Protocol C3651009

A PHASE 1B, 12-WEEK, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS FOLLOWING REPEATED SUBCUTANEOUS ADMINISTRATIONS OF PF-06946860 IN PATIENTS WITH CANCER AND CACHEXIA

Statistical Analysis Plan
(SAP)

Version: **4**

Date: 16 March 2022

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

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APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 02 Mar 2020	Original 27 Nov 2019 PACL 11 Feb 2020	N/A	N/A
2.0 26 May 2021	Amendment 1 08 Feb 2021	Protocol amendment	• Updated verbatim protocol wording throughout • Removed DXA throughout, as per protocol • Updated wording throughout to reflect removal of CCI PROs in Cohort 2 • Updated all timepoints to reflect new SoA • 'Free' replaced with 'unbound' throughout for both PK and PD endpoints • Sections 3.1.3 and 3.1.4: Removed max. vitals decrease/increase over first 12 weeks, as not required • Section 3.2 and 3.3: Additional wording added for clarification • Section 3.3.2: Calculations included for change from baseline, relative change from baseline, duration of suppression, maximum concentration and time to maximum concentration • Section 3.3.4: Wording simplified CCI [redacted] • Section 6.2: Added/removed some PK outputs • Section 6.3.1: Added/removed some immunogenicity outputs • Section 6.3.2: Additional wording added for clarification; Added some additional outputs; Analysis added for relative change from baseline GDF-15 • Section 6.3.3: Additional wording added for clarification • Section 6.3.4: Wording simplified • Section 6.3.5: Wording simplified • Section 7.2: Added further wording to describe interim analysis • Appendix 2: Added additional wording for immunogenicity terms
3 21 Oct 2021	Amendment 1 08 Feb 2021	Requirement for additional output for POM declaration Findings during BDRs	• Updated protocol title to match amendment 1 • Sections 3.2 and 6.2: Added clarification for C_{trough} • Sections 3.3.2 and 6.3.2: Added percent change from baseline; Changed summaries to be based on percent change from baseline. Removed duration of suppression of GDF-15 and reference to Emax and Tmax.

			• Sections 3.3.3 and 6.3.4: Added percent change from baseline for body weight • Section 6.1.1: Replaced 'severity' with 'grade' in description of TEAE table in second paragraph • Sections 6.1.3 and 6.1.4: Combined individual and mean plots • Section 6.1.4: Corrected endpoint for >500msec listing (QT rather than QTcF) • Section 6.2: Added individual concentrations (and removed quartiles/sd) to median and mean trough concentration plots • Section 6.3.2: Added individual concentrations (and removed quartiles) to median concentration plots • Section 6.3.4: Removed absolute summary and plot. Added summaries and plots for % change from baseline body weight; Additional analysis of body weight change from baseline • Section 6.3.5: Added change from baseline figures for select PROs [redacted] • Section 6.5.1: Added clarification on baseline data for summary • Appendix 5: Added example SAS code for additional body weight analysis [redacted]
4 16 Mar 2022	N/A	Additional PRO analysis required for clinical development	• Section 3.3.3: Corrected formatting • Sections 3.3.4.5 and 6.3.5.5: Added FAACT-5IASS calculation and analysis • Appendix 3: Additional dataset specified

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3651009. 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	***Endpoints***
Primary:	***Primary:***
• *To characterize the safety and tolerability of repeated subcutaneous administrations of PF-06946860 to participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Incidence of treatment emergent adverse events (AEs and SAEs), safety laboratory tests, vital signs (blood pressure and pulse rate) and standard ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).*

