# 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

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|---|---|
| **Study Intervention Number:** | PF-06946860 |
| **Study Intervention Name:** | Not Applicable (N/A) |
| **US IND Number:** | CCI |
| **EudraCT Number:** | Not Applicable (N/A) |
| **Protocol Number:** | C3651010 |
| **Phase:** | 1b |

**Short Title:** Study to Assess the Effect of PF-06946860 on Appetite Following Subcutaneous Administration to Patients With Anorexia and Advanced Cancer

## Protocol Amendment Summary of Changes Table

| **Document History** | | |
|---|---|---|
| **Document** | **Version Date** | **Summary and Rationale for Changes** |
| Amendment 2 | 08 October 2021 | The overall rationale for this amendment is to provide modifications and clarifications to the below select entry criteria and associated concomitant therapy requirements.<br><br>• Section 5.1: Inclusion criterion # 2: clarification of description of cancer diagnosis.<br><br>• Section 5.1: Inclusion criterion # 3: clarification of treatment options.<br><br>• Section 5.2: Exclusion criterion # 1: removed for simplification.<br><br>• Section 5.2: Exclusion criterion # 9 (# 8 in Protocol Amendment 2): clarification of HIV diagnosis.<br><br>• Section 5.2: Exclusion criterion # 13 (#12 in Protocol Amendment 2) and Section 6.5: clarification of description of treatments for anorexia, weight loss or cachexia and minor update to sentence structure describing ‘stable”.<br><br>• Section 5.2: Exclusion criterion # 15 (# 14 in Protocol Amendment 2) and Section 6.5: updates on the use of glucocorticoid therapy based on the current standard of care regimens common in the patient population and timing given the primary endpoint and minor update to sentence structure describing ‘stable”.<br><br>• Section 5.2: Exclusion criterion # 16 (#15 in Protocol Amendment 2) and Section 6.5: and minor update to sentence structure describing ‘stable”. |

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| | | • Section 5.2: Exclusion criterion # 20 (# 19 in Protocol Amendment 2) minor clarification to add "x" to "Inclusion of participants with alkaline phosphatase >3 ULN may be acceptable if they are deemed medically stable and fit for the study by both investigator and sponsor medically qualified personnel."<br><br>Additional updates and clarifications were made to the following sections:<br><br>• Schedule of activities: footnote "i" was added to the Qualitative Phone Interview (participant) at the Week 4 and Early Term/Discontinuation visits for flexibility.<br><br>• Sections 2.2.2.2 and 2.2.2.3: updated per the finalized supplemental CSRs for C3651001 and C3651002.<br><br>• Section 6.1.1: updated to include details of investigational product dosing details and administration timing.<br><br>• Section 9.5: added clarifying text to the interim analysis.<br><br>• Appendix 13: Abbreviations. |
| Amendment 1 | 22 June 2021 | The overall rationale for this amendment is to provide modifications and clarifications to the following exclusion criteria:<br><br>• Section 5.2: Exclusion criterion # 7: clarification of description and timing ascites symptoms.<br><br>• Section 5.2: Exclusion criterion # 15 and Section 6.5: updates based on the current standard of care regimens common in the patient population. |

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| | | • Section 5.2: Exclusion criterion # 17: Updated to clarify that receipt of at least one dose of PF-06946860 is exclusionary.<br><br>• Section 5.2: Exclusion criterion #20: updated to reflect variability of typical baseline levels observed in patient population with advanced cancer.<br><br>Additional updates based on the final 6-month NHP study report and minor edits for consistency and to improve readability as follows:<br><br>• SOA: footnote k: PD in footnote changed to GDF-15Section 2.2.1.3: NOAEL $C_{max,}$ $C_{av}$ and $AUC_{168H}$ values updated to reflect final 6-month NHP study report. Corresponding changes made to safety margins in Table 1 and overdose text in Section 8.4.<br><br>• Section 2.2.2.2: minor update in the text describing the total PF-06946860 PK.<br><br>• Section 2.2.2.3: baseline GDF-15 concentration updated from median to geometric mean to be consistent with reporting standards for the data that will be included in the supplemental Clinical Study Reports for completed Phase 1 studies.<br><br>• Section 4.3: description of dose rationale simplified by deleting repetitive text.<br><br>• Section 6.1.1: guidance provided on timing of IP dosing relative to standard of care treatment, if applicable.<br><br>• Section 8.5: administrative clarification:<br><br>  • On dosing days, pre-dose PK sample will be collected prior to IP administration.<br><br>• Section 8.6.1: administrative clarifications: |

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|---|---|---|
| | | • The actual date and time (24 hour clock time) of each sample will be recorded.<br><br>• On dosing days, pre-dose GDF-15 sample will be collected prior to IP administration.<br><br>• Section 10.4.4 Highly Effective Methods That are User Dependent<br><br>• Removal of "injectable" under Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation required template update.<br><br>The following items noted in the Protocol Administrative Change Letter dated 09 March 2021 have also been incorporated.<br><br>• Modification to Exclusion criterion # 1, Schedule of Activities Footnote 'j', Section 8.1.1.5 Qualitative Phone Interviews, Section 8.6.1 GDF-15, Section 10.13. Appendix 13: Abbreviations. |
| Original protocol | 18 December 2020 | N/A |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

## TABLE OF CONTENTS

## LIST OF TABLES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Short Title:** Study to Assess the Effect of PF-06946860 on Appetite Following Subcutaneous Administration to Patients with Anorexia and Advanced Cancer.

### Background and Rationale

Cachexia, or anorexia-cachexia syndrome, is a metabolic disorder and comorbidity that occurs with several chronic diseases including cancer, heart failure, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD). Cachexia is multifactorial, and is characterized by loss of appetite, weight, and skeletal muscle, leading to fatigue, functional impairment, increased treatment-related toxicity, poor quality of life, and reduced survival. Anorexia is a key component of the cachectic phenotype.[1] A meta-analysis of 30 randomized controlled trials from the European Organisation for Research and Treatment of Cancer (EORTC) showed that loss of appetite correlates with poor survival in cancer patients with advanced disease.[2]

The cytokine growth differentiation factor 15 (GDF-15), also known as Macrophage Inhibitory Cytokine 1 (MIC-1), is a member of the transforming growth factor beta (TGFβ) superfamily. In healthy individuals the major source of circulating GDF-15 is believed to be the liver, although it is also expressed by the kidneys, lung and adipose tissue;[3] and during pregnancy it is highly expressed by placental trophoblast.[4] GDF-15 is also secreted by tumor cells, macrophages and damaged cells.[5-8] In several chronic conditions such as cancer, heart failure, COPD, and CKD, circulating GDF-15 concentrations are markedly elevated compared to healthy levels.[9-12]

Elevated GDF-15 is associated with weight loss and anorexia-cachexia in patients with cancer.[13-16] It is hypothesized that anorexia-cachexia in patients with cancer is largely mediated via GDF-15 and that suppression of GDF-15 in these patients may lead to improvement in serious aspects of their disease such as anorexia leading to unintended weight loss, fatigue and impaired mobility. PF-06946860 is a recombinant humanized monoclonal antibody (immunoglobulin gamma-1 with kappa light chains [IgG1κ]) directed against GDF-15. This anti-GDF-15 humanized monoclonal antibody (mAb) binds to the GDF-15 protein preventing its interaction with GFRAL receptor. It is anticipated that PF-06946860, therefore, has the potential to promote appetite, mitigate fatigue, and ameliorate the malaise and weight loss associated with cachexia in advanced cancer.

The primary purpose of this study is to assess the effect of repeated subcutaneous administration of PF-06946860 on appetite in participants with advanced cancer, anorexia and elevated circulating GDF-15 levels. The study will also assess secondary and exploratory endpoints including fatigue, safety and body weight.

# Objectives, Estimands and Endpoints

## Part A

| 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 (ie, 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. |
| • 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 (ie, using the Censored analysis set). |
| • To characterize the **safety and tolerability** of repeated subcutaneous administrations of PF-06946860 compared to placebo in participants with anorexia and advanced cancer. | • Incidence of adverse events 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. |

| Objectives | Endpoints | Estimands |
|---|---|---|
| **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 and 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** of appetite and fatigue in participants with anorexia and advanced cancer. | • PGI-C (appetite), at Weeks 4 and 6.<br>• PGI-C (fatigue), at Weeks 4 and-6. | • N/A |
| • To characterize the unbound and total **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 **GDF-15** concentrations in participants with anorexia and advanced cancer. | • Serum concentrations of total GDF-15; and if feasible, unbound GDF-15, on Day 1 and Weeks 3, 4 and 6. | • N/A |
| • To assess the **immunogenicity** of PF-06946860 administered in participants with anorexia and advanced cancer. | • Incidence of ADA and, if applicable, NAb, in Part A of the study. | • N/A |

## Part B

In addition, the following objectives will be evaluated using data from Part B, as data permit:

