Protocol C3651010

A 6-WEEK, RANDOMIZED, DOUBLE BLIND, SPONSOR-OPEN STUDY TO ASSESS THE EFFECT OF REPEATED SUBCUTANEOUS ADMINISTRATION OF PF-06946860 ON APPETITE IN PARTICIPANTS WITH ADVANCED CANCER AND ANOREXIA, FOLLOWED BY AN 18-WEEK OPEN-LABEL TREATMENT PERIOD

Statistical Analysis Plan (SAP)

Version: **1**

Date: **13 Apr 2021**

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

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1 / 13APR2021	Original 18DEC2020	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 **Part A** of Study C3651010 (including follow-up for Part A if a participant does not continue to Part B of the study). 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. The methodology for summary and statistical analyses of the data collected in Part B of the study will be detailed in a supplemental SAP.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***	***Estimands***
Primary		
• *To evaluate the early effect of PF-06946860 compared to placebo on **appetite** in participants with anorexia and advanced cancer.*	• *Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score, at week 4.*	• *Estimand 1 (similar to "hypothetical") is intended to provide a population level estimate of the treatment effect on the change from baseline Appetite score for PF-06946860 compared to placebo in all evaluable participants under the scenario of no discontinuation of study intervention and without the potential confounding effects of prohibited medications, regardless of the participants' compliance with dosing (i.e. using the Censored analysis set)*
Secondary		
• *To evaluate the effect of PF-06946860 compared to placebo on **appetite** in participants with anorexia and advanced cancer.*	• *Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score, at weeks 1, 2, 3, 5 and 6.*	• *Estimand 1, as above*

Objectives	***Endpoints***	***Estimands***
• *To evaluate the effect of PF-06946860 compared to placebo on **fatigue** in participants with anorexia and advanced cancer.*	• *Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Fatigue score, at weeks 1, 2, 3, 4, 5 and 6.*	• *Estimand 2 (similar to "hypothetical") is intended to provide a population level estimate of the treatment effect on the change from baseline Fatigue score for PF-06946860 compared to placebo in all evaluable participants under the scenario of no discontinuation of study intervention and without the potential confounding effects of prohibited medications, regardless of the participants' compliance with dosing (i.e. using the Censored analysis set)*
• *To characterize the **safety and tolerability** of repeated subcutaneous (SC) administrations of PF-06946860 compared to placebo in participants with anorexia and advanced cancer.*	• *Incidence of adverse events* (AE) *and laboratory abnormalities, in Part A of the study.*	• *There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards, as applicable.*
Tertiary/Exploratory:		
• *To evaluate the effect of PF-06946860 compared to placebo on **body weight** in participants with anorexia and advanced cancer.*	• *Change from baseline in body weight,at weeks 3, 4 and 6.*	• *N/A*
• *To explore the relationship between **pain** and appetite/fatigue in participants with anorexia and advanced cancer*	• *Change from baseline score for patient reported 7-day recall PROMIS-Pain 1a, Cancer-Related Cachexia Symptom Assessment-Fatigue score and Cancer-Related Cachexia Symptom Assessment-Appetite score at Weeks 1, 2, 3, 4, 5 and 6.*	• *N/A*
• *To assess **patient global impression of change** (PGI-C) of appetite and fatigue in participants with anorexia and advanced cancer*	• *PGI-C (appetite), at Weeks 4 and 6.* • *PGI-C (fatigue), at Weeks 4 and 6.*	• *N/A*
• *To characterize unbound and total* pharmacokinetics (***PK)*** *of PF-06946860 administered in participants with anorexia and advanced cancer*	• *Serum unbound and total concentrations of PF-06946860, on Day 1 and Weeks 3, 4 and 6.*	• *N/A*
• *To characterize the effect of PF-06946860 administration on circulating* growth differentiation factor 15 (***GDF-15****) concentrations in*	• *Serum concentrations of total GDF-15; and if feasible, unbound GDF-15, on Day 1 and Weeks 3, 4 and 6.*	• *N/A*

Objectives	***Endpoints***	***Estimands***
participants with anorexia and advanced cancer.		
• *To assess the **immunogenicity** of PF-06946860 administered in participants with anorexia and advanced cancer.*	• *Incidence of* antidrug antibodies (*ADA) and, if applicable,* neutralizing antibodies *(Nab), in part A of the study.*	• *N/A*

Additional tertiary/exploratory objectives will be evaluated using data from **Part B** of Study C3651010, as data permit. These objectives are not addressed in this SAP but will be addressed in a supplemental SAP.