Secondary:	***Secondary:***
• *To characterize free and total PK of PF-06946860 administered to participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Serum unbound and total trough concentrations (C_{trough}) of PF-06946860 at Weeks 3, 6, 9, 12, and 15..*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To evaluate the immunogenicity profile of PF-06946860 in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Incidence of ADA and NAb, if applicable.*
• *To characterize the effect of repeated administrations of PF-06946860 on circulating GDF-15 concentrations in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Serum concentrations of total and, if feasible, unbound GDF-15 at time points specified in the schedule of activities (SoA)* in the protocol.
• *To evaluate the effect of PF-06946860 on Lumbar Skeletal Muscle Index (LSMI) measured by CT scan in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline LSMI measured by CT scan at time points specified in the schedule of activities (SoA)* in the protocol.
• *To evaluate the effect of PF-09646860 on body weight in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline body weight at time points specified in the schedule of activities (SoA)* in the protocol.
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• *Cohort 1 only: To evaluate the effect of PF-06946860 on Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) selected items in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline scores for selected PRO-CTCAE items at time points specified in Table 2* in the protocol.
• *Cohort 1 only: To evaluate the effect of PF-06946860 on fatigue as measured by the PROMIS-Fatigue questionnaire in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline score for PROMIS-Fatigue at time points specified in Table 2* in the protocol.
• *Cohort 1 only: To evaluate the effect of PF-06946860 on physical function as measured by the PROMIS-Physical Function questionnaire in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline score for PROMIS-Physical Function at time points specified in Table 2* in the protocol.
• *Cohort 1 only: To evaluate the effect of PF-06946860 on HRQoL as measured by FAACT in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline FAACT total and sub-scale scores at time points specified in Table 2* in the protocol.

• *Cohort 1 only: To evaluate the effect of PF-06946860 on Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Change from baseline PGI-S at time points specified in Table 2* in the protocol. • *PGI-C at time points specified in Table 2* in the protocol.
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[redacted]	[redacted]
• *To evaluate the effect of PF-06946860 on ability to complete anti-tumor treatment as originally prescribed in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Number and % of participants completing anti-tumor treatment as originally prescribed.*
• *To evaluate the effect of PF-06946860 on participant survival in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *Number and % of participants alive at last subject last visit (LSLV).*
• *To evaluate tumor burden in participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.*	• *The RECIST 1.1 categorization using CT scan at time points specified in the schedule of activities (SoA)* in the protocol.
• *To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.*	• *Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).*

There are no estimands for this study.

2.2. Study Design

This is a Phase 1b, open-label study in participants with advanced metastatic NSCLC , pancreatic cancer or colorectal cancer and cachexia, and elevated circulating GDF-15 concentrations, that are eligible for treatment with platinum-based systemic anti-tumor therapy. Baseline GDF-15 levels will be assessed at screening to determine eligibility for participation.

Following the 28-day screening period to confirm eligibility, the study will consist of a treatment period of 12weeks and a follow-up period of 12weeks. The total duration of participation in this study is approximately 24 weeks (not including the screening period).

During the 12-week treatment period in Cohort 1, participants will receive a total of 5 doses of PF-06946860, administered subcutaneously (SC), every 3 weeks (Q3W).

This study will consist of up to 2 cohorts. In each study cohort, approximately 8 participants will be enrolled such that approximately 6 evaluable participants complete the study. Participants who discontinue prior to completion of the study may be replaced, at the discretion of the investigator and sponsor. It is planned that the 2 cohorts will be enrolled sequentially and will follow similar schedules of activity. The optional Cohort 2 may be conducted at the discretion of the Sponsor, with data emerging from Cohort 1 informing the dose level and/or frequency to be administered in Cohort 2.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Incidence of treatment emergent adverse events (AEs and SAEs), safety laboratory tests, vital signs (blood pressure and pulse rate) and standard ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).

3.1.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

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

3.1.2. Laboratory Data

Safety laboratory tests (hematology, chemistry, urine testing and other clinical laboratory tests) will be performed on Day 1 and Weeks 3, 6, 9, 12, 15, 18 and 24.

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.

Baseline for all laboratory measurements is defined as the last result prior to dosing on Day 1.

3.1.3. Vital Signs

Vital sign measurements (blood pressure and pulse rate) will be taken on Day 1 and Weeks 3, 6, 9, 12, 15, 18 and 24.

Baseline is defined as the average of the triplicate measurements prior to dosing on Day 1.

Changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be calculated for each post baseline timepoint.