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Tertiary/Exploratory:** | | |
| • To assess **appetite** in participants with anorexia and advanced cancer, during the open-label treatment period. | • Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Appetite score, weekly from Week 7 to 24. | • N/A |
| • To assess **fatigue** in participants with anorexia and advanced cancer, during the open-label treatment period. | • Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Fatigue score, weekly from Week 7 to 24. | • N/A |
| • To characterize the **safety and tolerability** of repeated subcutaneous administrations of PF-06946860 in participants with anorexia and advanced cancer, during the open-label treatment period. | • Incidence of adverse events and laboratory abnormalities, in Part B of the study. | • There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards, as applicable. |
| • To assess **body weight** in participants with anorexia and advanced cancer, during the open-label treatment period. | • Change from baseline in body weight, at Weeks 12, 15, 18, 21 and 24. | • N/A |
| • To explore the relationship between **pain** and appetite/fatigue in participants with anorexia and advanced cancer, during the open-label treatment period. | • 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, weekly from Week 7 to 24. | • N/A |
| • To assess **patient global impression of change** of appetite and fatigue in participants with anorexia and advanced cancer, during the open-label treatment period. | • PGI-C (appetite), at Week 24.<br>• PGI-C (fatigue), at Week 24. | • N/A |
| • To characterize the unbound and total **PK** of PF-06946860 administered in participants with anorexia and advanced cancer, during the open-label treatment period. | • Serum unbound and total concentrations of PF-06946860, at Weeks 12, 18 and 24. | • N/A |
| • To characterize the effect of PF-06946860 administration on circulating **GDF-15** concentrations in participants with anorexia and advanced cancer, during the open-label treatment period. | • Serum concentrations of total GDF-15; and if feasible, unbound GDF-15, at Weeks 12, 18 and 24. | • N/A |

| Objectives | Endpoints | Estimands |
|---|---|---|
| • To assess the **immunogenicity** of PF-06946860 administered in participants with anorexia and advanced cancer, during the open-label treatment period. | • Incidence of ADA and, if applicable, NAb, in Part B of the study. | • N/A |

## Overall Design

This is a Phase 1b study in patients with advanced cancer, anorexia and elevated circulating GDF-15 levels. 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 dosing 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.

Potential participants will attend at least 2 clinic visits (Screening and Randomization) with the investigator. The Screening visit will occur no more than 28 days and no less than 5 days, prior to Randomization. The 5-day minimum duration between Screening and Randomization visits will ensure that all necessary data (including GDF-15 level) are available to inform the investigator's assessment of eligibility.

All study visits following Randomization may be conducted by a visiting Health Care Professional (HCP) at the patient's home. During selected home-HCP visits, the investigator will conduct Telehealth consults with the participant in order to assess patient safety. 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. The participant and investigator may select to have study visits for Part B conducted at home or in-clinic.

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 least 28 days and up to 35 days after the last administration of blinded IP. For study Part A, this contact may be done via a phone call, telehealth, at home or in the clinic, per investigator judgement. For study part B, a home-HCP + TeleHealth (or in-Clinic) visit will be conducted. Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

## Number of Participants

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).

## Intervention Groups and Duration

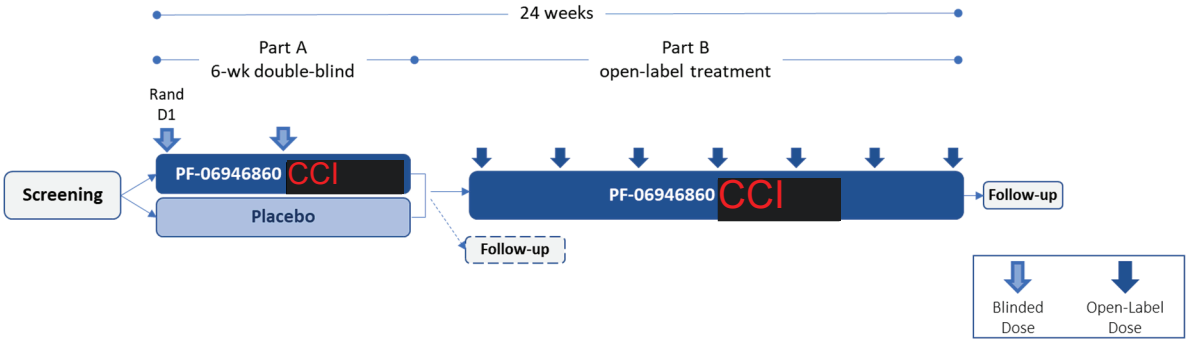
| | | |
|---|---|---|
| **Intervention Name** | PF-06946860 | Placebo |
| **ARM Name** | PF-06946860 Double-Blind Treatment followed by Open-Label Treatment | Placebo Double-Blind Treatment followed by Open-Label Treatment |
| **Type** | Biologic | Placebo |
| **Dose Formulation** | Solution for injection | Solution for injection |
| **Unit Dose Strength(s)** | CCI | Placebo |
| **Dosage Level(s)** | CCI | Placebo Q3Weeks |
| **Route of Administration** | Subcutaneous | Subcutaneous |
| **Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)** | IMP | IMP |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor |
| **Packaging and Labeling** | Study intervention will be provided in 6-mL glass vial with a 1 mL withdraw volume. Each vial will be labeled as required per country requirement. | Study intervention will be provided in 6-mL glass vial with a 1 mL withdraw volume. Each vial will be labeled as required per country requirement. |
| **Current/Former Name(s) or Alias(es)** | Not applicable | Not applicable |

## Data Monitoring Committee or Other Independent Oversight Committee: No

## Statistical Methods

Refer to Section 9.

## 1.2. Schema


24 weeks
Part A
6-wk double-blind
Part B
open-label treatment
Rand
D1
Screening
PF-06946860 CCI
Placebo
Follow-up
PF-06946860 CCI
Follow-up
Blinded
Dose
Open-Label
Dose

### 1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

| | Screening | Part A: Double-Blind | | | | Part B: Open-Label | | | | | | Part A: Follow-up[b] | Part B: Follow-up[c] | Early Term/ Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Identifier**<br>Abbreviations, see Appendix 13 | **v1** | **v2** | **v3** | **v4** | **v5** | **v6** | **v7** | **v8** | **v9** | **v10** | **v11** | **v12** | **v13** | |
| **Study Week (relative to Day 1)** | | **Rand** | **wk3** | **wk4[a,b]** | **wk6** | **wk9** | **wk12** | **wk15** | **wk18** | **wk21** | **wk24** | | | |
| **Study Day (relative to Day 1 dosing)** | **-28 to -5** | **Day 1** | **22** | **29** | **43** | **64** | **85** | **106** | **127** | **148** | **169** | **50** | **197** | |
| **Visit Window (days)** | | | **±1** | **±1** | **±1** | **±3** | **±3** | **±3** | **±3** | **±3** | **±3** | **+7** | **+7** | |
| Clinic Visit | X | X | | | | | | | | | | | | |
| Telehealth Visit[d] | | | X | X | X | | X | | X | | X | X | X | X |
| At-Home/Residential Care Facility Home-HCP Visit[d] | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Informed Consent and Registration | X | | | | | | | | | | | | | |
| Informed consent (caregiver)[e] | X | | | | | | | | | | | | | |
| Review of Eligibility Criteria | X | X | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Administration of blinded PF-06946860/placebo | | X | X | | | | | | | | | | | |
| Administration of open-label PF-06946860 | | | | | X | X | X | X | X | X | X | | | |
| Medical History, Demography and Height | X | | | | | | | | | | | | | |
| Record Prior or Concomitant treatments | X | X | → | → | → | → | → | → | → | → | → | X | X | X |
| Monitor Serious/nonserious AEs | X | X | → | → | → | → | → | → | → | → | → | X | X | X |
| Review contraception use | X | X | X | | X | X | X | X | X | X | X | X | X | X |
| Physical Examination (Height at Screening only)[f] | X | | | | | | | | | | | X | X | X |
| PRO (weekly) 7-day recall: appetite, fatigue, pain[g] | X | X[h] | → | → | → | →[i] | →[i] | →[i] | →[i] | →[i] | →[i] | X[i] | X[i] | X |
| PRO PGI-C: appetite and fatigue | | | | X | X | | | | | | X[i] | | | X |
| Qualitative Phone Interview (participant)[j] | | | | X[i] | | | X[i] | | | | | | | X[i] |
| Qualitative Phone Interview (care giver)[e,j] | | | | X | | | | | | | | | | X |
| Weight + Body Composition via BIA (BIA not at Screen) | X | X[h] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X |
| Blood and Urine samples: Clinical Lab Tests, Table 2 | X | X | X | | X | X | X | X | X | X | X | X | X | X |
| Pregnancy Test for female participants of childbearing potential (Blood and/or Urine) | X | X | | | X | | X | | X | | X | | | |
| Blood sample for GDF-15[k] | X | X | X | X | X | | X[i] | | X[i] | | X[i] | X[i] | X[i] | X |
| Blood sample for PF-06946860 PK[k] | | X | X | X | X | | X[i] | | X[i] | | X[i] | X[i] | X[i] | X |
| Blood sample for immunogenicity (ADA and NAb)[k] | | X | X | | X | | X[i] | | X[i] | | X[i] | X[i] | X[i] | X |
| Prep D1.5 banked biospecimen (serum)[k,l] | | X | | | | | | | | | | | | |

a. The investigator and participant must decide at the Week 4 visit if they wish to continue to the open-label treatment period.

b. Participants **not** continuing to Part B **only**. Follow-up contact 28 to 35 days from final dose of study drug. May occur via Clinic or TeleHealth+home-HCP visit, per PI judgement.

c. Participants continuing to Part B **only**. Follow-up contact 28 to 35 days from final dose of study drug. May occur via Clinic or TeleHealth+home-HCP visit, per PI judgement.

d. Participant and investigator may elect to have all post-randomization study visits for Part A conducted at-home or at clinic. A selection should be made, and efforts made, to have all Part A visits conducted using the same paradigm (home or clinic). If the participant chooses to do a visit at the clinic, the Telehealth visit will not be implemented. Additional Telehealth visits, home-HCP visits or phone calls may be scheduled, as needed per PI judgement. If operationally feasible, a nutritional consult via telehealth with a central vendor will be scheduled by the participant within the first 7 days after randomization.