2.1.1. Primary Estimand(s)

Estimand related to the change from baseline for the patient reported 7-day recall Appetite score (Part A):

Estimand 1 *(similar to "hypothetical") is intended to provide a population level estimate of the treatment effect on the change from baseline Appetite score for PF-06946860 compared to placebo in all evaluable participants under the scenario of no discontinuation of study intervention and without the potential confounding effects of prohibited medications, regardless of the participants' compliance with dosing (i.e. using the Censored analysis set).*

- *Population: Patients with advanced cancer, anorexia and elevated circulating GDF-15 levels.*
- *Variable: Change from baseline for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score at Week 4.*
- *Intercurrent Events:*
  a) *Discontinuation of study intervention – Data collected after a participant has discontinued study intervention will be censored and treated as missing data.*
  b) *Prohibited medications – Data collected after a participant has received prohibited medications, that would modulate the primary endpoint, will be censored and treated as missing data. The list of concomitant medications will be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.*
  c) *Inadequate compliance – Data collected after a participant has missed a dose will be censored and treated as missing data.*

  Missing data due to censoring, study withdrawal or other reasons, are assumed to be missing at random.
- *Population level summary: Difference in mean change from baseline for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score at Week 4 between PF-06946860 and placebo.*

This estimand will similarly be applied to the change from baseline at Weeks 1, 2, 3, 5 and 6.

2.1.2. Secondary Estimand(s)

Estimand related to the change from baseline for the patient reported 7-day recall Fatigue score (Part A):

Estimand 2 *will be similar to Estimand 1, except for the following: -*

- *Variable: Change from baseline for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Fatigue score at Weeks 1, 2, 3, 4, 5 and 6.*
- *Population level summary: Difference in mean change from baseline for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Fatigue score at Week 4 between PF-06946860 and placebo.*

Estimands related to safety and tolerability:

There are no defined estimands for the incidence of treatment emergent adverse events and laboratory abnormalities, and these endpoints will be analyzed using Pfizer data standards as applicable.

2.1.3. Additional Estimand(s)

Estimands related to tertiary/exploratory objectives:

Tertiary/exploratory endpoints may be analyzed using similar estimands or analyzed in a descriptive manner without reference to an estimand. Other supporting estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of results, compare to available literature and/or be used for future study planning as needed.

Additional estimand related to the change from baseline for the patient reported 7-day recall Appetite score (Part A):

Estimand 3 (similar to "treatment policy") may be used, dependant on the amount of censored data (based on a blinded review prior to database lock), to assess the robustness of the treatment effect on the primary endpoint. It is intended to provide a population level estimate of the treatment effect on the change from baseline Appetite score for PF-06946860 compared to placebo in all evaluable participants without regard to discontinuation of study intervention or administration of prohibited medications, regardless of the participants' compliance with dosing (i.e. using the Complete analysis set).

- Population: Patients with advanced cancer, anorexia and elevated circulating GDF-15 levels.
- Variable: Change from baseline for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score at Week 4.
- Intercurrent Events:
  a) Discontinuation of study intervention – All data collected, regardless of a participant's discontinuation of study intervention, will be included in the analysis.
  b) Prohibited medications – All data collected, regardless of a participant's use of prohibited medications, will be included in the analysis.

c) Inadequate compliance – All data collected, regardless of a participant's compliance (i.e. missed doses), will be included in the analysis.

- Population level summary: Difference in mean change from baseline for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score at Week 4 between PF-06946860 and placebo.

