.

Subjects will be stratified at randomization (Day 1) by the MRI-PDFF liver fat measurement determined by the Sponsor-identified central imaging vendor of images obtained during Screen 3:

- Screening liver fat ≥8% and <15%;
- Screening liver fat ≥15%;
- Subjects will then be stratified by the presence or absence of type 2 diabetes mellitus (T2DM).

For Baseline diabetic status, data will be obtained from the case report forms (CRFs). Screening liver fat was used as a binary variable for stratification purposes but Baseline liver fat will be used as a continuous covariate in the efficacy analysis to maximize the utility of information. Baseline diabetic status will only be included as a covariate in the primary analysis (analysis of covariance [ANCOVA]) if at least 1/3 of the subjects have T2DM.

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.

Adverse Events

For 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.

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.

Vital signs

Seated 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.

ECGs

Single 12-lead ECGs will be obtained on all subjects at times detailed in the Schedule of Activities given in the protocol. 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:

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

The maximum absolute value (post-dose) and the maximum increase from Baseline for QTcF, heart rate, PR and QRS, will be determined among overall post-Baseline measurements 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.

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.

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:

- 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 one dose of IP*; subjects are assigned to the randomized treatment regardless of what treatment was received. This is 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 one 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.

4.4. Other Analysis Sets

CCI [redacted]

Pharmacogenomic and biomarker data will be collected and retained for future analyses, but will not be analyzed for the purposes of CSR.

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 the primary endpoint:

1. The PF-05221304 + PF-06865571 combination is equal in effect to placebo.
2. The PF-05221304 monotherapy is equal in effect to placebo.
3. The PF-06865571 monotherapy is equal in effect to placebo.
4. The PF-05221304 + PF-06865571 combination is equal in effect to the PF-05221304 monotherapy.
5. The PF-05221304 + PF-06865571 combination is equal in effect to the PF-06865571 monotherapy.

[redacted]

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

1. The PF-05221304 + PF-06865571 combination is different from the effect of placebo.
2. The PF-05221304 monotherapy is different from the effect of placebo.
3. The PF-06865571 monotherapy is different from the effect of placebo.
4. The PF-05221304 + PF-06865571 combination is different from the effect of the PF-05221304 monotherapy.
5. The PF-05221304 + PF-06865571 combination is different from the effect of the PF-06865571 monotherapy.

The following confidence intervals (CIs) associated with the above hypotheses will be constructed:

1. 2-sided 90% CI
2. 2-sided 90% CI
3. 2-sided 90% CI
4. 2-sided 90% CI and 2-sided 50% CI
5. 2-sided 90% CI and 2-sided 50% CI

No adjustment for multiple comparisons will be made.

Interim analyses (IAs) may be performed for safety or efficacy (see Section 7 for further detail). IA 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 (STD), median, minimum (min), and maximum (max) values, will be provided for continuous endpoints. Some measures will be summarized using graphical representations by treatment and study day of visit, where appropriate.

Mixed Model for Repeated Measurements (MMRM)

This model will be used for the analysis of endpoints with more than one post-Baseline collection time point. All observed data collected during the post-Baseline treatment period will be utilized. The MMRM analysis will be performed with treatment, study day and treatment-by-study day interaction as fixed effects, Baseline value of the analysis endpoint, and Baseline whole liver PDFF. If the endpoint being analyzed is log-tranformed, the Baseline value of the analysis endpoint and the Baseline whole liver PDFF will also be log-transformed. Repeated measures model with unstructured correlation matrix will be utilized. 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 least square means (LSMs) and CIs at each time point. LSM difference for each comparison along with the CIs and 2-sided p-values will be provided. 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.

Analysis of Covariance

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 as covariates. Diabetes status will be included as a covariate for the primary endpoint only if at least 1/3 of the subjects have T2DM. If the endpoint being analyzed is log-tranformed, the Baseline value of the analysis endpoint and the Baseline whole liver PDFF will also be log-transformed. Estimates of treatment effects will be assessed using LSMs and CIs. Estimates of the mean differences for each comparison and the corresponding CI will be obtained from the model. 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 3.5x STD ± 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 CIs (see Section 5.1) 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.

5.3. Methods to Manage Missing Data

In case of continuous endpoints, all available data will be utilized in the MMRM. 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 upper limits of quantification such values will be truncated at the upper limit of quantification in all summary tables. If the concentrations are below the lower limits of quantification (LLQ) such values will be imputed by 0.5*LLQ. However, in listings they will appear as reported.

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 LLQ.)
In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint: Whole Liver PDFF

Primary Analysis

- **Analysis endpoint:** Whole liver PDFF
- **Analysis time points:** Day 42
- **Analysis population:** Full Analysis set
- **Analysis methodology:** Natural log-transformed individual relative change (RC) from Baseline to Day 42 in whole liver PDFF will be analyzed using the ANCOVA. The model will include natural log-transformed Baseline whole liver PDFF. Baseline diabetes status will be included as a covariate only if at least 1/3 of the subjects have T2DM.

