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

Investigational Product Number:	PF-06946860
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3651009
Phase:	1b

Short Title: Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Repeated Subcutaneous Administrations of PF-06946860 in Patients with Cancer and Cachexia

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 1	08 February 2021	The rationale for this amendment overall is to streamline participant workflow, minimize participant testing burden, and include more cancer populations. The rationale for other changes are based upon completion of the C3651001 and C3651002 CSRs, incorporate PACL items, incorporate protocol template items and correction of spelling errors. The updates are as follows: Addition of pancreatic and colorectal cancer throughout the protocol. Removal of DXA scan as a study procedure noted throughout protocol. Removal of PROs CCI [redacted] from Cohort 2 noted throughout protocol. Added flexibility for CT scan timing noted in SoA. Updates from current IB (Section 2.2) and added 6-month nonclinical monkey data to Section 2.2.3. Schema-updated based upon changes to the procedures and SoA. SoA: • Added a second screening GDF-15 samples to allow analysis using the internal Pfizer assay(s). The additional sample will serve as a baseline prior to standard-of-care anti-tumor therapy for patients who enter the study at the second cycle of standard of care

		anti-tumor therapy. • Added an immunogenicity sample at Week 15 since this is the end of the dosing interval after the last dose of PF-06946860. • Changed V13 from an at-home visit to a clinic visit with additional procedures noted in SOA and increased visit window from ±1 to ±3 days. • Added safety labs and pregnancy test to V14 noted in SOA. • Added pregnancy test to V15 noted in SoA. • CCI [redacted] Section 2.2.2: • Statement regarding the low risk of developing ADA was removed as ADA data from C3651001 and C3651002 are presented in Section 2.2.4. Section 2.2.4: • Updated based on emerging data from C3651001 and C3651002. Section 3: • PK endpoint has been updated to trough concentrations (C_{trough}) of PF-06946860 as this is a PK parameter of interest. Section 4.3: • Updated based on updated PK/PD modeling and simulation results. Safety

		margin updated based on 6-month monkey toxicology data. • Clarified if a different dosing frequency is selected for Cohort 2, this will be implemented via a protocol amendment. Section 5: • Inclusion Criterion # 3 modified for additional cancer types. • Inclusion Criterion # 6 modified for allowable therapies. • Inclusion Criterion # 8-minor corrections. • Exclusion Criterion #1-clarification of excluded cancer types. • Exclusion Criterion #2-updated for clarity. • Exclusion Criterion # 3-added for clarification of radiation therapy. • Exclusion Criterion # 13-removed second bullet. • Exclusion Criterion # 15-removed. Added the following sections to align with the updated protocol template: Sections 8.3.6, Section 8.3.7, 8.3.8 and 8.3.8.1. Section 8.0: • Blood volume increased based on additional samples for safety, biobank and internal assay.

		Section 8.4: • Overdose updated based on updated PK/PD simulation results and NOAEL from 6-month monkey toxicology study. Definition of overdose for this study was redefined based on operational considerations. Sections 8.5, 8.6 and 8.9: • Updated per updated protocol template text. • Section 8.6 updated per SOA. Section 8.8.1: • Updated Prep B2 and Prep 1.5 sample descriptions for clarity. Appendix 10.4: • Updated contraception requirements per emerging PK data from C3651001. Updated protocol to include PACL items: • A pre-dose PK sample will also be collected on Day 1 in addition to the post-dose PK sample. • Radiation as primary SOC is not permitted (allowed for metastases for palliative care) • Inclusion Criterion # 6-Paclitaxel or nab-paclitaxel is permitted as an allowable therapy. Therefore, the allowable therapies are a platin + pemetrexed ± pembrolizumab or a platin + **nab paclitaxel <u>or</u> paclitaxel** ± pembrolizumab as first or second line therapy.
Original protocol	27 November 2019	Not applicable (N/A)

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CCI [redacted]

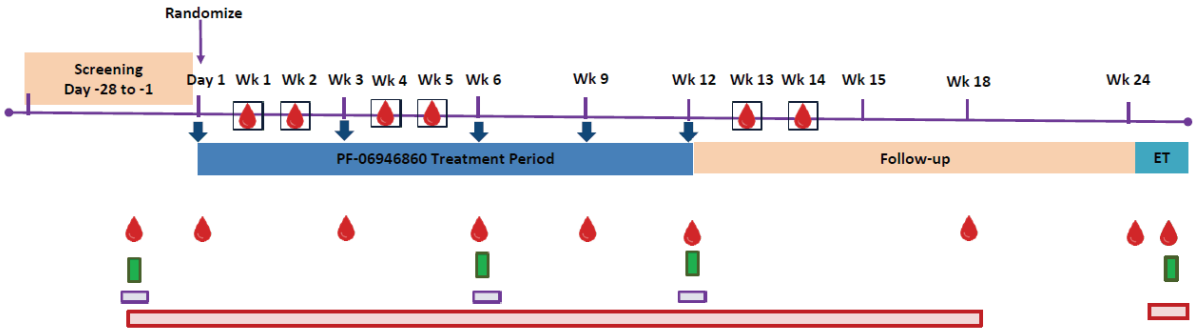
1. PROTOCOL SUMMARY

1.1. Synopsis

Not Applicable.

1.2. Schema

The following schema applies to Cohort 1.



Note: Participants will receive SOC anti-tumor therapy as prescribed by the PI.

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1.3. Schedule of Activities (SoA)

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.