e. This would only occur if a caregiver was available and willing to participate, and if the participant was in agreement with the caregiver completing the caregiver interview.

f. A full physical examination will be conducted at Screening. A symptom-directed PE may be conducted at any time during the study and/or at end of study as judged necessary by the investigator (eg, to assess previous findings or to assess ongoing/open AEs).

g. PRO (weekly) 7-day recall: appetite, fatigue, pain refers to the Cancer-Related Cachexia Symptom assessments for appetite and fatigue and the PROMIS pain assessment.

h. Devices (eg, weighing scales and ePRO) required for study procedures will be used at Day 1 clinic visit, and provided to participant for at-home use, as applicable.

i. Every effort must be made to conduct procedures as specified, however if this becomes infeasible due to progression or complications of underlying disease, non-completion will not be considered a protocol deviation as long as the participant's safety was preserved. Collection of safety samples should be prioritized.

j. Phone Interview will be conducted by central vendor within the 10 days following the Week 4 visit (ie, Day 29-39), or at early termination, if feasible. For Part B, a second participant interview will be conducted at week 12 ±10 days, or at early termination, if feasible.

k. On dosing days, blood samples for PK, GDF-15, immunogenicity and banked biospecimens will be collected prior to treatment administration.

l. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

## 2. INTRODUCTION

Cachexia, or anorexia-cachexia syndrome, is a metabolic disorder and comorbidity that occurs with several chronic diseases including cancer, heart failure, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD). Cachexia is multifactorial, and is characterized by loss of appetite, weight, and skeletal muscle, leading to fatigue, functional impairment, increased treatment-related toxicity, poor quality of life, and reduced survival. Anorexia is a key component of the cachectic phenotype.[1] A meta-analysis of 30 randomized controlled trials from the European Organization for Research and Treatment of Cancer (EORTC) showed that loss of appetite correlates with poor survival in cancer patients with advanced disease.[2]

The cytokine growth differentiation factor 15 (GDF-15), also known as Macrophage Inhibitory Cytokine 1 (MIC-1), is a member of the transforming growth factor beta (TGFβ) superfamily. In healthy individuals the major source of circulating GDF-15 is believed to be the liver, although it is also expressed by the kidneys, lung and adipose tissue;[3] and during pregnancy it is highly expressed by placental trophoblast.[4] GDF-15 is also secreted by tumor cells, macrophages and damaged cells.[5-8] In several chronic conditions such as cancer, heart failure, COPD, and CKD, circulating GDF-15 concentrations are markedly elevated compared to healthy levels.[9-12] Elevated GDF-15 is associated with weight loss and anorexia-cachexia in patients with cancer.[13-16] In addition, elevated circulating GDF-15 levels are associated with poor outcomes and survival in many cancers, heart failure, CKD and COPD.[17-23] In rodents and non-human primates, GDF-15 induces anorexia and weight loss[24-28] by acting through the glial cell-derived- neurotrophic factor (GDNF) family receptor alpha-like (GFRAL). Furthermore, increased GDF-15 levels are associated with cachexia in mouse tumor models, and inhibition of GDF-15 reverses weight loss and improves survival.[14]

It is hypothesized that anorexia-cachexia in patients with cancer is largely mediated via GDF-15 and that suppression of GDF-15 in these patients may lead to improvement in serious aspects of their disease such as anorexia leading to unintended weight loss, fatigue and impaired mobility.

PF-06946860 is a recombinant humanized monoclonal antibody (immunoglobulin gamma-1 with kappa light chains [IgG1κ]) directed against GDF-15. This anti-GDF-15 humanized monoclonal antibody (mAb) binds to the GDF-15 protein preventing its interaction with GFRAL receptor. It is anticipated that PF-06946860, therefore, has the potential to promote appetite, mitigate fatigue, and ameliorate the malaise and weight loss associated with cachexia in advanced cancer.

### 2.1. Study Rationale

The primary purpose of this study is to assess the effect of repeated subcutaneous administration of PF-06946860 on appetite in participants with advanced cancer, anorexia and elevated circulating GDF-15 levels. The study will also assess secondary and exploratory endpoints including fatigue, safety and body weight.

## 2.2. Background

A summary of relevant, currently available data is provided in this protocol. Additional detail, and further information for this compound, may be found in the investigator's brochure (IB).

### 2.2.1. Nonclinical Overview

#### 2.2.1.1. Nonclinical Pharmacology

PF-06946860 is a potent and highly selective binder of human GDF-15 compared to 10 other human transforming growth factor beta (TGFβ) family members. In vitro binding, to fragment crystallizable gamma (Fcγ) receptors was not observed, suggesting low potential to cause antibody dependent cell-mediated cytotoxicity (ADCC). However, PF-06946860 elicited relatively low binding to C1q, suggesting that the potential for complement-dependent cytotoxicity (CDC) cannot be ruled out. PF-06946860 did not cause cytokine release in human whole blood.

Consistent with the literature[24-28] exogenously administered mouse and human GDF-15 caused weight loss (both lean mass and fat mass) in mice, and administration of PF-06946860 reversed these observations. In a variety of GDF-15 secreting mouse tumor models (HT-1080, PA0165, NSX-26115 and RENCA), tumor implantation induced a cachectic phenotype that was either prevented or reversed by administration of PF-06946860. Treatment with PF-06946860 also consistently increased survival compared to control groups. Taken together, the data suggest that PF-06946860 has the potential to be a treatment for GDF-15 related cancer cachexia in humans.

#### 2.2.1.2. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical PK of PF-06946860 are provided in the IB. The PK of PF-06946860 in mouse was consistent with that for a typical human immunoglobulin G1 (IgG1) mAb. After weekly subcutaneous (SC) administration of PF-06946860 to mice and monkeys in repeat dose toxicity studies, there were no apparent sex related differences in systemic exposures, and accumulation was observed. After repeat dosing, mean systemic exposures increased in a less than dose proportional manner in mice and an approximately dose proportional manner in monkeys. PF-06946860 is not expected to affect the PK of small molecule drugs either via cytokine mediated effects on CYP enzymes or transporters. PF-06946860 is expected to undergo both non-specific proteolytic elimination and target-mediated elimination. As such, concomitant medications and/or disease states, that alter the expression of GDF-15, may potentially impact the elimination of PF-06946860.

#### 2.2.1.3. Nonclinical Safety

PF-06946860 was administered weekly in SC studies for 13 weeks (3 months) to mice and for 3- and 6-months to cynomolgus monkeys followed by a recovery phase of approximately 2 and 3 months, respectively.

No adverse effects were observed in any of the toxicity studies conducted with PF-06946860. The cardiovascular and renal systems, and hematology parameters were identified as potential nonadverse targets. Cardiovascular and renal observations were predominantly related to lower group mean organ weights but were nonadverse based on the small magnitude, lack of macroscopic, microscopic and functional correlates, and/or clinical sequelae. Hematology findings consisted of nonadverse increases in red blood cell mass parameters. Serum chemistry findings consisted of nonadverse increases in serum triglyceride concentration. Other nonadverse findings related to administration of PF-06946860 included small magnitude alterations in clinical chemistry parameters, minor decreases in organ weights, zymogen granule depletion in the pancreas, minimal increases in locomotor activity in mice, and microscopic findings (mononuclear cell infiltrates of choroid plexus and glomerulus) considered secondary to antidrug antibodies (ADA) and immune complex disposition in monkeys. Nearly all of the dosing phase findings in both species reversed by the end of the recovery phase.

The no-observed-adverse-effect levels (NOAELs) were the highest doses tested in the 3-month study in mice CCI [redacted] and the 3-month CCI [redacted] and 6-month (20 mg/kg/week) studies in monkeys. Systemic exposures of total PF-06946860 (maximum observed concentration [$C_{max}$], average concentration [$C_{av}$] and area under the curve from the time of dose administration up to 168 hours [$AUC_{168H}$]) at the NOAEL in the 3-month mouse study were 3190 µg/mL, 2010 µg/mL and 337,000 µg•h/mL, respectively. Systemic exposures of total PF-06946860 ($C_{max,}$ $C_{av}$ and $AUC_{168H}$) at the NOAEL in monkeys were 5520 µg/mL, 4340 µg/mL and 729,000 µg•h/mL, respectively, in the 3-month study and 934 µg/mL, 786 µg/mL and 132,000 µg•h/mL, respectively, in the 6-month study.

### 2.2.2. Clinical Overview

PF-06946860 has been evaluated in two completed Phase 1 single dose studies (C3651001 and C3651002) in healthy participants. A multiple dose Phase 1 study (C3651009) in cancer patients with cachexia is ongoing; no data from this ongoing study are currently available. Clinical data from the completed studies are provided in the IB for PF-06946860.

#### 2.2.2.1. Safety

CCI [redacted]

CCI

[redacted]

[redacted].

CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

## 2.3. Benefit/Risk Assessment

The C3651010 study is designed primarily to assess the effect of PF-06946860 on appetite, fatigue and safety in a population with advanced cancer and anorexia.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06946860 may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| No potential risks of clinical significance have been identified to date. | Assessment of risk is based on nonclinical toxicology studies up to 6 months in duration with no findings identified as adverse, and the results of 2 completed single dose administration studies in healthy participants show only mild AEs, no adverse trends in laboratory, ECG or vital signs safety monitoring and no SAEs. | Standard safety monitoring for a biological investigational product, including ADA/NAb monitoring will continue to be implemented. |
| **Study Intervention(s) PF-06946860** | | |
| Potential risks associated with PF-06946860 include the following:<br>1. Injection site reactions.<br>2. This will be the first administration of PF-06946860 to patients with a variety of cancer types and that may be receiving a variety of anti-tumor therapies. Therefore, this will be the first clinical experience to assess safety in this context. | Single doses of PF-06946860 were well-tolerated by study participants when administered subcutaneously at 0.1 to 300 mg in 2 completed Phase 1 studies. All AEs reported across the 2 completed studies were mild. The risk of injection site reaction is not anticipated to be elevated beyond that expected with any subcutaneously administered treatment. | Eligibility criteria have been selected to ensure that only appropriate participants, who are not at apparent increased risk, are included in the study (see Section 5).<br>Adverse events and clinical laboratory results will be monitored on an ongoing basis.<br>Injection site reactions will be monitored, and injections sites rotated. |
| Use of a placebo arm. | Use of a placebo arm represents a risk of lack of benefit for those not receiving active therapy. As there are no data on efficacy yet, this risk cannot be assessed. | As the endpoint under evaluation (appetite) is anticipated to change rapidly, the study has been designed with a short duration (6 weeks), and with the potential for participation in an optional OLT Part B where all participants would receive PF-06946860.<br>The study has also been designed with, a 2:1 randomization ratio, in order to increase participants' chances of receiving active therapy. |

### 2.3.2. Benefit Assessment

The available clinical data, summarized in Section 2.2.2, show that a single dose of PF-06946860 as high as 300 mg SC in healthy participants is safe and well tolerated. Efficacy has not yet been studied in humans.

Based upon nonclinical data, it is hypothesized that dosing with PF-06946860 will improve participants appetite and support maintenance of body weight. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06946860 may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

There are currently no approved therapies for cachexia. It is estimated that 50-80%[29] of patients with advanced malignant cancer suffer with cachexia which results in worse outcomes. Therefore, the development of PF-06946860 for the treatment of cachexia may satisfy an area of high unmet need.

### 2.3.3. Overall Benefit/Risk Conclusion

Considering all available clinical and nonclinical data, the benefit-risk profile of PF-06946860 is favorable and supports continued clinical development.

## 3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

### Part A

| 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 (ie, 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 (ie, using the Censored analysis set). |
| • To characterize the **safety and tolerability** of repeated subcutaneous administrations of PF-06946860 compared to placebo in participants with anorexia and advanced cancer. | • Incidence of adverse events 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 and 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** of appetite and fatigue in participants with anorexia and advanced cancer. | • PGI-C (appetite), at Weeks 4 and 6.<br>• PGI-C (fatigue), at Weeks 4 and 6. | • N/A |
| • To characterize the unbound and total **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 **GDF-15** concentrations in participants with anorexia and advanced cancer. | • 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 |
|---|---|---|
| • To assess the **immunogenicity** of PF-06946860 administered in participants with anorexia and advanced cancer. | • Incidence of ADA and, if applicable, NAb, in part A of the study. | • N/A |

## Part B

In addition, the following objectives will be evaluated using data from Part B, as data permit:

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Tertiary/Exploratory:** | | |
| • To assess **appetite** in participants with anorexia and advanced cancer, during the open-label treatment period. | • Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score, weekly from Week 7 to 24. | • N/A |
| • To assess **fatigue** in participants with anorexia and advanced cancer, during the open-label treatment period. | • Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Fatigue score, weekly from Week 7 to 24. | • N/A |
| • To characterize the **safety and tolerability** of repeated subcutaneous administrations of PF-06946860 in participants with anorexia and advanced cancer, during the open-label treatment period. | • Incidence of adverse events and laboratory abnormalities, in Part B of the study. | • There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards, as applicable. |
| • To assess **body weight** in participants with anorexia and advanced cancer, during the open-label treatment period. | • Change from baseline in body weight, at Weeks 12, 15, 18, 21 and 24. | • N/A |
| • To explore the relationship between **pain** and appetite/fatigue in participants with anorexia and advanced cancer, during the open-label treatment period. | • 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, weekly from Week 7 to 24. | • N/A |
| • To assess **patient global impression of change** of appetite and fatigue in participants with anorexia and advanced cancer, during the open-label treatment period. | • PGI-C (appetite), at Week 24.<br>• PGI-C (fatigue), at Week 24. | • N/A |

| Objectives | Endpoints | Estimands |
|---|---|---|
| • To characterize the unbound and total **PK** of PF-06946860 administered in participants with anorexia and advanced cancer, during the open-label treatment period. | • Serum unbound and total concentrations of PF-06946860, at Weeks 12, 18 and 24. | • N/A |
| • To characterize the effect of PF-06946860 administration on circulating **GDF-15** concentrations in participants with anorexia and advanced cancer, during the open-label treatment period. | • Serum concentrations of total GDF-15; and if feasible, unbound GDF-15, at Weeks 12, 18 and 24. | • N/A |
| • To assess the **immunogenicity** of PF-06946860 administered in participants with anorexia and advanced cancer, during the open-label treatment period. | • Incidence of ADA and, if applicable, NAb, in Part B of the study. | • N/A |

# 4. STUDY DESIGN

## 4.1. Overall 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 anorexia.

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.

Potential participants will attend 2 clinic visits (Screening and Randomization) with the investigator. The Screening visit will occur no more than 28 days and no less than 5 days, prior to Randomization. The 5-day minimum duration between Screening and Randomization visits will ensure that all necessary data (including GDF-15 level) are available to inform the investigator's assessment of eligibility.

All study visits following Randomization may be conducted by a visiting Health Care Professional (HCP) at the patient's home. During selected home-HCP visits, the investigator will conduct periodic Telehealth consults with the participant in order to assess patient safety (See Appendix 11 Study Conduct). 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. The participant and investigator may select to have study visits for Part B conducted at home or in-clinic.

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 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, at home or in the clinic, per investigator judgement. For study part B, a home-HCP+TeleHealth (or in-Clinic) visit will be conducted. Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

### 4.2. Scientific Rationale for Study Design

The primary purpose of this study is to assess the effect of repeated subcutaneous administrations of PF-06946860 on appetite in patients with advanced cancer, anorexia and elevated circulating GDF-15 levels. The study will also assess secondary and exploratory endpoints including fatigue, safety, body weight, immunogenicity, PK and PD.

#### 4.2.1. Population

As described in Section 2, it is hypothesized that anorexia-cachexia in patients with advanced cancer is largely mediated via GDF-15, and that suppression of GDF-15 in these patients may lead to improvement in serious aspects of their disease including appetite. This study, therefore, intends to enroll patients with advanced cancer, anorexia and elevated GDF-15 levels.

Across malignancies, cachexia is highly prevalent, impacting approximately half of patients with advanced cancer, including those solid tumor types selected for inclusion in this study. Elevated levels of circulating GDF-15 have been reported in literature in patients with a variety of tumor types experiencing anorexia and weight loss. Biospecimens from healthy adults[30] and patients with cancer (from both external commercial biorepositories and an internal study) were analyzed for GDF-15 levels. The cancer sample set contained 399 NSCLC, 116 pancreatic cancer, 157 colorectal cancer, 136 prostate cancer, 112 ovarian cancer and 144 breast cancer patients. These patients were mostly Caucasian, aged 29-90, and had an approximate ratio of 40%: 60% females to males (excluding breast and ovarian [100% female] and prostate [100% male]). The sample set of 739 apparently healthy volunteers were predominantly Caucasian, aged 20-79 and equally distributed males and females. Analysis of both the cancer and healthy sample sets using the Roche Elecsys assay,[30] confirmed literature-reported elevations in GDF-15 levels in cancer patients when compared to healthy subjects (elevations ranging from 2-fold [prostate and breast cancer] to 5-fold [pancreatic cancer]). An adhoc analysis of NSCLC patients from an internal Pfizer study demonstrated that higher GDF-15 levels were associated with a reduction in body

weight. These data were used to determine the degree of GDF-15 elevation necessary for inclusion in this study. GDF-15 levels above the 95th percentile of GDF-15 concentrations reported in these healthy subjects will be considered elevated [redacted].

In order to appropriately enroll patients who may be expected to derive benefit from treatment with PF-06946860, severity of anorexia (See Section 8.1.1.1) will be assessed at Screening and prior to Randomization using a self-reported questionnaire. Impaired appetite will be a requirement for inclusion into this study.

Studies to evaluate the development toxicity of PF-06946860 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

### 4.2.2. Duration of Dosing

The double-blind portion of this study (Part A) will be 6 weeks in duration. This is anticipated to be sufficient to detect an effect on the primary endpoint, appetite, while minimizing the required duration of study participation.

All participants completing the 6-week double-blind portion of the study will be given the option of receiving open-label PF-06946860 during study Part B. As efficacy has not yet been studied in a clinical setting, participation in study Part B will be optional with the purpose of providing continued access to participants who are deriving or may derive benefit (based on their own perception, along with that of their investigator).

The total duration of dosing with PF-06946860 in this study will be up to 24 weeks, as supported by completed nonclinical toxicity studies (Section 2.2.1).