This estimand will similarly be applied to the change from baseline at Weeks 1, 2, 3, 5 and 6.

2.2. Study Design

This is a Phase 1b study in patients with advanced cancer, anorexia and elevated circulating GDF-15 levels with the primary purpose of assessing the effect of PF-06946860 administration on appetite.

The study will be conducted in 2 parts. The initial 6-week treatment period will be a randomized, double-blind, placebo-controlled, parallel group study. Participants who meet the entry criteria will be randomized to study drug (PF-06946860 or placebo). The 6-week double-blind period will consist of a total of 2 SC doses, administered 3 weeks apart (Q3W). The 6-week double-blind treatment period will be followed by optional open-label treatment (OLT) with PF-06946860 of up to 18 weeks; the total duration of treatment would, therefore, be up to 24 weeks.

Approximately 40 participants will be randomly assigned to investigational product such that approximately 30 evaluable participants complete the 6-week double-blind portion of the study. The study will be randomized in approximately a 2:1 ratio (27 active: 13 placebo).

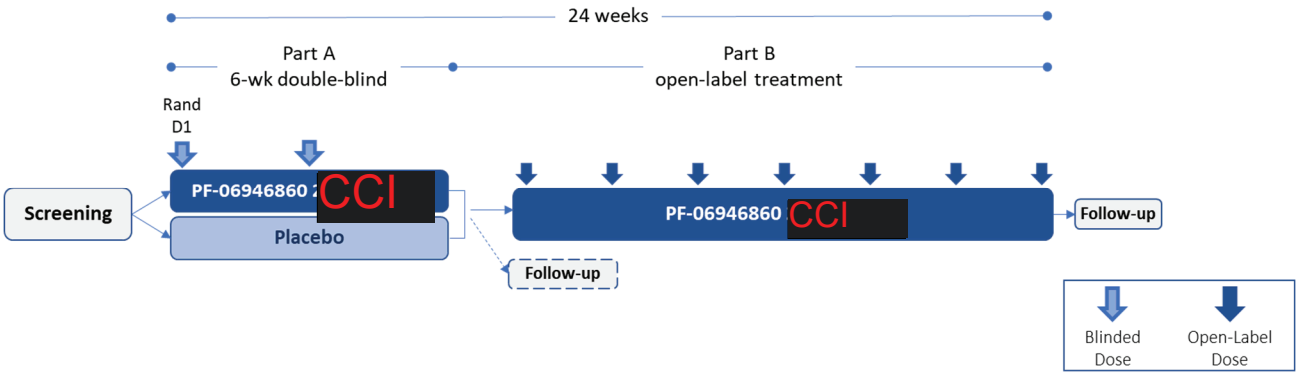
Potential participants will attend 2 clinic visits (Screening and Randomization) with the investigator.

All study visits following Randomization may be conducted by a visiting Health Care Professional (HCP) at the patient's home. Should the participant elect, at Randomization, to have all subsequent Part A study visits carried out at the investigator site rather than at home, this preference may be accommodated.

During the week 4 TeleHealth consult, the investigator and participant will decide whether to continue with the optional open-label treatment period. Participants opting to continue to the OLT period will receive their first dose of open-label PF-06946860 at the week 6 visit, coinciding with the last visit of the double-blind portion of the study.

Follow-up contact with all participants (whether participating in the 6-week double-blind only, or the OLT period) will be scheduled to occur at at least 28 days and up to 35 days after the last administration of IP. For study Part A, this contact may be done via a phone call, telehealth or in the clinic. Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

Figure 1 Schema



This SAP relates to the 6-week double blind (Part A) portion of the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

For all endpoints, baseline is defined as the measurement taken on Day 1 (unless otherwise specified) or, if that is not available, the last-pre-dose measurement at screening will be used, where appropriate.

For those participants continuing into Part B of the study, only data collected prior to dosing at Week 6 will be included in the summary and statistical analyses of Part A of the study.