Reporting results:

- Raw data: The sample size, mean, STD, median, min and max at Baseline and Day 42 visit will be presented for each treatment arm.
- %CBL: The sample size, mean, STD, median, min and max will be presented for each treatment arm at Day 42. The LSMs and their CI will be exponentiated to provide estimates of the RC which will be converted to percent change as follows:
  Percent change = 100* (RC - 1).

  Estimates of the mean relative changes between placebo and each active drug arm (PF-05221304 monotherapy, PF-06865571 monotherapy and PF-05221304 plus PF-06865571 combination) at Day 42, and the corresponding 90% CI will be obtained from the model. The 2-sided p-values will also be presented.

  PF-05221304 plus PF-06865571 combination will be compared to each monotherapy through estimates of the mean relative change and corresponding 50% and 90% CIs. The 2-sided p-values will also be presented.

Figures

- Mean + CI plot of the model-derived LSMs in %CFB for all treatment groups including the placebo group with 90% CI will be provided for Day 42 with treatment group on the X-axis.
- Mean + CI plot of the placebo-adjusted LSMs with 90% CI for the each active drug arm (PF-05221304 monotherapy, PF-06865571 monotherapy and PF-05221304 plus PF-06865571 combination) will be provided for Day 42 with treatment on the X-axis.
- Mean + CI plot of the LSM differences with 50% and 90% CIs for the comparison between the PF-05221304 plus PF-06865571 combination and each monotherapy will be provided for Day 42 with treatment on the X-axis.
- Box and whisker plots for individual percent change from Baseline versus treatment will be presented and overlaid with arithmetic means.

Reporting results:

The LSMs, 90% CI for the LSMs, difference between the LSM for each of the 5 treatment comparisons (same as those indicated for the primary analysis) , and the corresponding 90% CI (as well as 50% CI for the 2 comparions: the PF-05221304 plus PF-06865571 combination vs, each monotherapy) 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.

6.3. Other Endpoints

The below table lists the exploratory endpoints with the corresponding descriptive statistics to be presented. Full analysis set will be utilized.

Table 2. Exploratory Endpoints - Descriptive Summary

Exploratory Endpoints	Descriptive Statistics
Raw values and % CBL in ALT, AST, Alkaline Phosphatase and GGT, at all relevant collection time point(s) including follow-up	N, Mean, Median, STD, Min and Max at all planned day(s) of collection
Raw values and % CBL in Triglycerides, Total cholesterol, HDL-C, direct LDL-C, Total cholesterol/HDL-C ratio, and non HDL-C, at all relevant collection time point(s) including follow-up	N, Mean, Median, STD, Min and Max at all planned day(s) of collection
[redacted]	CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
Raw values and % CBL in Apolipoproteins (A1, B100 and C3). at all relevant collection time point(s)	N, Mean, Median, STD, Min and Max at all planned day(s) of collection
[redacted]	CCI [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Raw values and % CBL in plasma PCSK9, at all relevant collection time point(s) including follow-up	N, Mean, Median, STD, Min and Max at all planned day(s) of collection
[redacted]	CCI [redacted]

The LSMs, 90% CI for the LSMs, difference between the LSM for each of the 5 treatment comparisons (same as those indicated for the primary analysis) , and the corresponding 90% CI and the 2-sided p-values will be calculated using the MMRM/ANCOVA methods described in Section 5.2 as appropriate. The details of the model terms are provided in the below table.

Table 3. Exploratory Endpoints Modeling Details

Exploratory Endpoints	Description of the Model Terms
% CBL in ALT, AST, Alkaline Phosphatase and GGT, at all post-Baseline time points	Model: MMRM Response: natural log-transformed RC Covariates: Treatment, Study Day, Treatment*Study Day, log (Baseline value), log (Baseline whole liver PDFF)
% CBL in Triglycerides, Total cholesterol, HDL-C, direct LDL-C, Total cholesterol/HDL-C ratio, and non HDL-C at all post-Baseline time points	Model: MMRM Response: natural log-transformed RC Covariates: Treatment, Study Day, Treatment*Study Day, log (Baseline value), log (Baseline whole liver PDFF)
CCI [redacted]	[redacted]
% CBL in fasting plasma PCSK9 at Day 42	Model: ANCOVA Response: natural log-transformed RC Covariates: Treatment, log (Baseline value), log (Baseline whole liver PDFF)

In addition, figures will be generated for the following endpoints.