### 4.2.3. Endpoints and Procedures

The key objectives of this study are to assess the effect of PF-06946860 on serious aspects of disease, anorexia and fatigue, in this population. The primary objective of the study is to assess the early effect of PF-06946860 on appetite, this will be evaluated at Week 4. This Week 4 timepoint is intended to reflect the initial anticipated symptomatic change, while minimizing potential impact of any early termination in this fragile population. An additional assessment of appetite and fatigue endpoints across the entire 6-week double-blind period will be conducted. As the severity of pain may influence a participant's level of appetite, patient reported data on pain may be used as part of exploratory analyses. Appetite, fatigue and pain will be assessed weekly via questionnaires completed by the patient (see Section 8.1.1.3). A small number of fit-for-purpose questions has been selected to minimize patient burden. Additionally, phone interviews will be conducted with the patient and a caregiver, if feasible. This will allow a qualitative assessment of the overall participant/caregiver experience (see Section 8.1.1.5).

Participant safety will be monitored primarily via clinical laboratory test and adverse event monitoring with a combination of in-clinic, home-HCP and TeleHealth visits. To supplement the standard clinical safety laboratory tests assessed at this stage of development, CRP, albumin and pre-albumin will be included as measures of nutritional status.

As an amelioration of anorexia can be expected to precede improvement in body weight, an exploratory assessment of change in weight will be included in this study, see Section 8.6.2. The electronic scales, provided to each participant for use from the randomization visit onward, will also provide data on body composition as part of the same body weight measurement procedure. Given the prevalence of edema in this population, the data may be used as part of exploratory analyses.

As PF-06946860 is a monoclonal antibody, immunogenicity samples will be collected for the determination of ADA and NAb, if applicable.

Sparse PF-06946860 and GDF-15 concentrations will be measured in this study to (1) assess PF-06946860 exposure in this population; (2) understand the range of baseline GDF-15 values and variability in this population; and (3) provide preliminary information on the magnitude of GDF-15 response after PF-06946860 treatment.

Banked biospecimens will be collected for exploratory pharmacogenomic/genomic/ biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

#### 4.2.3.1. Participant Input into Design

Twelve patients and caregivers were interviewed in order to better understand what symptoms are most burdensome to patients and what might impact their decision to participate in a clinical study. All patients had cancer (prostate, non-small cell lung, colorectal or pancreatic cancers) and had experienced significant unintentional weight loss and other symptoms of cachexia.

Patient input was valuable in informing key outcomes. Of greatest interest were improved appetite and reduced fatigue, supporting the choice of appetite as the primary endpoint for the study.

Patients and caregivers also provided input on the study design which triggered incorporation of options to potentially enhance patient participation and retention, and highlighted the following additional considerations which are anticipated to be of value to patients:

- Option for home/tele-visits with physician or in-person physician appointments where feasible through double-blind portion of the study.
- Nutritional consultations eg, via TeleHealth. This will be included, if operationally feasible.
- Confirmed the importance to patients of including the option to receive open-label treatment following double-blind period.

- Patients emphasized the significance of having their overall experiences with the study treatment heard by the Sponsor. This led to the incorporation of qualitative phone interviews in order to facilitate a more holistic assessment.

- Highlighted the value of appropriate training, including to home HCPs, on important aspects of the disease and the potential social and psychological impact.

CCI [redacted]

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CCI [redacted]

### 4.4. End of Study Definition

A participant is considered to have completed the study if he/she has either completed Part A (including follow-up), or has completed Part A and has entered, and completed, the OL extension Part B.

The end of the study is defined as the date of the last visit of the last participant in the study.

## 5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

**Age and Sex:**

1. Male or female participants ≥18 (or the minimum country-specific age of consent if >18) at Screening.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

**Type of Participant and Disease Characteristics:**

2. Documented diagnosis of non-small cell lung, pancreatic, colorectal, prostate, breast or ovarian cancer which, in the treating oncologist's assessment, is considered advanced, for example:

   - Unresectable Stage III or IV **non-small cell lung** cancer.
   - Locally advanced or metastatic **pancreatic adenocarcinoma**.
   - Metastatic or recurrent **colorectal** cancer.
   - Metastatic **prostate** cancer.
   - Metastatic or recurrent **breast** cancer.
   - Refractory **ovarian** cancer.

3. Meets **any** of the following criteria at Randomization:

   i. Not currently receiving antineoplastic therapy. This may be, for example, a patient who:

      - Has chosen not to receive further therapy, for example for quality of life reasons;
      - Is not indicated for future antineoplastic therapy or has exhausted all treatment options;
      - Has stable disease where no antineoplastic therapy is judged to be necessary;
      - Is taking a break between antineoplastic treatments, where the break has begun at least 4 weeks prior to Randomization and is anticipated to be longer than the 6-week duration of the double-blind portion of this study.

        If such a patient has recently completed a course of antineoplastic therapy, the last dose of that therapy should be at least 4 weeks prior to Randomization (see Section 6.5).

   ii. Patients on standard of care systemic antineoplastic therapy or treatment without curative intent, (see Section 6.5).

4. Anorexia as defined by a score CCI in the Cancer-Related Cachexia Symptom Assessment-Appetite 7-day recall scale (see Appendix 7) at Screening **and** Randomization.

5. Serum GDF-15 levels of CCI (as measured using the Investigational Use Only Roche Elecsys GDF 15 assay)[30] at Screening.

6. Participants who are assessed by the investigator to be **able to participate** for the double-blind treatment period of **6 weeks**. In the investigator's judgement, the participant should be anticipated to be able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures during the double-blind portion of the study.

   In cases where the investigator is not the treating oncologist, the oncologist's assessment of the potential participant's suitability for inclusion must also be considered.

**Informed Consent:**

7. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

8. Willing to comply with all scheduled visits, treatment plan, laboratory tests, contraception guidelines, and other study procedures for at least the 6-week double-blind treatment period.

### 5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions:**

1. Receiving tube feedings or parenteral nutrition (either total or partial) at the time of Screening or Randomization.

2. Current active reversible causes of decreased food intake, as determined by the Investigator. These causes may include, but are not limited to:

   - Mechanical obstructions making patient unable to eat;

   - National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 oral mucositis.

3. Unresolved acute effects of any prior therapy, or uncontrolled symptoms (eg, pain, diarrhea) at Randomization that in the judgement of the PI makes the participant unsuitable for the study. For example, uncontrolled pain may be indicated by a recent (eg, within past 15 days) change in opioid treatment.

4. Current, severe gastrointestinal disease (including esophagitis, gastritis, malabsorption) at Randomization.

5. History of gastrectomy.

6. Persistent symptoms due to ascites at randomization, unresponsive to clinically indicated interventions.

7. Participants with known symptomatic brain metastases requiring steroids. Participants with asymptomatic or previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to Screening, have discontinued corticosteroid treatment for these metastases and are neurologically stable for at least 4 weeks (requires magnetic resonance imaging [MRI] confirmation) prior to Screening.

   Note that if radiation therapy becomes necessary for treatment of brain metastases or palliative treatment after Randomization, this will not be a reason for discontinuation.

8. Participants with active, uncontrolled bacterial, fungal, or viral infection, including but not limited to HBV, HCV, HIV or participants with known AIDS-related illness.

9. Undergoing major surgery (central venous access placement and tumor biopsies are not considered major surgery) within **4 weeks** prior to first dose of investigational product. Patient must be well recovered from acute effects of surgery prior to screening. Patient should not have plans to undergo major surgical procedures during the study.

10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

**Prior/Concomitant Therapy:**

Part A Double-Blind treatment period only:

11. Initiation of new systemic antineoplastic therapy (eg, chemotherapy, immunotherapy) within the **4 weeks** prior to the first dose of investigational product or planning to initiate antineoplastic therapy during the 6-week double-blind portion of the study.

12. Initiation of new treatment prescribed or self-administered and known to have an impact on anorexia, weight loss or cachexia, including but not limited to mirtazapine, olanzapine, cannabinoids, within the **4 weeks** prior to the first dose of investigational product or during the 6-week double-blind portion of the study; stable (ie, no significant change to dosage or frequency of administration in prior 4 weeks) therapy is permissible. See Section 6.5 Concomitant Therapy for details.

13. Radiation therapy other than localized palliative treatment (eg, pain management for bone metastases) within the **3 weeks** prior to the first dose of investigational product or during the 6-week double-blind portion of the study.

14. Initiation of new treatment with systemic glucocorticoids within the **4 weeks** prior to the first dose of investigational product or during the 6-week double-blind portion of the study; stable (ie, no significant change to dosage or frequency of administration in prior 4 weeks) steroid therapy eg, dexamethasone as part of pre-medication or daily oral prednisone is permissible. See Section 6.5 Concomitant Therapy for details.

15. Initiation of megestrol acetate within the **2 weeks** prior to the first dose of investigational product or during the 6-week double-blind portion of the study; stable (ie, no significant change to dosage or frequency of administration in prior 2 weeks) therapy is permissible. See Section 6.5 Concomitant Therapy for details.

Part B Open-Label treatment period: there are no restrictions on initiation of new therapy or changes to existing therapy during open-label treatment.

**Prior/Concurrent Clinical Study Experience:**

16. Received previous treatment with at least one dose of PF-06946860.

17. Actively receiving a concurrent investigational agent, or previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

**Diagnostic Assessments:**

18. Positive urine drug screen for illicit drugs at Screening, with the exception of cannabinoids per Prior/Concomitant Therapy criteria number 12 above. Results may be confirmed by a single repeat, if necessary. In addition, drugs which have been medically prescribed and reported to the investigator at the Screening visit may be permitted, if judged appropriate by the investigator and permitted by the Sponsor. Prescribed pain medications (eg, opioids, morphine, hydrocodone) do not need be cleared with the Sponsor.