The maximum decrease from baseline, over all measurements taken post-dose, will be calculated for supine systolic and diastolic blood pressures. The maximum increase from baseline, over all measurements taken post-dose, will be calculated for supine 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 minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

3.1.4. Electrocardiogram (ECG)

Standard 12-lead ECG (including heart rate, QT, QTcF, PR and QRS interval) will be obtained on Day 1 and Weeks 3, 6, 9, 12, 15, 18 and 24.

Baseline is defined as the average of the triplicate results prior to dosing on Day 1.

Change from baseline for heart rate, QT, QTcF, PR and QRS interval will be calculated for each post baseline timepoint.

The maximum absolute value (post-dose) and the maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF, PR and QRS.

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.

3.2. Secondary Endpoint(s)

- *Serum unbound and total trough concentrations (C_{trough}) of PF-06946860 at Weeks 3, 6, 9, 12 and 15.*

Serum concentrations of unbound and total PF-06946860 will be collected both pre- and post-dose on Day 1 and at Week 12, pre-dose only at Weeks 3, 6 and 9, and additionally at Weeks 1, 2, 4, 5, 13, 14, 15, 18 and 24.

Trough concentrations (C_{trough}) are defined as the samples measured pre-dose at Weeks 3, 6, 9 and 12, and at Week 15. Dose normalized C_{trough} will also be calculated, if appropriate.

3.3. Other Endpoint(s)

3.3.1. Immunogenicity (ADA, NAb)

- *Incidence of ADA and NAb, if applicable.*

ADA and NAb, if applicable, will be assessed on Day 1 and Weeks 2, 3, 6, 9, 12, 15, 18 and 24.

Baseline is defined as the pre-dose result on Day 1.

3.3.2. Pharmacodynamics (GDF-15)

- *Serum concentrations of total and, if feasible, unbound GDF-15 at time points specified in the schedule of activities (SoA)* in the protocol.

Serum concentrations of total and, if feasible, unbound GDF-15 will be measured both pre- and post-dose on Day 1 and Week 12, pre-dose only at Weeks 3, 6 and 9, and additionally at Weeks 1, 2, 4, 5, 13, 14, 15, 18 and 24.

Baseline is defined as the pre-dose result on Day 1. Trough timepoints are pre-dose at Weeks 3, 6, 9 and 12, and Week 15.

Change from baseline, relative change from baseline (i.e. post-dose / baseline) and percent change from baseline for total and, if feasible, unbound GDF-15, will be calculated for each post baseline timepoint. The maximum, maximum percent change from baseline and time to maximum, for total GDF-15 may also be calculated for each participant.

3.3.3. Efficacy

- *Change from baseline LSMI measured by CT scan at time points specified in the schedule of activities (SoA)* in the protocol.

Lumbar Skeletal Muscle Index (LSMI), measured by CT Scan, will be collected at Screening (Baseline) and Weeks 6 and 12. Change from baseline will be calculated for each post baseline timepoint.

- *Change from baseline body weight at time points specified in the schedule of activities (SoA)* in the protocol.

Body Weight will be collected on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 24.

Change from baseline and percent change from baseline will be calculated for each post baseline timepoint.

3.3.4. Patient-Reported Outcomes (PRO)

PRO data will be collected for Cohort 1 only.

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3.3.4.2. PRO CTCAE Items

- *Change from baseline scores for selected PRO-CTCAE items at time points specified in Table 2* in the protocol.

Data will be collected on Day 1 (Baseline) and Weeks 3, 6, 9, 12 and 18 using a 5-point scale.

Change from baseline will be calculated for each post baseline timepoint.

3.3.4.3. PROMIS Fatigue – Short Form 7a

- *Change from baseline score for PROMIS-Fatigue at time points specified in Table 2* in the protocol.

Data will be collected on Day 1 (Baseline) and Weeks 6, 12, and 18 using a 5-point scale.

The PROMIS Fatigue Short Form 7a has seven questions, each with five response options ranging in value from 1 to 5. A total raw score will be calculated as the sum of the responses to all seven questions.

The total raw score will then be translated into a T-score for each participant using the Fatigue 7a Short Form score conversion table, provided in Appendix 1.1. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10.

Change from baseline for PROMIS-Fatigue T-score will be calculated for each post baseline timepoint.