Visit Identifier	Screening[a]	Treatment								EOT	Follow Up[b]					ET
Visit Number	**v1**	**v2**	**v3**	**v4**	**v5**	**v6**	**v7**	**v8**	**v9**	**v10**	**v11**	**v12**	**v13**	**v14**	**v15**	
Study Week (relative to Day 1)			**w1**	**w2**	**w3**	**w4**	**w5**	**w6**	**w9**	**w12**	**w13**	**w14**	**w15**	**w18**	**w24**	
Study Day (relative to Day 1 dosing)	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**64**	**85**	**92**	**99**	**106**	**127**	**169**	
Visit Window (days)			**±1**	**±1**	**±3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±1**	**±1**	**±3**	**±7**	**±7**	
Clinic Visit	X	X			X			X	X	X			X	X	X	X
At-Home Visit[c]			X	X		X	X				X	X				
Informed Consent and Registration	X															
Review of Eligibility Criteria	X	X														
Medical History and Demography	X															
Record Prior or Concomitant treatments	X	X			X			X	X	X			X	X	X	X
Monitor Serious/nonserious AEs[d]	X	X	→	→	X	→	→	X	X	X	→	→	X	X	X	X
Review contraception use	X	X			X			X	X	X			X	X	X	X
Physical Examination[e]	X	X			X			X	X	X			X	X	X	X
Weight (+ Height at Screening only)	X	X			X			X	X	X			X	X	X	X
Supine vital signs[f]	X	X			X			X	X	X			X	X	X	X
Supine standard 12-Lead ECG[g]	X	X			X			X	X	X			X	X	X	X
CT scan	X[h,i]							X[h,i]		X[h,i,j]						X[j]
ECOG Performance	X									X			X	X	X	X
CCI [redacted]	[redacted]							[redacted]		[redacted]						
Randomization		X														
Administration of IP (PF-06946860, SC)[l]		X			X			X	X	X						
Anti-tumor therapy prescribed per SoC[m]		X	→	→	→	→	→	→	→	→						
Safety Labs (Blood and Urine):	X	X			X			X	X	X			X	X	X	X
Pregnancy Test for females (Blood and/or Urine)[n]	X	X			X			X	X	X			X	X	X	X
GDF-15 blood levels (Roche assay)[o]	X															
GDF-15 blood levels (Internal assay(s))[o,p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PF-06946860 serum PK[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA/NAb)[p]		X		X	X			X	X	X			X	X	X	X
Prep D1 banked biospecimen[q]		X														
Prep B1.5 & B2 banked biospecimen[q]		X	X		X			X	X	X	X		X	X	X	X
Patient Reported Outcomes (At home) (Cohort 1 only)[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient Reported Outcomes (At clinic) (Cohort 1 only)[s]		X			X			X	X	X				X		X
CCI [redacted]													[redacted]			[redacted]

Please see next page for table footnotes. Abbreviations: see Appendix 21: Abbreviations.

a. CT scan, CCI [redacted] and PROs (Cohort 1) are performed during the screening period to determine baseline values, but do not need to be reviewed to determine eligibility.

b. **Follow-up visits:** Number, length, and frequency of follow-up visits may be modified based on emerging data.

c. **At-Home visits**: The blood sampling to be conducted at these visits is intended to be done at home by a visiting health care professional for the participant's convenience, but blood sampling may be conducted at the clinic, at the discretion of the participant or investigator. If the participant will be coming to the clinic for clinical care on a day that a home visit is scheduled, the procedures for that visit can be performed at the clinic; and this will not be a protocol deviation.

d. **AEs** will be queried at each clinic visit using open-ended and nonleading verbal questioning of the participant. Any spontaneously reported AEs noted during the home visits will be captured.

e. **Full physical exam** will be conducted at Screening. **Abbreviated physical exams** planned at all other clinic visits, however full exams may be performed for findings during previous exam, new/open AEs, or at investigator discretion.

f. **Triplicate blood pressure and pulse rate** will be measured on Day 1; **single blood pressure and pulse rate** for all other clinic visits. See Section 8.2.3.

g. **Triplicate ECGs** on Day 1; **single ECG** for all other clinic visits. See Section 8.2.4.

h. CT scan: If a CT scan was performed within 3 weeks prior to the **Screening visit** and meets the quality and anatomical requirements, then a CT scan at screening is not needed. If a CT scan is being performed at the **Week 6** or **Week 12** visit as part of the standard of care, then an additional CT scan is not needed as long as CT quality matches the requirements outlined in the imaging guidelines. The RECIST 1.1 categorization is to be entered in the CRF after each scan. See Section 8.1.2.

i. **CT scans** can be done within ± 14 days of the Week 6 visit and within 7 days after the last dose of IP administration at the **Week 12** visit.

j. CT scan: To be completed at the ET visit if a CT scan has not been completed in the prior 6 weeks. However, a CT scan at the ET visit is not needed if the ET is before Week 4 or if a CT scan was performed at Week 12.

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l. **PF-06946860** dosing can be initiated at the start of the first or second cycle of the standard of care anti-tumor therapy. If the standard of care anti-tumor therapy is to be administered on the same day of dosing with PF-06946860, the IP will be the first drug administered during the clinic visit and must be given at least 0.5h prior to administration of SOC anti-tumor therapy. If SoC anti-tumor therapy is paused, adjusted or discontinued during the 12 week treatment period, this would not be considered a protocol deviation. PF-06946860 administration is to continue as prescribed by the protocol.

m. The **SoC anti-tumor therapy** may continue beyond the study 12-week PF-06946860 treatment period according to the SOC anti-tumor therapy for each cancer type and the treating physician's clinical judgment; this would not be considered a protocol deviation.

n. **Blood and/or Urine pregnancy** test may be performed at the discretion of the PI.

o. Two GDF-15 samples will be collected at Screening. One sample will be tested using the Roche GDF-15 assay for determination of enrollment eligibility. Another sample will be analyzed using the internal Pfizer GDF-15 assay(s).

p. **GDF-15, PK and Immunogenicity blood samples** will be collected as described in Section 10.19. On dosing days (Day 1, Weeks 3, 6, 9, and 12), these blood samples will be collected prior to PF-06946860 administration (ie, pre-dose). Additionally, on Day 1 and Week 12, **post-dose** blood samples will be collected, **one for PK and one for GDF-15** at each visit. These **post-dose** blood samples will be collected at a minimum of 3h post PF-06946860 administration or at a maximum by the end of the clinic visit.

q. **Prep D1, B1.5 and B2 banked biospecimen** samples collected during clinic visits will be collected prior to PF-06946860 administration. For Prep D1, 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.

r. During Cohort 1, participants will be provided with a hand-held device at the Screening visit once the informed consent document is signed and available eligibility criteria are confirmed for completion of CCI [redacted] at home for daily completion between **Screening** and **Week 18**, with a target of at least 7 consecutive days prior to **Day 1**. The hand-held device is to be returned at **Week 18**. CCI [redacted] for details related to specific timing refer to Table 2. If the participant early terminates prior to Week 18, the hand-held device is to be returned to the site. and for details related to specific timing refer to Table 2. If the participant early terminates prior to Week 18, the hand-held device is to be returned to the site.

s. At each clinic visit during Cohort 1, participants will complete questionnaires on a separate electronic device (tablet) available at the site. The devices will prompt the participant to complete the appropriate questionnaire(s). For additional details refer to Section 8.1.3 and for details related to specific timing refer to Table 2. If the participant early terminates prior to Week 18, the hand-held device is to be returned to the site.