19. Inadequate liver function at Screening as evidenced by any 1 of the following, which may be confirmed by a single repeat, if necessary:

    - Total serum bilirubin >1.5 x upper limit of normal (ULN) unless the participant has documented Gilbert syndrome;

    - Aspartate (AST) and/or Alanine aminotransferase (ALT) >3 x ULN; >5.0 x ULN if there is liver involvement by the tumor;

- Alkaline phosphatase >3 x ULN. Inclusion of participants with alkaline phosphatase >3 x ULN may be acceptable if they are deemed medically stable and fit for the study by both investigator and sponsor medically qualified personnel.

20. Inadequate renal function at Screening, including creatinine >2 mg/dL, or calculated Glomerular Filtration Rate (GFR) <30 mL/minute/1.73 $m^2$ as calculated by the modification of diet in renal disease (MDRD) equation.[31] Result may be confirmed by a single repeat, if necessary.

**Other Exclusions:**

21. Woman who is pregnant or breast-feeding.

22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

## 5.3. Lifestyle Considerations

### 5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

## 5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. This includes participants who consent and do not meet eligibility criteria as well as those who are not randomized for administrative reasons (eg, screening window has expired, delays in IP shipping, cohort filled). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who qualify for this study but are not randomized for administrative reasons, may be re-screened. Individuals who do not meet the criteria for participation in this study may be re-screened **once** if, in the judgement of the investigator, the reason for initial ineligibility is considered to be resolved, or there has been a change in eligibility status.

For individuals who are re-screening for any reason, all screening procedures must be repeated and the participant assigned a new SSID.

### 5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

Not Applicable.

## 6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to PF-06946860.

### 6.1. Study Intervention(s) Administered

| **Intervention Name** | PF-06946860 | Placebo |
|---|---|---|
| **ARM Name** | PF-06946860 Double-Blind Treatment followed by Open-Label Treatment | Placebo Double-Blind Treatment followed by Open-Label Treatment |
| **Type** | Biologic | Placebo |
| **Dose Formulation** | Solution for injection | Solution for injection |
| **Unit Dose Strength(s)** | CCI | Placebo |
| **Dosage Level(s)** | CCI | Placebo Q3Weeks |
| **Route of Administration** | Subcutaneous | Subcutaneous |
| **Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)** | IMP | IMP |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor |
| **Packaging and Labeling** | Study intervention will be provided in 6-mL glass vial with a 1 mL withdraw volume. Each vial will be labeled as required per country requirement. | Study intervention will be provided in 6-mL glass vial with a 1 mL withdraw volume. Each vial will be labeled as required per country requirement. |
| **Current/Former Name(s) or Alias(es)** | Not applicable | Not applicable |

### 6.1.1. Administration

Each dose of investigational product must be administered by appropriately qualified health care personnel (whether administered at home or in a clinic setting). During the double-blind portion (Part A) of the study, investigational product will be administered at a dose of CCI or placebo Q3W SC for a total of 2 doses (6 weeks). If the participant continues to the optional OLT period (Part B), up to 7 additional doses of PF-06946860 CCI will be administered starting at the Week 6 visit (for participants entering the OLT period). Each dose is comprised of two 1 mL SC injections which are to be administered consecutively. For participants who are receiving standard of care systemic antineoplastic treatment, premedication is permitted consistent with institutional guidelines, and, unless specifically noted in Section 6.5, may include an antihistamine, anti-inflammatory agent, or pain reliever. In such cases, PF-06946860 is to be administered first, followed by any required premedications. If the standard of care systemic antineoplastic treatment is to be administered on the same day of dosing with study drug (PF-06946860 or placebo in Part A or PF-06946860 in Part B), where feasible, the study drug will be administered prior to the standard of care antineoplastic treatment.

## 6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff or designated healthcare personnel may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is administered at home by the designated healthcare personnel, both used and unused, must be returned to the investigator by the designated healthcare personnel. Returned study intervention must not be redispensed to the participants.

7. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

### 6.2.1. Preparation and Dispensing

Investigational Product, PF-06946860 CCI [redacted] and placebo will be prepared by qualified personnel according to the IP manual. The study intervention will be administered in a blinded fashion to the participants in Part A and open-label in Part B.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

### 6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including, but not limited to, the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be administered at the study visits summarized in the SoA.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

### 6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

Part A of this study is participant- and Investigator-blinded and Sponsor-open. Part B of the study will be open to the participant, Investigator, and Sponsor or Sponsor-designate personnel responsible for study monitoring activities (including all site monitoring activities).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

## 6.4. Study Intervention Compliance

The study intervention will be administered to participants directly by an appropriately qualified individual. The date and time of each dose administered will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by designated healthcare personnel if the study intervention is administered at the participant's home or a member of the study site staff other than the person administering the study intervention if the study intervention is administered at the clinic.

Deviation(s) from the protocol-specified dosage regimen should be recorded in the CRF.

A record of the number of the study drug (Investigational Product, PF-06946860 CCI or placebo vials) administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or missed doses, will also be recorded in the CRF.

## 6.5. Concomitant Therapy

The date and time of administration of any background and/or concomitant therapies as well as the name and dosage regimen must be recorded.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

**Prohibited in the 4 weeks prior to first dose of IP and during Part A**

- Initiation of new systemic **antineoplastic therapy** (eg, chemotherapy, immunotherapy) within the 4 weeks prior to the first dose of investigational product or planning to initiate antineoplastic therapy during the 6-week double-blind portion of the study.

- If a participant has recently completed a course of **antineoplastic therapy**, the last dose of that therapy should be at least 4 weeks prior to Randomization.

- Initiation of new treatment prescribed or self-administered and known to have an impact on **anorexia, weight loss or cachexia**, including but not limited to mirtazapine, olanzapine, cannabinoids, within the 4 weeks prior to the first dose of investigational product or during the 6-week double-blind portion of the study; stable (ie, no significant change to dosage or frequency of administration in prior 4 weeks) therapy is permissible.

- Initiation of new treatment with systemic **glucocorticoids** is prohibited within the 4 weeks prior to the first dose of investigational product or during the 6-week double-blind portion of the study; stable (ie, no significant change to dosage or frequency of administration in prior 4 weeks) steroid therapy eg, dexamethasone as part of pre-medication or daily oral prednisone is permissible.

  While use of glucocorticoids for antiemetic prophylaxis as part of standard of care treatment protocols is permitted under conditions described here, every effort should be made not to administer such medications within the 7 days prior to the **Day 1 and Week 4** PRO assessments (see Section 8.1.1).

  Inhaled or topical steroid use is not restricted.

**Prohibited in the 3 weeks prior to first dose of IP and during Part A**

- **Radiation therapy** other than localized palliative care (eg, pain management for bone metastases) within the 3 weeks prior to the first dose of investigational product or during the 6-week double-blind portion of the study.

**Prohibited in the 2 weeks prior to first dose of IP, and during Part A**

- Initiation of **megestrol acetate** within the 2 weeks prior to the first dose of investigational product or during the 6-week double-blind portion of the study; stable (ie, no significant change to dosage or frequency of administration in prior 2 weeks) therapy is permissible.

**Open-Label treatment period:**

- There are no restrictions on initiation of new therapy, or changes to existing therapy, during the open-label treatment part of the study.

### 6.5.1. Rescue Medicine

There is no specific rescue therapy to reverse AEs observed with PF-06946860. There is no approved medication to treat anorexia associated with cancer-cachexia. Standard medical supportive care must be provided to manage any AEs or changes to underlying symptoms.

Note that, following the 6-week double blind portion of the study, there are no protocol-specified restrictions on concomitant medications (see Section 6.5).

## 6.6. Dose Modification

There is no dose modification of PF-06946860 anticipated for a given participant in this study.

## 6.7. Intervention After the End of the Study

No intervention will be provided to study participants following Part B of the study.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Progression of underlying disease such that the investigator no longer considers participation appropriate, or of potential benefit to the participant.

- Hospitalization that in the opinion of the investigator would render continued participation unfeasible.

Note that discontinuation of investigational product does not represent withdrawal from the study. If investigational product is permanently discontinued, the participant will remain in the study for follow up. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

## 7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

### 7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### 7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

## 8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner. For selected procedures which are not feasible due to progression or complications of underlying disease, as indicated in the SoA, non-completion will not be considered a protocol deviation as long as the participant's safety was preserved. In all cases, collection of safety data should be prioritized.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 220 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

## 8.1. Efficacy Assessments

### 8.1.1. Patient Reported Outcomes

All patient-reported outcome (PRO) assessments are completed electronically by study participants at home, or at the clinic, following a schedule of assessments as per the SoA. Every effort should be made to have the study participant complete all patient-reported outcome assessments before any other clinical assessments that take place during a study visit.

The PRO/eCOA Training Manual will be provided separately.

#### 8.1.1.1. Cancer-Related Cachexia Symptom Assessment – Appetite

The Cancer-Related Cachexia Symptom Assessment-Appetite (Appendix 7) 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".

#### 8.1.1.2. Cancer-Related Cachexia Symptom Assessment – Fatigue

The Cancer-Related Cachexia Symptom Assessment-Fatigue (Appendix 8) 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".

#### 8.1.1.3. PROMIS Pain 1a

While not considered an efficacy endpoint, the severity of pain may influence a participant's level of appetite. The PROMIS Pain 1a (Appendix 9) 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". These data may be used as part of exploratory analyses.

#### 8.1.1.4. Patient Global Impression of Change (PGI-C)

The PGI-C (Appendix 10) 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".

#### 8.1.1.5. Qualitative Phone Interviews

Qualitative interviews will be conducted with the participant by telephone at times indicated in the SoA. Additionally, where a caregiver is available and willing to participate, similar qualitative phone interviews may be conducted with a caregiver, as indicated in the SoA. Note that both the participant and their caregiver must provide consent (Appendix 1*)* for the caregiver to participate in the phone interviews.