3.3.4.4. PROMIS Physical Function – Short Form 8c

- *Change from baseline score for PROMIS-Physical Function at time points specified in Table 2* in the protocol.

Data will be collected on Day 1 (Baseline) and Weeks 6, 12, and 18 using a 5-point scale.

The PROMIS Physical Function Short Form 8c has eight questions each with five response options ranging in value from 1 to 5. A total raw score will be calculated as the sum of the responses to all eight questions.

The total raw score will then be translated into a T-score for each participant using the Physical Function 8c Short Form score conversion table, provided in Appendix 1.1. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10.

Change from baseline for PROMIS-Physical Function T-score will be calculated for each post baseline timepoint.

3.3.4.5. FAACT Total and Sub Scale Scores

- *Change from baseline FAACT total and sub-scale scores at time points specified in Table 2* in the protocol.

Data will be collected on Day 1 (Baseline) and Weeks 6, 12, and 18 using a 5-point scale.

See Appendix 1.2 for FAACT scoring guidelines showing the calculation of FAACT subscales and two total scores.

Additionally, FAACT-5IASS (FAACT 5-item Anorexia Symptoms Subscale) will be calculated (using only items C6, ACT6, ACT7, ACT10 and ACT3, and a similar scoring system as for the other sub-scales): -

1. Add up the scores (with or without reversing)
2. Multiply by 5
3. Divide by the number of items answered

Change from baseline for FAACT total scores and subscales (including 5IASS) will be calculated for each post baseline timepoint.

3.3.4.6. PGI-S

- *Change from baseline PGI-S at time points specified in Table 2* in the protocol.

Data will be collected on Day 1 (Baseline) and Weeks 3, 6, 9, 12 and 18 using a 5-point scale.

Change from baseline will be calculated for each post baseline timepoint.

3.3.4.7. PGI-C

- *PGI-C at time points specified in Table 2* in the protocol.

Data will be collected at Weeks 12 and 18 using a 7-point scale.

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

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3.3.6. Completion of Anti-Tumor Treatment

- *Number and % of participants completing anti-tumor treatment as originally prescribed.*

Information regarding each participant's anti-tumor treatment (e.g. change of dose) will be collected.

3.3.7. Number and % of Participants Alive at LSLV

- *Number and % of participants alive at last subject last visit (LSLV).*

Any deaths during the study will be collected.

3.3.8. RECIST 1.1 Categorization

- *The RECIST 1.1* (overall) *categorization using CT scan at time points specified in the schedule of activities (SoA)* in the protocol.

Data will be collected at Screening (Baseline) and Weeks 6 and 12.

3.4. Baseline Variables

N/A

3.5. Safety Endpoints

See Section 3.1 for details.

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
Enrolled/Randomly assigned to investigational product	*"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 investigational product and who take at least 1 dose of investigational product*
Safety	*All participants randomly assigned to investigational product and who take at least 1 dose of investigational product*
PK	*All randomized participants who received a dose of PF-06946860 and in whom at least 1 serum concentration value is reported*
PD	*All randomized participants who received a dose of PF-06946860 and in whom at least 1 serum GDF-15 concentration is reported*
Immunogenicity	*All randomized participants who received a dose of PF-06946860 with at least 1 ADA result reported*
Efficacy	*All participants randomly assigned to investigational product and who take at least 1 dose of investigational product*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

Unless otherwise stated, all summaries and plots will be presented by treatment, if appropriate.

5.2.1. Analyses for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

5.2.2. Analyses for Categorical Endpoints

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

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

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

In listings, BLQ values will be reported as "<LLOQ", where LLOQ will be replaced with the value for the LLOQ.

For PK and PD summary tables and plots of mean/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 (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/statistician.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

Adverse events will be summarised by treatment and overall and in accordance with sponsor reporting standards using the safety population defined in Section 4.

Incidence and CTCAE grade of treatment emergent adverse event (TEAE) tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment and overall.

6.1.2. Laboratory Data

Laboratory data will be listed and summarized by treatment, in accordance with the sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.1.2.

6.1.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarised by treatment and time point, according to sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.1.3.