3.1. Primary Endpoint(s)

- ***Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score, at Week 4***

The Cancer-Related Cachexia Symptom Assessment-Appetite is a self-reported questionnaire that measures the severity of anorexia. It was developed based on qualitative research with patients as well as review of literature and other existing relevant measures. The measure consists of 1 question that asks study participants to rate their appetite over the past 7 days from 0-"no appetite" to 10-"very good appetite". The assessments will be completed electronically by study participants at home, or at the clinic.

3.2. Secondary Endpoint(s)

- ***Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score, at Weeks 1, 2, 3, 5 and 6***

See section 3.1.

- ***Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Fatigue score, at Weeks 1, 2, 3, 4, 5 and 6***

The Cancer-Related Cachexia Symptom Assessment-Fatigue is a self-reported questionnaire that measures the severity of fatigue. It was developed based on qualitative research with patients as well as review of literature and other existing relevant measures. The measure consists of 1 question that asks study participants to rate their fatigue over the past 7 days from 0-"no fatigue" to 10-"worst possible fatigue". The assessments will be completed electronically by study participants at home, or at the clinic.

- ***Incidence of adverse events and laboratory abnormalities, in Part A of the study***

See section 3.5.

3.3. Other Endpoint(s)

- ***Change from baseline in body weight, at Weeks 3, 4 and 6***

Body weight will be recorded using an electronic scale (provided to the participant for their use at home). During each weight measurement, from Randomization onward, body composition data (including total body water, fat mass and fat-free mass, if possible) will be captured via bioelectrical impedance analysis (BIA), as feasible.

- ***Change from baseline score for patient reported 7-day recall PROMIS-Pain 1a at Weeks 1, 2, 3, 4, 5 and 6***

The PROMIS Pain 1a is a self-reported measure that assesses the intensity of the participant's pain in the past 7 days from 0-"no pain" to 10-"worst imaginable pain".

- ***PGI-C (appetite), at Weeks 4 and 6 and PGI-C (fatigue) at Weeks 4 and 6***

The PGI-C is a measure consisting of 2 questions that asks study participants to rate the overall change in their symptoms of appetite and fatigue since they started the study on a 7 point verbal rating scales that ranges from "Much better" to "Much worse".

The PGI-C (appetite and fatigue) categories will be combined to produce a 5-point scale as defined below:-

Category	Definition
Much Better	1
Somewhat Better	2-3
No Change	4
Somewhat Worse	5-6
Much Worse	7

- ***Serum unbound and total concentrations of PF-06946860, on Day 1 and Weeks 3, 4 and 6.***

- ***Serum concentrations of total GDF-15; and if feasible, unbound GDF-15, on Day 1 and Weeks 3, 4 and 6.***

Relative change from baseline (i.e. post-dose / baseline) will be derived at each post-baseline timepoint.

- ***Incidence of ADA and, if applicable, NAb, in part A of the study.***

- ***Change from baseline in body composition endpoints, at Weeks 3, 4 and 6***

During each weight measurement from Randomization onward, and using electronic scale provided to the participant, body composition data (including total body water, fat mass and fat-free mass, if possible) will be captured via bioelectrical impedance analysis (BIA), as feasible.

3.4. Baseline Variables

Not applicable.

3.5. Safety Endpoints

3.5.1. Adverse Events

An AE is considered treatment emergent (TEAE), relative to a given treatment, if the event starts during the effective duration of treatment, i.e. starting on, or after, the date and time of the first dose, but before the end of Part A (i.e. Week 6 for subjects continuing to Part B; or follow-up contact (28-35 days after last dose), for those subjects not continuing to Part B of the study)).

A 3-tier approach for summarizing AEs will not be used due to the low number of participants planned to be recruited.

3.5.2. Laboratory Data

Safety laboratory tests (hematology, chemistry, urinalysis and other clinical laboratory tests) will be performed as described in the protocol.