[redacted]

2. INTRODUCTION

Cachexia 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 manifests as marked involuntary body weight loss, muscle atrophy, and reduced appetite, progressing to significant functional impairment and increased risk of death.

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;[1] and during pregnancy it is highly expressed by placental trophoblast.[2] GDF-15 is also secreted by tumor cells, macrophages and damaged cells.[3-7] In several chronic conditions such as cancer, heart failure, COPD, and CKD, circulating GDF-15 concentrations are markedly elevated compared to healthy levels.[8-11] Elevated GDF-15 is associated with weight loss/cachexia in cancer[12-15] and also heart failure[16,17] patients. In addition, elevated circulating GDF-15 levels are associated with poor outcomes and survival in many cancers, heart failure, CKD and COPD.[18-24] In rodents and non-human primates, GDF-15 induces anorexia and weight loss[25-29] 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] GFRAL is a transmembrane protein with a short cytoplasmic domain lacking any signaling function and requires the tyrosine kinase co-receptor RET for signaling. Its expression is largely restricted to the area postrema and the nucleus tractus solitarius. Signaling is mediated via dimers of circulating GDF-15 binding to a co-receptor complex composed of 2 GFRAL molecules and 2 RET molecules leading to an activated pentameric activated receptor complex.[26-29]

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. It is anticipated that binding of the mAb to circulating GDF-15 will prevent its interaction with the GFRAL receptors and promote appetite and increase body weight in patients with cachexia.

2.1. Study Rationale

Non-Small Cell Lung Cancer (NSCLC) is a common type of cancer with a high prevalence of cachexia.[30] NSCLC has been observed to be associated with elevated circulating GDF-15 levels and this elevated concentration of GDF-15 correlates with lower body weight.[13] Therefore, it is hypothesized that cachexia in NSCLC is largely mediated via GDF-15 and that suppression of GDF-15 in these patients may lead to improvement in serious aspects of cachexia such as anorexia leading to unintended weight loss, fatigue and impaired mobility.

Similar observations have been made in other cancers. In colorectal cancer, elevations in GDF-15 have been reported as compared to levels in healthy individuals, and higher elevation correlated with lower survival.[31,32] Elevated GDF-15 has also been reported in patients with pancreatic cancer.8 Animal and clinical data suggest that GDF-15 is a key driver of cachexia in cancer, and cachexia in pancreatic cancer has been shown to correlate with decreased survival.[33]

This study is intended to obtain safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) data following administration of PF-06946860 to a limited number of participants in the target patient population, prior to exposure to a larger group of patients with cancer and cachexia.

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 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[25-29] 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.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical PK of PF-06946860 are provided in the IB Section 5.2. 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 did not induce inflammatory cytokine release in vitro, therefore it 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.

2.2.3. 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 and the 3-month CCI 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 964 µg/mL, 827 µg/mL and 139,000 µg•h/mL, respectively, in the 6-month study.

2.2.4. Clinical Overview

PF-06946860 has been evaluated in 2 completed Phase 1 single dose studies in healthy participants, C3651001 and C3651002. Clinical data from the completed studies are provided in the IB for PF-06946860.

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[redacted]

CCI

[redacted]

2.3. Benefit/Risk Assessment

This study is designed primarily to assess safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06946860 in participants with non-small cell lung cancer, pancreatic cancer or colorectal cancer and cachexia.

The available clinical data show the single dosing of PF-06946860, in healthy participants, to be safe and well tolerated. Efficacy has not yet been studied in humans.

Based upon pre-clinical data, it is possible that dosing with PF-06946860 will improve participants appetite and support maintenance of body weight; and there may be mitigation of the anorexia and emetogenic effect of platinum-based chemotherapy.

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

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.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the **safety and tolerability** of repeated subcutaneous administrations of PF-06946860 to participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.	• Incidence of treatment emergent adverse events (AEs and SAEs), safety laboratory tests, vital signs (blood pressure and pulse rate) and standard ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).
Secondary:	**Secondary:**
• To characterize unbound (free) and total **PK** of PF-06946860 administered to participants with NSCLC, pancreatic cancer or colorectal cancer and cachexia.	• Serum unbound and total trough concentrations (C_{trough}) of PF-06946860 at Weeks 3, 6, 9, 12, and 15.

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

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

4. STUDY DESIGN

4.1. Overall Design

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

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

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

This study will consist of up to 2 cohorts. In each study cohort, approximately 8 participants will be enrolled such that approximately 6 evaluable participants complete the study. Participants who discontinue prior to completion of the study may be replaced, at the discretion of the investigator and sponsor. It is planned that the 2 cohorts will be enrolled sequentially and will follow similar schedules of activity. The optional Cohort 2 may be conducted at the discretion of the Sponsor, with data emerging from Cohort 1 informing the dose level and/or frequency to be administered in Cohort 2 (see Section 4.3).

Based on emerging data, the dose, schedule, length and number of follow-up visits required may be adjusted; in this case, details will be provided to the investigator in writing or via a protocol amendment, as appropriate, prior to initiation of the cohort.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety, tolerability, PK, PD and immunogenicity of PF-06946860 following repeated SC administrations to adult patients with advanced metastatic NSCLC, pancreatic cancer or colorectal cancer and cachexia, with elevated concentrations of circulating GDF-15.