Interviews will be conducted by trained moderators and are anticipated to be approximately 30 minutes in duration. Using the transcripts and interviewer field notes, dominant trends will be identified in each interview and compared across all the interviews to describe the participant/caregiver experience with a focus on the themes or patterns in the way the treatment experience is described, and the importance of any improvements reported. Following the analysis, 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.

### 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Injection site reactions will be assessed as part of standard safety/AE monitoring. Additional assessments may be conducted at investigator discretion and/or until any symptoms resolve. Injection site reactions may include but are not limited to: erythema, induration, ecchymosis, pain and pruritus. The size and severity of injection site reactions will be assessed and

documented. If deemed appropriate by the investigator, a consultation with a dermatologist may be performed. Documentation of a reaction may include items such as investigator notes, photographs, dermatologist report and/or clinic notes.

### 8.2.1. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

A full physical examination will be conducted at Screening and will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. Height will also be measured and recorded at Screening only.

Symptom-directed assessments may be carried out by acceptably trained HCP (eg, RN at Home-HCP visits), if necessary.

### 8.2.2. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or up to the time of the final planned follow-up visit after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

### 8.2.3. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced prior the participant’s receiving the study intervention. Pregnancy tests will also

be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

### 8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). AEs will be assessed based on CTCAE 5.0.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

#### 8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of up to the time of the final planned follow-up visit, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

#### 8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

#### 8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

### 8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

### 8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by eg, skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by eg, skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information

Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

#### 8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

#### 8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

### 8.3.6. Cardiovascular and Death Events

Not applicable.

### 8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

### 8.3.8. Adverse Events of Special Interest

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

#### 8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

### 8.3.9. Medical Device Deficiencies

Not applicable.

### 8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| Medication errors | All (regardless of whether associated with an AE) | Only if associated with an SAE |

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

### 8.4. Treatment of Overdose

Based on preliminary population PK/PD simulation, doses greater than approximately CCI administered when exposure is expected to be at steady-state, are projected to result in exposure exceeding the NOAEL from the 6-month toxicology study in monkeys (Section 2.2.1.3). The definition of overdose for this trial is based on the operational aspects of the protocol design. Given the nature of this study ie, subcutaneous dose administered in the participant's home by a trained healthcare provider, and the allowed visit window, an overdose will be defined as more than 2 doses of PF-06946860 CCI administered in a period of 3 weeks.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06946860 (whichever is longer). The duration of monitoring required will be provided by the sponsor.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain blood samples for PK, PD, and/or immunogenicity analyses within 5-7 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

### 8.5. Pharmacokinetics

Blood samples of approximately 6 mL, to provide a minimum of 2 mL serum, will be collected for measurement of serum unbound and total concentrations of PF-06946860 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. On dosing days, predose PK sample will be collected prior to IP administration. Collection of samples within the protocol-allowed visit window (±1, ±3 or +7 days, as defined in SoA) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of PF-06946860. Samples collected for analyses of PF-06946860 concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, and/or evaluation of bioanalytical methods, or for other internal exploratory purposes.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of serum unbound and total concentrations of PF-06946860 will be analyzed using validated analytical methods in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

### 8.6. Pharmacodynamics

#### 8.6.1. GDF-15

Blood samples of approximately 6 mL, to provide a minimum of 2 mL serum, will be collected for measurement of serum concentrations of total GDF-15, and if feasible, unbound GDF-15 at time points specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. On dosing days, predose GDF-15 sample will be collected prior to IP administration. Collection of samples within the protocol-allowed visit window (±1, ±3 or +7 days, as defined in SoA) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples collected for PD analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, and/or evaluation of bioanalytical methods, or for other internal exploratory purposes.

At Screening, serum GDF-15 concentrations will be measured using the IUO Roche Elecsys GDF-15 assay, which will be validated in a CLIA accredited central laboratory. Post Screening, serum samples will be analyzed for total GDF-15 and, if feasible, unbound GDF-15, using validated analytical methods in compliance with applicable SOPs. In addition, screening samples may also be analyzed in these methods for exploratory purposes.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

GDF-15 concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

### 8.6.2. Body Weight

At Screening, body weight will be recorded using a calibrated scale at the investigator site.

Any scale used during the study must report weight in either pounds (lb) or kilograms (kg), and be accurate to the nearest 0.2 lb (or 0.1 kg); ie, the device must be able to distinguish a difference between 150.4 lb (68.4 kg) versus 150.2 lb (68.3 kg). The scale must be placed on a stable, flat surface.

At the Randomization visit, an electronic scale will be provided to the participant for their use (at home) for the remainder of the study. Where possible, the same scale should be used for all body weight measurements from the Randomization visit onward.

Weight measurements should be taken under the following conditions, where feasible:

- After void of urine;
- After removal of shoes, socks, bulky layers of clothing and jackets so that only light clothing remains;

- While remaining still during the measurement.

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.

## 8.7. Genetics

### 8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

### 8.7.2. Banked Biospecimens for Genetics

A 2-mL blood sample optimized for DNA isolation Prep D1.5 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and anorexia/cachexia. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

## 8.8. Biomarkers

There are no additional biomarkers planned for this study aside from GDF-15 (described in Section 8.6).

### 8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

### 8.8.2. Specified Protein Research

Specified protein research is not included in this study.

### 8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

## 8.9. Immunogenicity Assessments

Blood samples of approximately 6 mL, to provide a minimum of 2 mL serum, will be collected for determination of ADA and NAb as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response, to evaluate safety or efficacy aspects related to concerns arising during or after the study, and/or evaluation of bioanalytical methods, or for other internal exploratory purposes.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Immunogenicity information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

### 8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

## 9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

### 9.1. Estimands and Statistical Hypotheses

#### 9.1.1. Estimands

*Estimand related to the **appetite** primary objective:*

**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 (ie, 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 appetite secondary objective (ie, change from baseline at Weeks 1, 2, 3, 5 and 6).

Alternative estimands for the primary objective may be used in order to examine the robustness of the results and will be detailed in the SAP.

*Estimand related to the* **fatigue** *secondary objective:*

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 the* ***safety and tolerability*** *secondary objective:*

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.

*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. Details of these estimands and analyses will be presented in the SAP.

### 9.2. Sample Size Determination

A sufficient number of participants will be screened to achieve approximately 40 participants (approximately 27 participants in the PF-06946860 200 mg Q3W arm and 13 participants in the placebo arm) randomly assigned to study intervention in approximately a 2:1 ratio. This is expected to ensure completion of Part A of the study of approximately 30 evaluable participants (approximately 20 PF-06946860: 10 placebo), assuming a discontinuation rate of 25%. There is no required sample size for Part B of the study.

The study sample size has been chosen to provide sufficient data for an initial assessment of efficacy in the population for facilitating internal decision making and may be used for future study planning. Completion of 30 participants, with a 2:1 ratio, gives acceptable Operating Characteristics in that:

- The probability of achieving statistical significance (at the 5% significance level, using a 1-sided t-test) for a true effect of 4 versus placebo for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Appetite score (ranging 0-10) at 4 weeks is approximately 80%.

- An observed effect of 2.7 versus placebo for the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Appetite score at 4 weeks should achieve statistical significance (at the 5% significance level, using a 1-sided test).

A conservative estimate of the between-subject standard deviation for the change from baseline in the patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Appetite score of 4.2 has been used. This estimate was based on the observed variability of a similar appetite scale in a double-blind controlled clinical trial assessing the effect of megestrol acetate on appetite in patients with far-advanced cancer.[32]

Evaluable participants are defined as in Section 9.3.

Participants who withdraw from the study will not be replaced.

### 9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

| 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. |
| 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. |
| 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. |

## 9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

### 9.4.1. General Considerations

For objectives relating to Part A of the study, each treatment arm (PF-06946860 or placebo) will be reported separately through the 6-week double-blind treatment period only (including follow-up for any participants not continuing onto Part B of the study).

#### 9.4.1.1. Analyses for Continuous Endpoints

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), and the Kenward-Roger approximation will be used for estimating degrees of freedom. Additional terms may be fitted in the model (eg, cancer type, PROMIS-Pain 1a change from baseline score), as appropriate.

### 9.4.2. Primary Endpoint(s)

Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Appetite score will be analyzed using Estimand 1 and an MMRM model (as per Section 9.4.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 6 using the *Censored* analysis set. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs), at Week 4, will be provided. No adjustments will be made for multiplicity.

### 9.4.3. Secondary Endpoint(s)

| Endpoint | Statistical Analysis Methods |
|---|---|
| Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment-Appetite score, at Weeks 1, 2, 3, 5 and 6. | Results related to this endpoint will be obtained from the Primary Analysis model above.<br><br>Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs), at each week, will be provided. No adjustments will be made for multiplicity. |
| 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. | Change from baseline for patient reported 7-day recall Cancer-Related Cachexia Symptom Assessment–Fatigue score will be analyzed using Estimand 2 and an MMRM model (as per Section 9.4.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 6 using the Censored analysis set.<br><br>Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs), at each weeks, will be provided. No adjustments will be made for multiplicity. |
| Incidence of adverse events and laboratory abnormalities, in Part A of the study. | All safety analyses will be performed on the safety population. The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations, as appropriate. |

### 9.4.4. Tertiary/Exploratory Endpoint(s)

Details on the analyses of Tertiary/Exploratory endpoints will be described in the SAP.