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Participant Analysis Set	***Description***
Enrolled/Randomly assigned to study intervention	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Evaluable	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized study intervention.*

Safety	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*

Defined Analysis Set	***Description***
Censored	*For participants who discontinue study intervention, receive prohibited medication and/or miss a dose, all observations post-discontinuation, post-medication or post-missed dose will be censored and treated as missing data.*
Complete	For participants who discontinue study intervention, receive prohibited medication and/or miss a dose, all observations post-discontinuation, post-medication or post-missed dose will be included in the analysis set.
PK	*All participants randomly assigned to study intervention and who take at least 1 dose of PF-06946860 and in whom at least 1 PK concentration value is reported.*
Pharmacodynamic (PD)	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 PD (GDF-15) concentration value is reported.*
Immunogenicity	*All participants randomly assigned to study intervention and who take at least 1 dose of PF-06946860 and in whom at least 1 ADA result is reported.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no formal hypothesis tests planned for this study and no statistical decision rules will be applied.

5.2. General Methods

The analyses related to the primary, secondary and exploratory endpoints will be based on the appropriate population for analysis (see Section 4).

Unless otherwise stated, all summaries and plots will be presented by treatment group. The following treatment group labels (or similar) will be used: -

Placebo
PF-06946860 CCI Q3W

5.2.1. Summary Analyses for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation (SD), median and range (minimum and maximum) values. For endpoints to be analysed on the natural log scale ($\log_e$), the geometric mean and geometric coefficient of variation (CV) will additionally be calculated.

5.2.2. Summary Analyses for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.2.3. Mixed Models Repeated Measures (MMRM) Analysis

The mixed effects repeated measures (MMRM) model will include participant as a random term, and baseline, time (as a factor), baseline-by-time interaction, treatment and treatment-by-time interaction as fixed terms in the model. An unstructured covariance matrix will be fitted to the repeated times within subject (other covariance matrices will be considered if necessary, e.g. if convergence is not obtained or model fit is not adequate*), and the Kenward-Roger approximation will be used for estimating degrees of freedom. Additional terms may be fitted in the model (e.g. cancer type, PROMIS-Pain 1a change from baseline score), as appropriate.*

Least-squares (LS) means (and 90% CIs) and mean differences versus placebo (and 90% CIs), at each timepoint, will be provided. Means and differences averaged over the timepoints may also be included. No adjustments will be made for multiplicity.

Example SAS code is provided in Appendix 1.

5.3. Methods to Manage Missing Data

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

In all PD data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLQ).

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero.

In listings, BLQ values (for PK or PD) will be reported as "<LLQ", where LLQ will be replaced with the value for the LLQ.

For PK and PD summary tables and plots of median profiles, 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 (i.e. not done) or NS (i.e. no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

6. ANALYSES AND SUMMARIES

For all endpoints the analyses will be carried using the Censored Analysis Set, defined in Section 4, unless otherwise specified. Baseline is defined in Section 3.

6.1. Primary Endpoint(s)

6.1.1. Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score, at Week 4.

6.1.1.1. Main Analysis

Absolute values and changes from baseline in the Cancer-Related Cachexia Symptom Assessment–Appetite score will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1. Tables will present all data from the baseline and post-baseline timepoints (including follow-up for Part A for those participants that do not continue to Part B of the study).

The primary analysis will be an MMRM (as described in Section 5.2.3) applied to the change from baseline at Weeks 1, 2, 3, 4, 5 and 6, that will be used to estimate the treatment effect related to the primary Estimand 1 (as described in Section 2.1.1).

The following results from the above primary analysis will be plotted:

- Profile plots of the LS Means (including 90% confidence intervals [CIs]) over time, with a separate line for each treatment group
- Profile plots of the LS Mean differences to Placebo (including 90% CIs) over time

Standard SAS output will be provided to support the main statistical summary table for the secondary analysis model, but will not be included in the Clinical Study Report (CSR).

Statistical Model Diagnostics

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

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses

excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

6.1.1.2. Sensitivity/Supplementary Analyses

An additional exploratory analysis (for the primary endpoint only), examining the robustness of results for the primary endpoint, may be performed to estimate the treatment effect related to Estimand 3 (as described in Section 2.1.3). The same summaries and analysis as the main analysis (Section 6.1.1.1) will be performed and reported, but applied to the Complete Analysis Set (as described in Section 4).