Elevated concentrations of circulating GDF-15 have been reported in literature[12-15,] in patients experiencing weight loss with a variety of tumor types (including lung cancer) and a greater magnitude of elevation was associated with worse survival. Biospecimens from healthy adults[34] and patients with cancer (from both external commercial biorepositories and an internal study) were analyzed for GDF-15 concentrations. The cancer sample set contained 399 NSCLC, 116 pancreatic cancer, and 157 colorectal cancer patients. These patients were mostly Caucasian, aged 29-90, and had an approximate ratio of 40%: 60% females to males. 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,[34] confirmed literature reported elevations in GDF-15 concentrations in NSCLC, pancreatic cancer, and colorectal cancer patients in comparison to healthy subjects (approximately 4-fold, 5-fold, and 4-fold, respectively). An ad-hoc analysis of samples from NSCLC patients from an internal Pfizer study demonstrated that higher GDF-15 concentrations were associated with a reduction in body weight. These data were also used to determine the degree of GDF-15 elevation necessary for inclusion in this study. GDF-15 concentrations above the 95th percentile of GDF-15 concentrations reported in these healthy subjects will be considered elevated (≥CCI).

In addition, published clinical data and internal animal model data suggest that administration of platinum therapy can induce increases in serum GDF-15 concentrations. Clinical literature and internal animal model data[35] also suggest that the nausea, emesis and anorexia observed with platinum therapy may be mediated, at least in part, by platinum-induced elevations in GDF-15.

Therefore, it is hypothesized that cachexia in many types of cancer, including NSCLC, pancreatic cancer, and colorectal cancer, is largely mediated via GDF-15 and that suppression of GDF-15 in these patients may lead to improvement in serious aspects of cachexia such as anorexia leading to unintended weight loss, fatigue and impaired mobility. Furthermore, given the observations of GDF-15 elevation with platinum therapy, patients receiving standard of care anti-tumor treatment that includes systemic platinum-based therapy, may be a specific population that could potentially gather additional benefit from GDF-15 inhibition.

Study C3651009 represents the first administration of PF-06946860 in patients with cancer and cachexia. As such, an open-label design and a small sample size have been implemented in order to transparently establish an initial assessment of clinical safety, PK, PD and immunogenicity of this novel therapy.

A treatment duration of 12 weeks is consistent with available pre-clinical toxicology coverage and to support development of PF-06946860 in subsequent Phase 2 studies. A treatment duration of 12 weeks should provide sufficient safety information to inform subsequent PF-06946860 Phase 2 studies. After the 12-week treatment period, participants will be followed up for 12 weeks post last dose. Based on the preliminary population PK/PD simulation results, it is anticipated that at 12 weeks post last dose of CCI PF-06946860 the unbound PF-06946860 concentrations will be below the level that would be expected to fully suppress GDF-15.

PF-06946860 will be dosed via subcutaneous injections, every 3 weeks. However, the dosing frequency in Cohort 2 may be adjusted based upon emerging data from Cohort 1.

In addition to the characterization of safety, tolerability, PK, PD and immunogenicity of PF-06946860, this study will include exploratory assessment of key parameters needed in future studies to characterize the efficacy of PF-06946860. Cachexia is characterized by involuntary anorexia and weight loss, involving skeletal muscle mass depletion. Therefore, body composition via CT-scan derived lumbar skeletal index will be measured. In addition to lumbar skeletal muscle index, assessment of the impact of PF-06946860 on other aspects of cachexia, CCI will be studied. These will be measured through the use of electronic Patient Reported Outcome (ePRO) instruments administered to patients at home and during clinic visits. These initial exploratory data will be collected during Cohort 1 and will be used to start the process of validation of these instruments for use in the clinical development in the target population (cancer patients with cachexia). Validation of these instruments in early studies will enable a better assessment of the effect of PF-06946860 on how patients feel.

CCI

The baseline assessments for the CT scan-derived LSMI, CCI and PROs will be performed during the screening period, but do not need to be reviewed to determine eligibility.

PF-06946860 dosing can be initiated at the start of a participant's first or second cycle of standard of care anti-tumor therapy. Flexibility in the initiation of PF-06946860 is intended to minimize any interference with the evaluation, diagnosis, and/or initiation of standard of care anti-tumor therapy.

At the present time, embryo-fetal developmental toxicology studies with PF-06946860 have not been conducted. Consequently, to prevent pregnancy, the protocol includes contraceptive provisions for both male and female participants (see Section 5.3.1 and Appendix 4 Section 10.4.4).

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.

4.3. Justification for Dose

CCI

CCI [redacted]

[redacted]

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

[redacted]

CCI [redacted]

[redacted]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last follow up visit.

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 of the following criteria apply:

Age and Sex:

1. Male or female participants ≥18 years of age (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).

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Documented histologic or cytologic diagnosis of advanced metastatic NSCLC, advanced/unresectable pancreatic cancer, or metastatic colorectal cancer by American Joint Committee on Cancer (AJCC) criteria

4. Cachexia, defined using Fearon's criteria:[36]

    - Body Mass Index (BMI) <20 kg/m^2 with involuntary weight loss of >2% within 6 months prior to screening; or

    - Involuntary weight loss of >5% within 6 months prior to screening irrespective of BMI; or

      If medical record documentation is unavailable, patient's report will suffice to estimate involuntary body weight loss.

5. Serum GDF-15 levels of ≥CCI (as measured using the Investigational Use Only Roche Elecsys GDF-15 assay[34]) at screening.

6. Participants considered eligible for systemic anti-cancer treatment/therapy at the time of screening, who:

   - Are diagnosed with advanced metastatic NSCLC who will be treated with:
     - A platinum + pemetrexed ± pembrolizumab; or
     - A platinum + nab paclitaxel or paclitaxel ± pembrolizumab; or
     - Pembrolizumab alone.
   - Are diagnosed with advanced/unresectable pancreatic cancer who will be treated with:
     - FOLFIRINOX; or
     - Nab-Paclitaxel + Gemcitabine;
     - Gemcitabine.
   - Are diagnosed with metastatic colorectal cancer who will be treated with:
     - FOLFOX +/- Biologic (Bevacizumab or Cetuximab/Panitumumab); or
     - FOLFIRI +/- Biologic (Bevacizumab or Cetuximab/Panitumumab); or
     - FOLFOXIRI +/- Biologic (Bevacizumab or Cetuximab/Panitumumab); or
     - Pembrolizumab for MSI-H.
   - Will be entering the study at the first or second cycle of their current course of anti-cancer treatment/therapy.

     Note: Other therapies can be considered upon discussion with the Pfizer medical monitor.