Table 4. Figures for Exploratory Endpoints

Exploratory Endpoints	Figure Descriptions
CCI [redacted]	[redacted]
% CBL in fasting plasma PCSK9 at Day	Box and whisker plot of individual % CBL versus treatment will be presented and overlaid

42	with arithmetic means.
% CBL in Triglycerides, Total cholesterol, HDL-C, direct LDL-C, Total cholesterol/HDL-C ratio, and non HDL-C at Baseline and all post-Baseline time points	Line plot of LSMs with 90% CIs for all treatment groups including the placebo group with time on X-axis. Four (4) lines corresponding to the 4 treatment groups will be overlaid on the same plot.
% CBL in AST, ALT, ALP, GGT at Baseline and all post-Baseline time points	Line plot of LSMs with 90% CIs for all treatment groups including the placebo group with time on X-axis. Four (4) lines corresponding to the 4 treatment groups will be overlaid on the same plot.
CCI [redacted]	[redacted]

CCI [redacted]

- **Pharmacogenomic and biomarker data:**

  Pharmacogenomic and biomarker data will be collected and retained for future analyses, but will not be analyzed for the purposes of CSR.

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 ≥8% and <15%;
- Screening liver fat ≥15%.

[redacted]

CCI [redacted]

CCI [redacted] If any site enrolls 50% or more of the total number of subjects in the study site-specific analysis may be conducted.

6.5. Baseline and Other Summaries and Analyses

A breakdown of demographic data will be provided for age, race, weight, height and body mass index. Each of these will be summarized by sex at birth and treatment in accordance with the sponsor reporting standards. In addition, the demographic data will be summarized by treatment only in accordance with the sponsor reporting standards. Baseline summary of fasting glucose, triglycerides, HDL-C, waist circumference, AST, ALT, alkaline phosphatase, GGT and whole liver PDFF will be presented for each treatment group and overall. Baseline summary of stratification factors, namely, diabetes status (presence or absence) and MRI-PDFF categories (≥8% and <15% or ≥15%) will be provided. The number and proportion of subjects enrolled in each study site will also be presented.

Summary tables will show end of study subject disposition and will show which subjects were analyzed for pharmacodynamic (FAS) CCI [redacted] 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 the study treatments.

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.

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 treatment-emergent adverse events (TEAEs) and AEs occurring prior to randomization will only be listed.

Laboratory Data

All planned, quantitative, standard safety laboratory data presented in Table 7 of the protocol and non-standard safety laboratory data that are not reported independently will be listed and summarized in accordance with the sponsor reporting standards as applicable. Baseline is as defined in Section 3.5.2.

Vital Signs

Absolute values and changes from Baseline in seated 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 one line for each treatment, with all treatments on the same plot, including the placebo.

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 including follow-up.

Maximum absolute values and maximum changes from Baseline for vital signs, over all measurements taken post-dose after randomization 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 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.

Electrocardiogram

Absolute values and changes from Baseline in QT, heart rate, QTcF, QTc, 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 day. On each plot there will be one line for each treatment, with 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, 90% CI) 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 after randomization) 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.

Non-standard Safety Analysis

Serum Creatinine, Serum Cystatin C and Associated eGFRs

Absolute values and changes from Baseline in Scr, serum cystatin C, eGFRs obtained from Scr 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 one 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.

7. INTERIM ANALYSES

If, after randomization of approximately 50% subjects of planned number of subjects, a monthly safety review reveals that the study meets one or more criteria listed in Protocol *Section 3.3, an interim analysis will be performed in an un-blinded manner by a pre-specified IRC, independent from study team.* CCI [redacted]

Before any interim analysis is initiated, 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. The analysis details will be documented and approved in an interim analysis SAP or final SAP.

An IA will be conducted after approximately 50% of randomized subjects reach their Week 6 visit (ie, Visit 10 in Schedule of Activities) or drop out of the study before that visit.

The analysis sets for the IA are:

[redacted]

CCI [redacted]

1. Safety Analysis Set: All randomized and treated subjects

2. Efficacy/PD Analysis Set: All randomized and treated subjects who completed their Week 6 visit (ie, Visit 10 in Schedule of ActivityActivityActivities) or discontinued the study.

For whole liver PDFF, triglycerides (and total cholesterol, HDL-C, direct LDL-C, Total cholesterol/HDL-C ratio, and non HDL-C, AST, ALT, ALP, GGT), the descriptive summarization and inferential statistical analysis (ANCOVA or MMRM) as indicated in Section 6 will be performed using the Efficacy/PD Analysis Set. Standard safety data as described in the IRC Charter[2] will be summarized using the Safety Analysis Set. The figures related to these descriptive and inferential analyses will be using the "Efficacy/PD Analysis Set".

For whole liver PDFF and triglycerides, additional analysis related to predictive probability will be conducted. The Bayesian predictive probability[3] that the following decision critera will be met at the end of the study given the interim data will be calculated using Pfizer internal validated software[4]. The IRC Statistician will utilize the IA outputs (from ANCOVA analysis for whole liver PDFF and MMRM analysis for triglycerides) to compute the predictive probabilities, and will then provide the probability values to the unblinded programmer to be included in the IA table outputs.