6.2. Secondary Endpoint(s)

6.2.1. Change from Baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Appetite Score, at Weeks 1, 2, 3, 5 and 6

Summaries and analysis for Weeks 1, 2, 3, 5 and 6 of the Cancer-Related Cachexia Symptom Assessment-Appetite score will be presented as part of the primary analysis described in section 6.1.1.1.

6.2.2. Change from Baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Fatigue Score, at Weeks 1, 2, 3, 4, 5 and 6

The Cancer-Related Cachexia Symptom Assessment-Fatigue score will be summarized and analysed in a similar way to the primary endpoint, as described in Section 6.1.1.1.

6.2.3. Incidence of Adverse Events and Laboratory Abnormalities, in Part A of the Study

See section 6.6.

6.3. Other Endpoint(s)

6.3.1. Change from baseline in body weight, at Weeks 3, 4 and 6

Body weight will be summarized and analysed in a similar way to the primary endpoint, as described in Section 6.1.1.1.

Absolute values and changes from baseline in the body composition endpoints will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

6.3.2. Change from baseline score for patient reported 7-day recall PROMIS-Pain 1a at Weeks 1, 2, 3, 4, 5 and 6

Absolute and change from baseline in the PROMIS-Pain 1a score will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

Scattter plots will be produced of the change from baseline PROMIS-Pain 1a score versus: -

- Both the change from baseline Cancer-Related Cachexia Symptom Assessment-Appetite and -Fatigue scores

- The residuals from the MMRM analysis of both the change from baseline Cancer-Related Cachexia Symptom Assessment-Appetite and -Fatigue scores

Plots will be trellised by timepoint (with separate colours for each treatment group) and also produced with all timepoints on the same plot. Y=X line and correlation coefficient will be included on the plots.

6.3.3. PGI-C (appetite), at Weeks 4 and 6

PGI-C (appetite) data will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.2.

6.3.4. PGI-C (fatigue), at Weeks 4 and 6

PGI-C (fatigue) data will be summarized descriptively by treatment group and timepoint as described in 5.2.2.

6.3.5. Serum unbound and total concentrations of PF-06946860, on Day 1 and Weeks 3, 4 and 6

PK analyses will be performed using the PK analysis set, as defined in Section 4.

Presentations for serum unbound and total concentrations of PF-06946860 will include: -

- A listing of concentrations sorted by participant and timepoint
- A summary of concentrations by timepoint, where the set of statistics will include n, arithmetic mean, SD, coefficient of variation (CV%), minimum, Q1, median, Q3, maximum, geometric mean, geometric CV%, and the number of concentrations above the LLQ
- Individual concentration-time plots (on a linear scale)
- Median concentration-time plot (on a linear scale), Q1 and Q3 may be included
- Mean (±SD) concentration-time plot (on a linear scale).

6.3.6. Serum concentrations of total GDF-15; and if feasible, unbound GDF-15, on Day 1 and Weeks 3, 4 and 6

PD analyses will be performed using the PD analysis set, as defined in Section 4.

Presentations for total and, if feasible, unbound GDF-15 levels (as data permit) will include: -

- A listing of concentrations sorted by treatment group, participant and timepoint. The listing will also include the relative change from baseline
- A summary of concentrations (absolute values and relative changes from baseline) by treatment group and timepoint, where the set of statistics will include (as data permit) n, arithmetic mean, SD, CV%, minimum, Q1, median, Q3, maximum, geometric mean, geometric CV% and the number of concentrations above the LLQ (for absolute values only)
- Individual concentration-time plots (for absolute values and relative change from baseline) by treatment group (on a linear scale). There will be separate spaghetti plots for each treatment group

- Median concentrations-time plots (for absolute values and relative change from baseline) by treatment group (on a linear scale, all treatments on the same plot), Q1 and Q3 may be included
- Mean (±SD, if appropriate) concentrations-time plots (for absolute values and relative change from baseline) by treatment group (on a linear scale, all treatments on the same plot).