7. Adequate liver function as evidenced by liver enzymes, including:

   - Total serum bilirubin ≤1.5 x upper limit of normal (ULN) unless the participant has documented Gilbert syndrome;
   - Aspartate and Alanine aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;
   - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

8. Adequate renal function, including creatinine ≤2 mg/dL, or Glomerular Filtration Rate (GFR)) ≥30 mL/minute/1.73 m^2 as calculated by the modification of diet in renal disease (MDRD) equation[37] (Appendix 18).

Weight: Not Applicable (N/A)

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. All other forms of cancers not specified in Inclusion Criterion #3 unless currently considered cured (>5 years without evidence of recurrence).

2. 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 randomization.

3. Planned radiation therapy as part of the primary anti-tumor therapy regimen. However, localized radiation therapy for symptomatic relief is permitted and if this becomes necessary after randomization, it will not be a reason for discontinuation.

4. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

5. Active hepatitis B virus (HBV) or hepatitis C virus (HCV).

6. Confirmed positive test for human immunodeficiency virus (HIV).

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

- National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 oral mucositis;
- NCI CTCAE Grade 3 or 4 Gastrointestinal (GI) disorders [nausea, vomiting, diarrhea, and constipation];
- mechanical obstructions making patient unable to eat.

8. Receiving tube feedings or parenteral nutrition (either total or partial) at the time of Screening.
9. Undergoing major surgery (central venous access placement and tumor biopsies are not considered major surgery) within 4 weeks prior to randomization. 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. Severe gastrointestinal disease (including esophagitis, gastritis, malabsorption).
11. History of gastrectomy.
12. Cachexia caused by other reasons, as determined by the investigator, including, but not limited to:
    - Severe COPD requiring use of home O_2;
    - New York Heart Association (NYHA) class III-IV heart failure;
    - Acquired Immunodeficiency Syndrome (AIDS).
13. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF, New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinical significant episode of thrombo embolic disease.
    - Ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE Grade ≥2.

Prior/Concomitant Therapy:

14. 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).

Prior/Concurrent Clinical Study Experience:

15. Enrollment in a previous study with PF-06946860.

Diagnostic Assessments:

16. Elevated blood pressure that cannot be controlled by medications (eg, >150/90 mmHg) despite optimal medical therapy.

Other Exclusions:

17. Woman who is pregnant or breast-feeding.

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

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 , 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, 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 entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06946860	PF-06946860
ARM Name	PF-06946860 Cohort 1	PF-06946860 Cohort 2
Type	Biologic	Biologic
Dose Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)	CCI and diluent	TBD
Dosage Level(s)	CCI Q3W	TBD
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

During all clinic visits, the dose of investigational product must be administered in the office by study personnel. PF-06946860 is to be administered first, followed by any premedications administered at the clinic (eg, antihistamine, anti-inflammatory agent, or pain reliever) and then the standard of care prescribed anti-tumor therapy. If the standard of care anti-tumor therapy is to be administered on the same day of dosing with PF-06946860, PF-06946860 will be the first drug administered during the clinic visit and must be given at least 0.5h prior to administration of the standard of care anti-tumor therapy. If the standard of care anti-tumor therapy is paused, adjusted or discontinued during the 12-week treatment period, this would not be considered a protocol deviation. PF-06946860 administration is to continue as prescribed by the protocol. The standard of care anti-tumor therapy may either be shorter or may continue beyond the study 12 week PF-06946860 treatment period according to the standard of care anti-tumor therapy for each cancer type and the treating physician's clinical judgment; this would not be considered a protocol deviation. Similarly, adjustments to the standard of care anti-tumor therapy dose or duration, including treatment holidays are at the discretion of the PI.

Premedication is permitted for all participants, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory agent, or pain reliever.

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, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff 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 temperature since previously documented for all site storage locations upon return to business.

3. 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). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product (IP) manual.

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. See the IP manual for storage conditions of the study intervention.

8. 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. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. 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.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). 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, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

Investigational Product, PF-06946860 ([redacted]), and diluent (depending upon the dose) will be used to prepare doses for administration. See the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

This is an open-label study; however, the specific investigational product dispensed to the participant will be assigned using an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site will contact the IRT prior to the start of investigational product administration for each participant. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the

participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product 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. The site will record the investigational product assignment on the applicable case report form, if required.

Investigational product will be dispensed at the clinic study visits as 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.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

Participants may be entering the study at the first or second cycle of their current course of standard of care anti-tumor therapy. Participants will receive standard of care anti-tumor therapy as described in the Inclusion criteria (See Section 5.1) and will receive any other supportive treatments or interventions as indicated by standard of care for their clinical condition.

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

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions (eg, paracentesis) received by participants from screening until the end of study visit will be recorded on the case report form (CRF) with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within the 28 days before the first dose of IP will be documented as a prior treatment. Treatments taken after the first dose of IP will be documented as a concomitant treatment.

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 at the end 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 investigational product. If investigational product is permanently discontinued, the participant will remain in the study for follow up. Note that discontinuation of investigational product does not represent withdrawal from the study.

If a safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with IP may be stopped in an individual participant at investigator discretion.

Any participant who prematurely withdraws after being randomized and during active study intervention, (Day 1 through Week 12) should return for an early withdrawal visit and then enter into the follow-up period.

See Section 1.3 for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Criteria for Discontinuation

Discontinuation of IP must occur for a participant meeting any of the following conditions:

- Criteria for a potential Hy's law case are met (see Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum beta human chorionic gonadotropin (β-hCG) testing.

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) 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.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment 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 investigational product 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 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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

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. Refer to Appendix 19 for a proposed chronology of procedures. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if 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.

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.

Any changes in the timing or addition of time points (eg, additional follow up visits) 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.

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 490 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

The following procedures will be conducted as part of exploratory assessments.

8.1.1. Body Weight

Weight will be recorded using a calibrated scale (with the same scale used if possible for the duration of the study) reporting weight in either pounds (lb.) or kilograms (kg), and accuracy 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.

Weight measurement should be taken under the following conditions:

- After void of urine;
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains;
- While remaining still during the measurement.

8.1.2. Imaging Assessment

8.1.2.1. CT Scan

CT scans will be acquired throughout the study to monitor the tumor burden and evaluate the Lumbar Skeletal Muscle Index, in addition to other potential exploratory muscle quality parameters. The standard process to obtain serial CT scans will be outlined in an Image Acquisition Manual. The sites will be provided with guidance on obtaining CT images of the chest, abdomen, and pelvis that meet the quality requirement of this study.