### 9.4.5. Other Analyses

Selected data collected at Screening may be reported. These data include demographic data, prior and concomitant medications, GDF-15 levels, height, weight and appetite score. 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

(eg, 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.

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.

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.

### 9.5. Interim Analyses

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, conducting a sample size re-estimation, adapting the study, 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.

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.

### 9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use an internal review committee (IRC) or a data monitoring committee (DMC).

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

#### 10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### 10.1.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

### 10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

### 10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

### 10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the study monitoring plan (SMP).

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

### 10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the SMP.

Description of the use of computerized system is documented in the Data Management Plan.

### 10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

### 10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

### 10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand (SToD).

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

## 10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

**Table 2. Protocol-Required Safety Laboratory Assessments**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hemoglobin<br>Hematocrit<br>RBC count<br>MCV<br>MCH<br>MCHC<br>Platelet count<br>WBC count<br>Total neutrophils (Abs)<br>Eosinophils (Abs)<br>Monocytes (Abs)<br>Basophils (Abs)<br>Lymphocytes (Abs) | BUN and creatinine<br>Glucose<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>Total<br>$CO_2$ (bicarbonate)<br>AST,<br>ALT<br>Total bilirubin<br>Alkaline phosphatase<br>Uric acid<br>CRP<br>Pre-albumin<br>Albumin<br>Total protein | pH<br>Glucose (qual)<br>Protein (qual)<br>Blood (qual)<br>Ketones<br>Nitrites<br>Leukocyte esterase<br>Urobilinogen<br>Urine bilirubin<br>Microscopy[a] | • Pregnancy test (β-hCG)[c]<br><br><u>At screening only:</u><br>• FSH[b]<br>• Urine drug screening<br>• Hepatitis B surface antigen<br>• Hepatitis C antibody<br>• HIV |

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

## 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br><br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:<br><br>  • Is associated with accompanying symptoms.<br><br>  • Requires additional diagnostic testing or medical/surgical intervention.<br><br>  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.<br><br>• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.<br><br>• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br><br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br><br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.<br><br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.<br><br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br><br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br><br>• Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.<br><br>• Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs. |

### 10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **An SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br><br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br><br>In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation |

and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a

Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

### 10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

| **Safety Event** | **Recorded on the CRF** | **Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness** |
|---|---|---|
| SAE | All | All |
| Nonserious AE | All | None |
| Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure | All AEs/SAEs associated with exposure during pregnancy or breastfeeding.<br><br>Occupational exposure is not recorded. | All (and EDP supplemental form for EDP)<br>Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure. |

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

| GRADE | Clinical Description of Severity |
|---|---|
| 1 | MILD adverse event |
| 2 | MODERATE adverse event |
| 3 | SEVERE adverse event |
| 4 | LIFE-THREATENING consequences; urgent intervention indicated |
| 5 | DEATH RELATED TO adverse event |
| An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. | |

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

**Follow-up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

### 10.3.4. Reporting of SAEs

**SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

**SAE Reporting to Pfizer Safety via CT SAE Report Form**

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

## 10.4. Appendix 4: Contraceptive Guidance

### 10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 22 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

### 10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with a low user dependency, as described below, during the intervention period and for at least 22 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 22 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s) In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

### 10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

**Highly Effective Methods That Have Low User Dependency**

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

**Highly Effective Methods That Are User Dependent**

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

## 10.5. Appendix 5: Genetics

### Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06946860 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in CSR or in a separate study summary or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

## 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

### Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

## 10.7. Appendix 7: Cancer-Related Cachexia Symptom Assessment – Appetite

**On average, how would you rate your appetite during the past 7 days?**

| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

No appetite — Very good appetite

## 10.8. Appendix 8: Cancer-Related Cachexia Symptom Assessment – Fatigue

**On average, how would you rate your physical fatigue during the past 7 days?**

| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

No fatigue — Worst possible fatigue

## 10.9. Appendix 9: PROMIS Pain 1a

**Pain Intensity – 1a**

**Please respond to the question by marking one box.**

**Pain Intensity**
**In the past 7 days…**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Global07 | How would you rate your pain on average?..... | ☐ 0 No pain | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 | ☐ 7 | ☐ 8 | ☐ 9 | ☐ 10 Worst imaginable pain |

## 10.10. Appendix 10: Patient Global Impression of Change

**Compared to before you started the study, how would you rate your appetite now?**

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

**Compared to before you started the study, how would you rate your physical fatigue now?**

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

## 10.11. Appendix 11 Study Conduct

### 10.11.1. Telehealth Visits

Telehealth visits may be conducted during this study and used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments to be performed during a telehealth visit are outlined in the SoA, and may include:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

### 10.11.2. Nutritional Advice Consult

If operationally feasible, a nutritional consult with a registered dietician via telehealth with a central vendor will be scheduled by the participant within the first 7 days after randomization.

### 10.11.3. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. Additional details will be provided separately.

## 10.12. Appendix 12 Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

### 10.12.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per protocol language regarding eligibility exclusions due to infection.

### 10.12.2. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse event (SAE) and appropriate medical intervention provided. The participant should be discontinued from the study. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required. It is recommended that the investigator discuss permanent discontinuation of study intervention with the study medical monitor.

## 10.13. Appendix 13: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

| | **Term** |
|---|---|
| Abs | absolute |
| ADA | antidrug antibodies |
| ADCC | antibody dependent cell-mediated cytotoxicity |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| $AUC_{168H}$ | area under the curve from the time of dose administration up to 168 hours |
| $AUC_{inf}$ | area under the concentration-time curve from time 0 to infinity |
| $AUC_{last}$ | area under the concentration-time curve from 0 to time of last measurable concentration |
| $AUC_{\tau}$ | area under the concentration-time curve from 0 to time t |
| AV | atrioventricular |
| BBS | Biospecimen Banking System |
| β-hCG | Beta-human chorionic gonadotropin |
| BIA | bioelectrical impedance analysis |
| BUN | blood urea nitrogen |
| $C_{av}$ or $C_{avg}$ | average concentration |
| CDC | complement-dependent cytotoxicity |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CKD | chronic kidney disease |
| CL/F | apparent clearance of drug from eg, plasma |
| CLIA | clinical laboratory improvement amendments |
| $C_{max}$ | maximum observed concentration |
| $CO_2$ | carbon dioxide (bicarbonate) |
| CONSORT | Consolidated Standards of Reporting Trials |
| COPD | chronic obstructive pulmonary disease |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CRO | contract research organization |
| CRP | C-reactive protein |
| CRU | clinical research unit |
| CSR | Clinical Study Report |
| CT | clinical trial |
| CTCAE | Common Terminology Criteria for Adverse Events |

| | **Term** |
|---|---|
| CYP | cytochrome P450 |
| DC | discontinuation |
| DCT | data collection tool |
| DILI | drug-induced liver injury |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| DU | dispensable unit |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCOA | electronic clinical outcome assessment |
| eCRF | electronic case report form |
| EDP | exposure during pregnancy |
| EMA | European Medicines Agency |
| $E_{max}$ | maximal effect |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ET | early termination |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| Fcγ | fragment crystallizable gamma |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GDF-15 | growth differentiation factor 15 |
| GDNF | glial cell-derived- neurotrophic factor |
| GFR | Glomerular Filtration Rate |
| GFRAL | family receptor alpha-like |
| GGT | gamma-glutamyl transferase |
| HBV | hepatitis B virus |
| HCP | Health Care Professional |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRT | hormone replacement therapy |
| IB | Investigator's Brochure |
| ICD | informed consent document |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID | identification |
| IgG1 | immunoglobulin G1 |
| IgG1κ | immunoglobulin gamma-1 with kappa light chains |
| IMP | investigational medicinal product |
| IND | investigational new drug |

| | **Term** |
|---|---|
| INR | international normalized ratio |
| IP | investigational product |
| IP manual | investigational product manual |
| IPAL | Investigational Product Accountability Log |
| IRB | institutional review board |
| IRC | internal review committee |
| IRT | interactive response technology |
| IUO | investigational use only |
| IWR | interactive Web-based response |
| LBBB | left bundle branch block |
| LFT | liver function test |
| mAb | monoclonal antibody |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MDRD | modification of diet in renal disease |
| MIC-1 | Macrophage Inhibitory Cytokine 1 |
| MMRM | mixed-effect model repeated measure |
| MRI | magnetic resonance imaging |
| msec | millisecond |
| N/A | not applicable |
| NAb | neutralizing antibodies |
| NCI | National Cancer Institute |
| NIMP | noninvestigational medicinal product |
| NOAEL | no-observed-adverse-effect level |
| NSCLC | non-small cell lung cancer |
| OL | open-label |
| OLT | open-label treatment |
| PD | pharmacodynamic(s) |
| PE | physical examination |
| PGI-C | patient global impression of change |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PRO | patient reported outcome |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | prothrombin time |
| PVC | premature ventricular contraction/complex |
| Q3W | 3 weeks apart |
| Qual | qualitative |
| RBC | red blood cell |
| RN | registered nurse |
| RNA | ribonucleic acid |

| | **Term** |
|---|---|
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV2 | severe acute respiratory syndrome coronavirus 2 |
| SC | subcutaneous |
| SMP | study monitoring plan |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SSID | single subject identifier |
| SToD | study team on demand |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{½}$ | terminal phase half-life |
| TBili | total bilirubin |
| TEAE | treatment-emergent adverse event |
| TGFβ | transforming growth factor beta |
| $T_{max}$ | time to reach $C_{max}$ |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |
| WOCBP | woman/women of childbearing potential |

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