In all presentations, the relative changes will be presented as percent change from baseline ([relative change from baseline -1]*100).

Relative change from baseline (i.e. post-dose / baseline) unbound GDF-15 concentration may also be analysed in a similar way to the primary endpoint, as described in Section 6.1.1.1. Both the relative change and the baseline will be on the log scale. LS means (and 80% CIs) and mean differences versus placebo (and 80% CIs) will be obtained for each treatment at each timepoint. These will be back transformed prior to presentation to give relative changes from baseline, presented as percent change from baseline ([relative change from baseline -1]*100) and ratios of relative changes from baseline, presented as percent change from placebo ([ratio of relative change from baseline -1]*100). Plots of these back-transformed LS means and differences (including 80% CIs) will also be produced over time (all treatments on the same plot with different colours/symbols for each treatment). If this analysis is deemed inappropriate (e.g. due to a large number of data below the level of quantification), the analysis may not be performed, may be simplified (e.g. fewer timepoints, different covariance matrix) or may be replaced by an alternative analysis.

6.3.7. Incidence of ADA and, if applicable, NAb,in Part A of the study

Immunogenicity analyses will be performed on the immunogenicity analysis set defined in Section 4. Definitions for ADA and NAb terms are defined in Appendix 2.

Immunogenicity analyses will include:

- A listing of ADA and NAb results for all participants and, if appropriate, a listing of ADA and NAb data, including onset and titer for all ADA-positive participants
- A summary (both table and figure, if appropriate) of the overall incidence of ADA, incidence of NAb, as well as the percentage of participants who are ADA positive and NAb positive at each timepoint.

If appropriate (e.g. the number of ADA-positive participants is ≥3), the additional analyses below may be performed:

- A spaghetti plot of individual participant ADA and NAb titer over time
- A summary of ADA and NAb titer by time
- Analysis of unbound and total PF-06946860 concentration by ADA and NAb status. This may include summary tables and box and/or spaghetti plots of concentration data by ADA and NAb status

- Analysis of unbound and/or total PF-06946860 concentration by ADA and NAb titer tertile which may include summary tables and box plots of concentration data by titer tertile
- Analysis of unbound and/or total GDF-15 concentration (as data permit) by ADA and NAb status which may include summary tables and box and/or spaghetti plots of concentration data by ADA and Nab status
- Analysis of unbound and/or total GDF-15 concentration (as data permit) by ADA and NAb titer tertile which may include summary tables and a box plot of concentration data by titer tertile
- An individual plot of unbound and total PF-06946860 concentration, unbound and/or total GDF-15 concentration (as data permit), ADA and NAb titer in ADA-positive participants.

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic data, prior and concomitant medications, GDF-15 levels (at screening, using the Roche Elecsys assay), height, weight and appetite score at screening will be summarised. *In addition, a subset of medical history data will be reported; this will include primary cancer diagnosis and staging at time of screening, date of initial diagnosis, body weight history (e.g., weight 6 months ago or 'usual' weight prior to current cancer diagnosis), where feasible.*

Other data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, will be considered source data, and will not be required to be reported, unless otherwise noted.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition by treatment group and will show which participants were analyzed for efficacy (Censored and Complete Analysis sets) as well as for safety, PK, PD and immunogenicity. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment group and overall.

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

6.5.3. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

6.5.4. Population PK

As permitted by data, and determined by the sponsor, the PK/PD relationship between serum PF-06946860 concentration and the effect on primary, secondary and/or tertiary endpoints may be explored using a population PK/PD approach. The population PK/PD analysis, if conducted, will be reported in a separate report.

6.5.5. Banked Biospecimens

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

6.5.6. Qualitative Phone Interviews

Qualitative interviews will be conducted with the participant and may additionally be conducted with the the caregiver. A *comprehensive summary report that fully describes the study objectives, methods, participants and results of the qualitative interviews will be prepared and will not be reported in the CSR.*

6.6. Safety Summaries and Analyses

Analysis of adverse events and laboratory abnomatities will use the the Safety Analysis Set defined in Section 4.