If a CT scan was performed within 3 weeks prior to the Screening visit and meets the quality and anatomical requirements, then a CT scan at screening is not needed. If a CT scan was not performed prior to Screening, a CT scan should be performed after other eligibility criteria (such as medical history, diagnosis) have been confirmed. The CT scan may be performed without receipt of safety laboratory and GDF-15 sample results. If a CT scan is being performed at the Week 6 or Week 12 visit as part of the standard of care, then an

additional CT scan is not needed as long as CT scan quality matches the requirements outlined in the Image Acquisition Manual.

Monitoring of the tumor burden will be performed by the local imaging site following standard RECIST 1.1 criteria (outlined in Appendix 17). The RECIST 1.1 categorization is to be entered in the CRF after each scan.

CT scans will also be required to be sent to a central imaging review facility for evaluation of the Lumbar Skeletal Muscle Index and exploratory measures of muscle quality. Central image review is not a complete medical review of the participant and will not include any tumor assessments. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the principal investigator (PI). All follow up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

8.1.3. Patient-Reported Outcomes (Cohort 1)

All patient-reported outcome (PRO) assessments are implemented on an ePRO device (hand-held device for home use and tablet for clinic use) and completed by study participants at home, or at the clinic, following a schedule of assessments as per the SoA and Table 2. Every effort should be made to have the study participant complete all patient-reported outcome assessments before any other clinical assessments that take place at the clinical site.

The site user guide will be provided separately.

Table 2. Patient Reported Outcomes for Cohort 1

Patient Reported Outcome (PRO) Measure Planned	Frequency	Assessment	Number of Questions	Completion Time
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRO-CTCAE selected items: taste change, decreased appetite, fatigue, nausea, vomiting	Conducted at clinic visits on Day 1 (Baseline), Week 3, Week 6, Week 9, Week 12 and Week 18	At the clinic	9	~3 minutes
Patient Global Impression of Severity (PGI-S) (1 item: appetite)	Conducted at clinic visits on Day 1 (Baseline), Week 3, Week 6, Week 9, Week 12 and Week 18		1	
Patient Global Impression of Change (PGI-C) (2 items: appetite and fatigue)	Conducted at clinic visits on Week 12 and Week 18		2	
PROMIS-Fatigue 7a ("Past 7 days" recall version)	Conducted at clinic visits on Day 1 (Baseline), Week 6, Week 12, and Week 18		7	~14 minutes
PROMIS-Physical Function 8c (no recall version)	Conducted at clinic visits on Day 1 (Baseline), Week 6, Week 12, and Week 18		8	
FAACT	Conducted at clinic visits on Day 1 (Baseline), Week 6, Week 12, and Week 18		39	

CCI [redacted]

8.1.3.2. Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Initiated and sponsored by the US National Cancer Institute, the PRO-CTCAE (Appendix 9) is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients enrolled in cancer clinical trials. It was designed to complement the Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for investigator or clinician-reported adverse events in cancer trials. The PRO-CTCAE item library is composed of 124 self-report items reflecting 78 symptomatic adverse events drawn from the CTCAE arranged by organs and systems. Each adverse event is assessed relative to one or more attributes that include the presence/absence/amount (P), frequency (F), severity (S), and interference (I) with usual or daily activities. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. PRO-CTCAE data will be collected and analyzed and reported separately from CTCAE AE data and will not be reconciled with each other. Adverse events for this study will be assessed, recorded, and reported in the standard manner with investigators using CTCAE.

From the 78 symptomatic adverse events, the following were selected to be administered in the study, each with a 7-day recall period: taste changes (S), decreased appetite (S and I), nausea (S and F), vomiting (S and F), fatigue (S and I).

8.1.3.3. Patient's Global Impression of Severity (PGI-S)

The Patient's Global Impression of Severity (PGI-S) (Appendix 10) is a single item measure that asks the study participants to evaluate their current severity of lack of appetite on a 5-point verbal response scale that ranges from "None" to "Very severe".

The PGI-S is recommended by Food and Drug Administration (FDA) for use as an anchor measure to generate an appropriate threshold that represents meaningful within-individual change in the target patient population.

8.1.3.4. Patient's Global Impression of Change (PGI-C)

The PGI-C (Appendix 11) is a single item measure that asks study participants to rate the overall change in their level of appetite and fatigue since they started the study on a 7-point verbal rating scales that ranges from "Much better" to "Much worse".

The PGI-C is recommended by FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-individual change in the target patient population.

8.1.3.5. PROMIS – Fatigue (version 7a)

The PROMIS Fatigue 7a (Appendix 12) is a self-reported measure that assesses a range of symptoms in the past 7 days from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles.

The short form 7A consists of 7 items that study participants will rate from 1: "Never" to 5: "Always". A global raw score ranging from 7 to 35 is calculated and can be translated into a T-score (Mean = 50, standard deviation (SD) = 10) using the applicable score conversion table provided in the PROMIS User's Manual.

8.1.3.6. PROMIS – Physical Function (version 8c)

The PROMIS Physical Function short form 8C (Appendix 13) is a self-reported 8-item measure that assesses capability rather than actual performance of physical activities. It includes the functioning of one's upper extremities (dexterity) and lower extremities (walking and mobility), as well as instrumental activities of daily living. A single Physical Function capability score is obtained from a short form. A global raw score ranging from 8 to 40 is calculated and can be translated into a T-score (Mean = 50, SD = 10) using the applicable score conversion table provided in the PROMIS User's Manual.

8.1.3.7. Functional Assessment of Anorexia-Cachexia Therapy (FAACT)

The Functional Assessment of Anorexia-Cachexia Therapy (FAACT) (Appendix 14) measures combines the Functional Assessment of Cancer Therapy - General (FACT-G) core instrument and anorexia and cachexia subscale (ACS).

FACT-G is a summated score of 27 items pertaining to physical well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and social well-being (7 items) in the past 7 days. Each of the items uses a 5-point (0 to 4) scale. ACS is a 12-item summated scale containing items specific to patients' perceptions of appetite and weight, also using the 5-point scale. Adding the 12 ACS items to the FACT-G produces the 39-item Functional Assessment of Anorexia-Cachexia Therapy (FAACT). Higher scores are associated with a higher health-related quality of life. For additional details regarding scoring refer to FACIT User's Manual.