Safety:

S-C1: At least 95% confident that change from Baseline to Day 42 in triglycerides level with the combination treatment ACC+DGAT is less than the ACC monotherapy treatment

Predictive probability of meeting S-C1 at the end of study, based on interim data, will be computed.

Efficacy:

E-C1: At least 95% confident that the relative reduction from Baseline to Day 42 in whole liver PDFF with the combination treatment ACC+DGAT is larger than the DGAT monotherapy treatment

Predictive probability of meeting E-C1 at the end of study, based on interim data, will be computed.

8. REFERENCES

1. *McGill, R., John W. Tukey and W. A. Larsen. 1978. "Variations of Box Plots." American Statistician 32:12-16*
2. *C3711001 Internal Review Committee (IRC) Charter Amendment 1.*
3. *Grieve AP (1991) Predictive probability in clinical trials: Biometrics, 47(1) 323-9*

4. *Pfizer Internal Predictive Probability Calculation Tool: http://shiny-stats.pfizer.com/Statistics/predictive_probabilities/calculator_v1.0/*

9. APPENDICES

9.1. 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.

Calculation of %CBL

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

9.2. Predictive Probability

```
#R Code to calculate predictive probability from 'Interim Predictive Probability Calculator'

#Version: 1.01

#Created: 07-Aug-2019



#Inputs:

i_e_dir <- 2    # direction of effect of interest

                  # 1 = Group 1 is greater than Group 2; 2 = Group 1 is less than Group 2

i_e_tv <- 0     # tv = target value

i_e_sig <- 0.95    # confidence level

i_e_nAtot <- 28   # sample size for Group 1 at study end

i_e_nPtot <- 28    # sample size for Group 2 at study end

# The following inputs will be taken from the ANCOVA (liver fat) or MMRM (trigylcerides) interim analysis

i_r_nAint <-    # sample size for Group 1 at interim

i_r_nPint <-     # sample size for Group 2 at interim

i_r_meanA <-    # model-adjusted mean for Group 1 at interim from MMRM or ANCOVA

i_r_meanP <-     # model-adjusted mean for Group 2 at interim from MMRM or ANCOVA

i_r_sigma <-      # ssigma estimated at interim from MMRM or ANCOVA



  # Adapted from equations 1-4 from 'Bayesian Interim Predictive Analysis Guidance' document (v1.0 19 September 2018)



  # Derived:

  i_nAU <- i_e_nAtot-i_r_nAint
```

```
 i_nPU <- i_e_nPtot-i_r_nPint

 if(i_e_dir==1){ #Greater than

  z <- qnorm(i_e_sig)

 } else if(i_e_dir==2){ #Less than

  z <- qnorm(1-i_e_sig)

 }


 #Calculate numerator of equation:

 postSD <- i_r_sigma*sqrt((i_e_nAtot+i_e_nPtot)/(i_e_nAtot*i_e_nPtot))

 num_eq <- i_e_tv + z*postSD - (i_r_meanA - i_r_meanP)


 #Calculate denominator of equation:

 den_eq <-
i_r_sigma*sqrt(((i_nAU/i_e_nAtot)^2)*(1/i_r_nAint+1/i_nAU)+((i_nPU/i_e_nPtot)^2)*(1/i_
r_nPint+1/i_nPU))


 #Determine predictive probability:

 eq_result <- num_eq/den_eq

 if(i_e_dir==1){ #Greater than

  predProb <- 1-pnorm(eq_result)

 } else if(i_e_dir==2){ #Less than

  predProb <- pnorm(eq_result)

 }


#Predictive probability:
```

```
print(paste0(100*predProb,"%"))
```

Example Output: Summary of Predictive Probability for IA

Safety:

Treatment	LSM (S.E.)	Difference vs. PF-05221304 (S.E)	Predictive Probability of Passing S-C1*
PF-06865571 + PF-05221304 (ie, DGAT + ACC)	xx.xx (xx.xx)	xx.xx (xx.xx)	0.xx
PF-05221304 (ie, ACC)	xx.xx (xx.xx)		

*S-C1 is the safety criterion defined in Section 7
S.E = Standard Error

Efficacy:

Treatment	LSMeanLSMeanLSM (S.E.)	Difference vs. PF-06865571 (S.E)	Predictive Probability of Passing S-C1*
PF-06865571 + PF-05221304 (ie, DGAT + ACC)	xx.xx (xx.xx)	xx.xx (xx.xx)	0.xx
PF-06865571 (ie, DGAT)	xx.xx (xx.xx)		

*E-C1 is the efficacy criterion defined in Section 7
S.E = Standard Error