Individual plots of change from baseline systolic and diastolic blood pressure and pulse rate, versus time, will be produced with all participants on the same plot, paged by treatment. Separate colours will be used for each participant with a black solid line added for the mean.Maximum decrease from baseline for supine systolic and diastolic blood pressures and maximum increase from baseline for supine pulse will be summarised by treatment, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for supine vital signs will also be summarised descriptively by treatment using categories as defined in Appendix 4. Numbers and percentages of participants 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.

6.1.4. Electrocardiogram (ECG)

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarised by treatment and time point using sponsor reporting standards using the safety population defined in Section 4. Tables will be paged by parameter. Baseline is as defined in Section 3.1.4.

Individual plots of change from baseline QT, heart rate and QTcF, versus time, will be produced with all participants on the same plot, paged by treatment. Separate colours will be used for each participant with a black solid line added for the mean.Maximum increase from baseline for QTcF will be summarised by treatment, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for QTcF, PR and QRS will also be summarised descriptively by treatment using categories as defined in Appendix 4. Numbers and percentages of participants 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.

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

6.2. Secondary Endpoint(s)

Presentations for serum unbound and total PF-06946860 concentrations for participants in the PK population (as defined in Section 4) will include: -

- A listing of all concentrations sorted by dose, participant ID, and nominal time point. The concentration listing will also include the actual times.
- Individual concentration-time plots (semi-log scale) by dose using actual time post first dose. There will be separate spaghetti plots for each dose. All timepoints will be included and trough timepoints may be highlighted, e.g. using symbols.
- A summary of all concentrations by dose and nominal time point, where the set of statistics will include n, mean, standard deviation, coefficient of variation (CV, %),

median, minimum, maximum and the number of concentrations at or above the lower limit of quantification (NALQ).
- A summary of C_{trough} and dose normalized C_{trough}, if appropriate, by dose and nominal time point, where the set of statistics will include n, arithmetic mean, standard deviation, CV (%), median, geometric mean, geometric CV (%), Q1, Q3, minimum, maximum, and NALQ.
- Median concentration-time plot (semi-log scale, all timepoints) by dose using nominal time (all doses on the same plot).
- Median trough concentration-time plot (linear scale) by dose using nominal time (all doses on the same plot), individual concentrations may be included.
- Mean trough concentration-time plot (linear scale) by dose using nominal time (all doses on the same plot), individual concentrations may be included.

No formal inferential statistics will be applied to the pharmacokinetic data.

Additional PK analyses may be performed if deemed appropriate, and may not be included in the CSR.

6.3. Other Endpoint(s)

6.3.1. Immunogenicity (ADA, NAb)

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, titer, and if appropriate, duration (number of days participant is ADA positive or NAb positive) for all ADA-positive participants.
- A summary of the incidence of ADA and NAb by dose and all doses combined.
- A summary of the percentage of participants who are ADA positive and NAb positive by time and by dose and all doses combined. The cumulative % of ADA-positive and NAb-positive participants may also be be included.
- If appropriate, spaghetti plots of individual participant ADA and NAb titer by dose
- If appropriate (e.g. the number of ADA-positive participants for each dose is ≥3), a summary of ADA and NAb titer by time for each dose.

6.3.2. Pharmacodynamics (GDF-15)

All PD analyses will be performed on the PD population as defined in Section 4. Baseline is as defined in Section 3.3.2.

Presentations for total and/or unbound (as data permit) GDF-15 concentrations will include: -

- A listing of all concentrations (absolute values, change from baseline, relative change from baseline and percent change from baseline) sorted by treatment (dose), participant ID and nominal time point. The listing will also include the actual times. The maximum,

maximum percent change from baseline and time to maximum, for total GDF-15 may also be included.
- Individual concentration-time plots (for absolute values and percent change from baseline) by treatment using actual time. There will be separate spaghetti plots for each treatment. All timepoints will be included and trough timepoints may be highlighted, e.g. using symbols.
- A summary of concentrations (absolute values and percent changes from baseline) by treatment and nominal time point, where the set of statistics will include n, mean, standard deviation, CV (%), minimum, Q1, median, Q3, maximum, and geometric mean, geometric CV (%)and NALQ (for absolute values only).
- Median concentration-time plot (for absolute values and percent change from baseline) by treatment using nominal time (all treatments on the same plot), individual concentrations may be included on the plot.
- A summary of the maximum, maximum percent change from baseline and time to maximum, for total GDF-15 may be produced.