CCI [redacted]

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements, imaging and other safety assessments may be obtained at any time during the study as part of standard of care or to assess any perceived safety concerns.

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.

In addition to the safety monitoring as detailed in the SoA, safety monitoring for this open-label Phase 1b study will include monthly reviews of all available data to screen for trends in AEs, vital signs, ECGs and safety laboratories.

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 include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. and weight will also be measured and recorded, (height will be measured at screening only).

An abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

A full physical examination will be conducted at screening only; Abbreviated physical exams planned at all other clinic visits, however full exams may be performed for findings during previous exam, new/open AEs, or at investigator discretion. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Eastern Cooperative Oncology Group (ECOG)

Assessment of ECOG performance status (see Appendix 16) may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

8.2.3. Vital Signs

Blood pressure and pulse rate will be assessed at times specified in the SoA.

Blood pressure and pulse rate measurements will be assessed supine with a completely automated device. Manual techniques will be used only if an automated device is not available. On Day 1, blood pressure and pulse rate will be measured in triplicate, approximately 2 to 4 minutes apart. The average of these triplicate measurements collected prior to dosing on Day 1, will serve as each participant’s baseline value. At all other visits, a single measurement will be collected. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.4. Electrocardiograms

Standard 12-Lead ECGs should be collected at times specified in the SoA section of this protocol. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. Participants should be in a quiet environment and not speak during the resting period or measurement.

On Day 1, triplicate standard 12-lead ECGs will be obtained approximately 2 to 4 minutes apart. The average of the triplicate ECG measurements collected prior to dosing on Day 1 will serve as each participant's baseline value. At all other visits, a single standard 12-lead ECG will be collected. To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) any postdose QTc interval is increased by ≥60 msec from the baseline **and** is >470 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. In addition, if verified QTc values continue to exceed the criteria above, immediate correction for reversible causes including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the corrected QT (Fridericia method) (QTcF) interval should be performed. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.5. 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.

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 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.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.6. 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. Urine pregnancy tests will be provided by the central lab. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the PF-06946860. 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 institutional review boards (IRBs)/ethics committees (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 it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

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 investigational product), through and including a minimum of up to the time of the final planned follow-up visit, after the last administration of the investigational product.

Follow-up by the investigator continues throughout and after the active collection period and until the event 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 conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from 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 Forms.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately 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.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

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.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

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, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure 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 investigational product 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

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until approximately 130 days that is at least 5 terminal half-lives after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. 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 investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product 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 investigational product;
- 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 an 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 simulations, doses greater than approximately 11,000 mg, 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 2.2.3). 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 clinic), and the allowed visit window, an overdose will be defined as more than 2 doses of PF-06946860 CCI SC administered in a period of 3 weeks.

There is no specific treatment for an overdose of PF-06946860, and the sponsor recommends general supportive medical care as clinically indicated.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.

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. Obtain blood samples for PK, PD and/or immunogenicity analysis approximately 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).

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

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

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 for PK samples will be drawn from the arm contralateral to any drug infusion.

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 times may change; the actual date and time (24-hour clock time) of each sample will be recorded.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the protocol-allowed visit window (±1, ±3, ±7 days, as defined in the SoA) will not be captured as protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

The blood sampling to be conducted during the at home visits (per SoA) is intended to be done at home by a visiting health care professional for the participant's convenience, but blood sampling may be conducted at the clinic, at the discretion of the participant or investigator

Samples will be used to evaluate the PK of PF-06946860. Samples collected for analysis of PF-06946860 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during, or after, the study, for metabolite identification and/or evaluation of bioanalytical methods, or for other internal exploratory purposes. Any such data generated may not be included in the CSR.

Genetic analyses will not be performed on PK 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.

8.6. Pharmacodynamics of 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 times may change; the actual date and time (24-hour clock time) of each sample will be recorded.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the protocol-allowed visit window (±1, ±3, ±7 days, as defined in the SoA) will not be captured as protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

The blood sampling to be conducted during the at home visits (per SoA) is intended to be done at home by a visiting health care professional for the participant's convenience, but blood sampling may be conducted at the clinic, at the discretion of the participant or investigator.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes.

At screening, 2 GDF-15 samples will be collected. One GDF-15 sample will be analyzed using the IUO Roche Elecsys GDF-15 assay, for determination of enrollment eligibility. This assay will be validated in a CLIA accredited central laboratory. The second screening sample will be analyzed using the internal Pfizer GDF-15 assay(s).

All serum PD samples will be analyzed for total GDF-15 and, if feasible, unbound GDF-15, using validated analytical methods in compliance with applicable SOPs.

PD samples collected in this study may also be analyzed using the Roche assay and/or a fit-for-purpose validated analytical method in compliance with applicable SOPs. These data may be included in the CSR, if deemed appropriate.

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.

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 4-mL blood sample optimized for deoxyribonucleic acid (DNA) isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response and cachexia. Genes and other analytes (eg, proteins, ribonucleic acid (RNA), nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further 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.

8.8.1. Banked Biospecimens for Biomarkers

A 10-mL whole blood sample for serum (Prep B2) and a 6-mL whole blood sample for plasma (Prep B1.5) will be collected as local regulations and IRB/ECs allow.

Banked biospecimens may be used for research related to drug response and cachexia. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked samples to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked samples. The optional additional research does not require the collection of any further 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.

8.9. Immunogenicity Assessments

Blood samples of approximately 6 mL, to provide a minimum of 2 mL of 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 the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes and may not be included in the CSR.

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.

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 statistical analysis plan (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

There are no statistical hypotheses or estimands for this study.

9.2. Sample Size Determination

A sample size of approximately 6 participants per cohort has been chosen based on the need to minimize first exposure to patients of a new chemical entity and the requirement to provide adequate safety, tolerability and PK/PD assessment. Approximately 8 participants will be assigned to the investigational product such that approximately 6 evaluable participants complete the study, per cohort.

The additional second cohort may be included if needed to meet study objectives, as informed by data emerging from this study.