6.6.1. Adverse Events

Adverse events will be summarised by treatment group and overall, in accordance with sponsor reporting standards.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment group and overall, in accordance with the sponsor reporting standards.

7. INTERIM ANALYSES

7.1. Introduction

As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

A formal interim analysis may be performed to assess efficacy and/or safety. Interim analysis results may be used for internal business decisions regarding future study planning or stopping for futility. If a formal interim analysis is conducted, details of the timing, objectives, decision criteria and analyses will be documented in an internal charter or in the final SAP (via an amendment).

Following completion of Part A, the data will be analyzed, and a report written. The results of Part A will not be used to make any changes to the design or conduct of Part B.

7.2. Interim Analyses and Summaries

N/A

8. REFERENCES

Not applicable.

9. APPENDICES

Appendix 1. Statistical Methodology Details

Example SAS code for MMRM Model:

```
proc mixed data = dataset method=reml;
        class subject treatment time;
        model cfb = treatment base time base*time time*treatment / ddfm=kr residual
outp=resid_out;
        repeated time /subject=subjid type = un;
        lsmeans treatment*time/diff cl alpha=0.1;
        ods output lsmeans=lsmeans_out;
        ods output diffs=diffs_out;
run;
```

Appendix 2. Definitions of Immunogenicity Terms

Treatment-induced ADA	Baseline ADA titer is missing or negative and participant has ≥ 1 post-treatment positive ADA titer.
Treatment-boosted ADA	Baseline ADA titer is positive and participant has a ≥ 4-fold dilution increase in ADA titer from baseline in ≥ 1 post-treatment sample.
ADA-positive participant	A participant with ≥ 1 treatment-induced or treatment-boosted ADA response.
ADA-negative participant	An ADA evaluable participant (a participant with ≥ 1 post-treatment ADA result) without treatment-induced or treatment-boosted ADA response. Participant either has (1) all ADA-negative results throughout the study or (2) is ADA positive at baseline but did not become treatment-boosted post dose.
ADA incidence	The percent of ADA-positive participants.
Treatment-induced NAb	Baseline NAb titer is missing or negative or ADA-negative and participant has ≥ 1 post-treatment positive NAb titer.
Treatment-boosted NAb	Baseline NAb titer is positive and participant has a ≥ 4-fold dilution increase in NAb titer from baseline in ≥ 1 post-treatment sample.
NAb-positive participant	An ADA-positive participant with ≥ 1 treatment-induced or treatment-boosted NAb response. For ADA-positive (treatment-boosted) participants, participant is NAb positive only if the participant has ≥1 treatment-induced or treatment-boosted NAb response at the visit where the participant has a treatment-boosted ADA response. For visits where the participant did not show a boosted ADA response, the participant is classified as NAb-negative for the visit even if the participant has post-treatment positive NAb titer for that visit.
NAb-negative participant	(1) an ADA-negative participant or (2) an ADA-positive participant without treatment-induced or treatment-boosted NAb response (i.e. participant has all NAb-negative results throughout the study or participant is NAb positive at baseline but did not become treatment-boosted post dose).
NAb incidence	The percent of NAb-positive participants.

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	antidrug antibodies
AE	adverse event
BLQ	below the limit of quantitation
CI	confidence interval
CSR	clinical study report
CV	coefficient of variation
GDF-15	growth differentiation factor 15
HCP	Healthcare professional
LLQ	lower limit of quantitation
LS	least-squares
mg	milligrams
MMRM	mixed-effects model with repeated measures
N/A	not applicable
NAb	neutralizing antibodies
ND	not done
NS	no sample
OLT	open-label treatment
PD	pharmacodynamic(s)
PGI-C	Patient global impression of change
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
Q1	lower quartile
Q3	upper quartile
Q3W	3 weeks apart
QQ	quartile-quartile
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SC	subcutaneous
SD	standard deviation
SOP	standard operating procedure
TEAE	treatment-emergent adverse event