Relative change from baseline (i.e. post-dose / baseline) unbound GDF-15 concentration at Week 4 may also be modelled (as data permit), if appropriate. The analysis will be performed on the log scale using an analysis of covariance with log baseline and treatment as fixed terms in the model. Back transformed least squares means (and 80% confidence intervals) will be obtained for each treatment. Plots of these back-transformed LS means (including 80% CIs) will also be produced (all treatments on the same plot with different colours/symbols for each treatment). The relative changes will be presented as percent change from baseline ([relative change from baseline -1]*100).

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, or may be replaced by an alternative analysis.

Additional PD, and/or population PK/PD, analyses may be performed if deemed appropriate, and will not be included in the CSR.

6.3.3. Analysis of PK and PD Data by Immunogenicity Status

If appropriate, the additional analyses below may be performed: -

- Spaghetti plots of unbound and total PF-06946860 concentrations by ADA and NAb status
- Spaghetti plots of total and unbound (as data permit) GDF-15 concentrations by ADA and NAb status
- Individual plots of unbound and total PF-06946860 concentration, total and unbound (as data permit) GDF-15 concentration, ADA and NAb titer in ADA-positive participants.

6.3.4. Efficacy

Changes from baseline in LMSI (measured by CT scan) and body weight, and percent change from baseline (for body weight only), will be summarised descriptively by treatment

(if appropriate) and timepoint, as described in Section 5.2.1, using the efficacy population defined in Section 4. Baseline is as defined in Section 3.3.3.

Individual plots of change from baseline, and percent change from baseline (for body weight only), versus time will be produced with all participants on the same plot, paged by treatment (if appropriate). Separate colours will be used for each participant with a black solid line added for the mean.

Change from baseline body weight will be analyzed using a mixed effects repeated measures model including subject as a random term, and baseline, nominal time (as a factor) and baseline-by-nominal-time interaction as fixed terms in the model. Treatment and treatment-by-nominal-time interaction will also be include as fixed terms in the model, if appropriate (see Appendix 5 for example SAS code). A compound symmetry covariance matrix will be fitted to the repeated times within subject (other covariance matrices will be considered if necessary, e.g. compound symmetry with heterogeneity; additionally it may be necessary to restrict the timepoints included in the model, e.g. up to Week 12 only). Least squares (LS) means, standard errors and 90% confidence intervals will be obtained for each treatment at each time point. A plot of the LS means (including 90% CIs) will also be produced over time (all treatments on the same plot with different colours/symbols for each treatment).

CCI [redacted]

These analyses of change from baseline body weight may not be included in the CSR.

6.3.5. Patient-Reported Outcomes (PRO)

Summaries will be produced using the efficacy population defined in Section 4.

CCI [redacted]

6.3.5.2. PRO CTCAE Items

Changes from baseline for the PRO CTCAE will be summarised by time point as described in Section 5.2.2. Baseline is as defined in Section 3.3.4.2.

6.3.5.3. PROMIS Fatigue

Changes from baseline for the PROMIS Fatigue T-score will be summarised by time point as described in Section 5.2.1. Baseline is as defined in Section 3.3.4.3.

An individual plot of change from baseline T-score will be produced with all participants on the same plot, paged by treatment. Separate colours will be used for each participant with a black solid line added for the mean. These plots may not be included in the CSR.

6.3.5.4. PROMIS Physical Function

Changes from baseline for the PROMIS Physical Function T-score will be summarised by time point as described in Section 5.2.1. Baseline is as defined in Section 3.3.4.4.

An individual plot of change from baseline T-score will be produced with all participants on the same plot, paged by treatment. Separate colours will be used for each participant with a black solid line added for the mean. These plots may not be included in the CSR.

6.3.5.5. FAACT Total and Sub Scale Scores

Changes from baseline for the FAACT total scores and subscales (including the 5IASS) will summarised by time point as described in Section 5.2.1. Baseline is as defined in Section 3.3.4.5.

For the ACS, 5IASS, FACT-G total and FAACT total scores, individual plots of change from baseline will be produced with all participants on the same plot, paged by score treatment. Separate colours will be used for each participant with a black solid line added for the mean. These plots may not be included in the CSR.

6.3.5.6. PGI-S

Changes from baseline for the PGI-S will be summarised by time point as described in Section 5.2.2. Baseline is as defined in Section 3.3.4.8.

An individual plot of change from baseline will be produced with all participants on the same plot, paged by treatment. Separate colours will be used for each participant with a black solid line added for the mean. These plots may not be included in the CSR.

6.3.5.7. PGI-C

Absolute values for PGI-C on the 5-point scale will be summarised by time point as described in Section 5.2.2.

An individual plot of absolute values will be produced with all participants on the same plot, paged by treatment. Separate colours will be used for each participant with a black solid line added for the mean. These plots may not be included in the CSR.

CCI

[redacted]

[redacted]

[redacted]

6.3.7. Completion of Anti-Tumor Treatment

The number and % of participants completing anti tumor treatment as originally prescribed will be presented by treatment using the efficacy population defined in Section 4.

6.3.8. Number and % of Participants Alive at LSLV

The number and % of participants alive at LSLV will be presented by treatment using the efficacy population defined in Section 4.

6.3.9. RECIST 1.1 Categorization

The RECIST 1.1 categorization will be summarised by treatment and time point as described in Section 5.2.2 using the efficacy population defined in Section 4.

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

A baseline table (or separate tables, as required) will be produced, by treatment and overall, summarising the following baseline data (if available): type of cancer; stage of cancer; duration of cancer; serum GDF-15 at screening; chemotherapy treatment as described in Sections 5.2.1 or 5.2.2 (as appropriate).

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition for each phase of the study (screening, open-label treatment and follow-up) and will additionally show which participants were analysed for efficacy, PK, PD, immunogenicity as well as for safety. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.3. Demographic Data

Demographic data (age, gender, race, ethnicity, weight, body mass index and height) will be summarised by treatment and overall (if applicable) in accordance with the sponsor reporting standards.

6.5.4. Banked Biospecimens

Banked biospecimens will be collected and retained for future analyses, but will not be analyzed specifically for this study and will not be included in the CSR.

6.5.5. 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.

6.5.6. Treatment Compliance

A summary table of treatment compliance will be produced according to current sponsor reporting standards.

6.6. Safety Summaries and Analyses

See Section 6.1 for details.

7. INTERIM ANALYSES

7.1. Introduction

As this is an open-label 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 PK, PD and/or safety. Interim analysis results may be used for internal business decisions regarding future study planning. If a formal interim analysis is conducted, details of the timing, objectives, decision criteria (if applicable) and analyses will be documented in an internal charter or in the final SAP.

7.2. Interim Analyses and Summaries

If an interim analysis is performed, a subset of the analyses outlined in Section 6 will be produced, e.g. for safety (e.g. AE's, SAE's, deaths, labs, vitals, ECG, Resist), PK/PD , ADA/NAb, baseline, participant disposition and demographic data.

8. REFERENCES

N/A

9. APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. PROMIS Score Conversion Tables

Fatigue 7a - Adult v1.0		
Short Form Conversion Table		
Raw Score	T-score	SE*
7	29.4	5.3
8	33.4	4.8
9	36.9	4.3
10	39.6	4.0
11	41.9	3.8
12	43.9	3.5
13	45.8	3.3
14	47.6	3.2
15	49.2	3.1
16	50.8	3.0
17	52.2	3.0
18	53.7	3.0
19	55.1	3.0
20	56.4	2.9
21	57.8	2.9
22	59.2	2.9
23	60.6	2.9
24	62.0	2.9
25	63.4	2.9
26	64.8	2.9
27	66.3	2.9
28	67.8	2.9
29	69.4	2.9
30	71.1	3.0
31	72.9	3.0
32	74.8	3.1
33	77.1	3.3
34	79.8	3.6
35	83.2	4.1

*SE = Standard Error on T-score metric

PROMIS Item Bank v2.0 Physical Function - Short Form 8c		
Raw Sum Score	T Score	SE
8	15	2.7
9	17.4	2.8
10	19.5	2.7
11	21.2	2.6
12	22.7	2.5
13	24	2.4
14	25.3	2.4
15	26.4	2.3
16	27.5	2.2
17	28.5	2.2
18	29.5	2.1
19	30.4	2.1
20	31.3	2
21	32.2	2
22	33	2
23	33.8	2
24	34.7	2
25	35.5	2
26	36.3	2
27	37.1	2
28	38	2.1
29	38.9	2.1
30	39.8	2.1
31	40.8	2.2
32	41.9	2.2
33	43	2.3
34	44.3	2.4
35	45.7	2.6
36	47.5	2.9
37	49.6	3.3
38	52.3	3.8
39	54.9	4.1
40	61.3	6.1

Appendix 1.2. FAACT Scoring Guidelines

FAACT Scoring Guidelines (Version 4) – Page 1

Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FAACT).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____= **PWB subscale score**

SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____= **SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____= **EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
	GF5	0	+	_____	=_____
Score range: 0-28	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____= **FWB subscale score**

Subscale	Item Code	Reverse item?		Item response	Item Score
ANOREXIA	C6	0	+	_____	=_____
CACHEXIA	ACT1	0	+	_____	=_____
SUBSCALE	ACT2	4	-	_____	=_____
(ACS)	ACT3	4	-	_____	=_____
	ACT4	4	-	_____	=_____
Score range: 0-48	ACT6	4	-	_____	=_____
	ACT7	4	-	_____	=_____
	ACT9	4	-	_____	=_____
	O2	4	-	_____	=_____
	ACT10	4	-	_____	=_____
	ACT11	4	-	_____	=_____
	ACT13	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 12: _____
Divide by number of items answered: _____ **= AC subscale score**

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____ = _____ = **FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FAACT total score:
Score range: 0-156

_____ + _____ + _____ + _____ + _____ = _____ = **FAACT Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**ACS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix 2. Definitions of Immunogenicity Terms

ADA evaluable population	All participants with ≥ 1 post-treatment ADA result.
NAb evaluable population	ADA-positive participants with ≥ 1 post-treatment NAb result, plus all ADA-negative participants. An ADA-positive participant without any post-treatment NAb data is excluded from the analysis population.
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 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	A NAb evaluable participant who is either (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. Data Set Descriptions

To explore the data further separate SAS datasets and .csv files will be provided by the clinical programmer to the statistician.

Four datasets are to be created (all are to include participant ID, treatment and time point):

- PROs (2 datasets) to include all endpoints in Section 3.3.4 at all time points. Two datasets:
  - [redacted]
  - one for weekly data to include baseline, absolute and change from baseline for all questions and total / T-scores (where applicable).

[redacted]

An additional .xlsx dataset will be provided by the clinical programmer to the statistician, ordered by participant and timepoint, with columns for the following endpoints: -

- Participant ID
- Age
- Gender
- Roche GDF-15 (at screening)
- Timepoint
- Absolute and change from baseline Pfizer total and unbound GDF-15
- Absolute and change from baseline body weight
- RECIST categorization
- [redacted]
- Absolute and change from baseline PGI-S (appetite)
- Absolute PGI-C (appetite and fatigue)
- Absolute and change from baseline PRO-CTCAE items (taste change, decreased appetite, fatigue, nausea, vomiting)
- Absolute and change from baseline FAACT-AS
- Absolute and change from baseline FAACT-5IASS
- Absolute and change from baseline PROMIS Fatigue T-score
- Absolute and change from baseline PROMIS Physical function T-score

Appendix 4. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Absolute value of QTcF (msec)	>470 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed.

Appendix 5. Example SAS Code

```
proc mixed data = dataset;
  class subject time treat;
  model cfb = base treat time treat*time base*time / solution ddfm =
kr residual;
  repeated time / subject = subject type = cs r rcorr;
  lsmeans treat*time / diff cl alpha=0.1;
run;
quit;
```

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

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