Participants who discontinue prior to completion of the study may be replaced, at the discretion of the sponsor.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled/Randomly assigned to investigational product	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol
Evaluable	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product
Safety	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product
PK	All randomized participants who received a dose of PF-06946860 and in whom at least 1 serum concentration value is reported
PD	All randomized participants who received a dose of PF-06946860 and in whom at least 1 serum GDF-15 concentration is reported
Immunogenicity	All randomized participants who received a dose of PF-06946860 and in whom at least 1 ADA result is reported
Efficacy	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in 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. Details of the analysis of all exploratory/tertiary endpoints will be described in the SAP.

9.4.1. Efficacy Analyses

Analyses of the exploratory efficacy assessments defined in Section 8.1 will be described in the SAP. These analyses will be performed on the efficacy population.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, blood pressure (BP), pulse rate and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by time (and cohort, if applicable).

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated (by cohort, if applicable):

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>470-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

9.4.3. Pharmacokinetic Analyses

All PK analyses will be performed on the PK population.

The serum concentration of unbound and total PF-06946860 will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Serum unbound and total C_{trough} will be summarized by time (and cohort, if applicable). No formal inferential statistics will be applied to the pharmacokinetic data. Details of planned analyses will be given in the SAP.

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

9.4.4. Other Analyses

Demographic data, GDF-15 concentration, height, weight, CT scan, ECOG, CCI [redacted], PROs (Cohort 1) and AEs, collected at screening, may be reported. Other data collected at screening, that are used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted.

9.4.4.1. Pharmacodynamic Analyses

All PD analyses will be performed on the PD population.

The serum concentration of total GDF-15 and, if feasible, unbound GDF-15, will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Details of planned analyses will be given in the SAP.

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

9.4.4.2. Immunogenicity Analyses

Immunogenicity analyses will be performed on the Immunogenicity population.

Incidence of ADA and NAb, if applicable, will be summarized. The number of ADA-positive and NAb-positive participants will be summarized by time, if appropriate. Potential impact of ADA and/or NAb on PK, PD and safety may be assessed, if appropriate. Details of planned analyses will be given in the SAP.

9.5. Interim Analyses

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

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

9.5.1. Data Monitoring Committee

This study will not use 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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), 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 Code of Federal Regulations (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 investigational product, 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 subinvestigators 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.

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, Health Insurance Portability and Accountability Act (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.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory 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 any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional 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 shall 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 natural persons 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. 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 European Clinical Trials Database (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 standard operating procedures (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 US Basic 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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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 US Basic Results document is 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 European Medicines Agency (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 contribute 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 electronic CRF (eCRF) that are transcribed 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.

10.1.8. Study and Site Closure

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 contract research organization (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.

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 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) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product 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 concerns.

Table 3. Protocol-Required Safety Laboratory Assessments

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

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; CRP = C-reactive protein; FSH = follicle-stimulating hormone; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDRD = Modification of diet in renal disease; pH = power of hydrogen;qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a.Glomerular Filtration Rate (GFR) will be calculated using the modification of diet in renal disease (MDRD) equation.
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review board/ethics committee (IRB/EC). Serum or urine β-hCG for female participants of childbearing potential.
d. For confirmation of postmenopausal status only.

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. • 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 (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • 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 <u>NOT</u> 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. • 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.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- 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.
- 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 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 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 Common Terminology Criteria for Adverse Events (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 Clinical Trial (CT) Serious Adverse Event (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 investigational product 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 investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and exposure during pregnancy [EDP] supplemental form for EDP) 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 investigator's brochure (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 investigational product caused the event, then the event will be handled as "related to investigational product" 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 professionals.
- 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 and Collection of Pregnancy Information

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 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), 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 study intervention(s). 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 (WOCBP)

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 age 60 years or older or no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
     - Females 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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
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;
    - injectable.
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.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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).

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 includes 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 investigational product.

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.

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.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- 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 the clinical study report (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 (see Section 8.7.2 and 8.8.1) will be stored indefinitely or other 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 drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (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 (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 sample for acetaminophen 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 liver function test (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: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) atrioventricular (AV) block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate

<40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.


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10.9. Appendix 9: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events PATIENT (PRO-CTCAE™)

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 28 July 2019

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.10. Appendix 10: Patient's Global Impression of Severity (PGI-S)

Patient Global Impression of Severity (PGI-S) Items

1. How would you rate your current lack of appetite?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

10.11. Appendix 11: Patient's Global Impression of Change (PGI-C)

Patient Global Impression of Change (PGI-C) Items

1. 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

2. 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

10.12. Appendix 12: PROMIS – Fatigue (version 7a)

PROMIS Item Bank v.1.0 - Fatigue -Short Form 7a

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

10.13. Appendix 13: PROMIS – Physical Function (version 8c)

PROMIS® Item Bank v2.0 – Physical Function – Short Form 8c

Physical Function – Short Form 8c

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA9	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA15	Are you able to stand up from an armless straight chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		No difficulty at all	**A little bit of difficulty**	**Some difficulty**	**A lot of difficulty**	**Can't do because of health**
PFB50	How much difficulty do you have doing your daily physical activities, because of your health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

10.14. Appendix 14: Functional Assessment of Anorexia-Cachexia Therapy (FAACT)

FAACT (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C6	I have a good appetite	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight	0	1	2	3	4
ACT3	Most food tastes unpleasant to me	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
ACT13	My general health is improving	0	1	2	3	4

CCI [redacted]

[redacted]

[redacted]

[redacted]

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

10.16. Appendix 16: ECOG Performance Status

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

10.17. Appendix 17: RECIST 1.1 Tumor Assessment Criteria RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from Eisenhauer E.A., et al.[38]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

a. Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).

b. Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.

c. Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

d. Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete response: Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial response: Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR, or progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective progression: 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate: Progression has not been documented, and:

    1. One or more target measurable lesions have not been assessed; or

    2. Assessment methods used were inconsistent with those used at baseline; or

    3. One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or

    4. One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 4. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following Table 5 will be used:

Table 5. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

10.18. Appendix 18: Modification of Diet in Renal Disease Equation

GFR (mL/min/1.73m^2) = 175 x standardized $S_{cr}^{-1.154}$ x age$^{-0.203}$ x 1.212 [if black] x 0.742 [if female].

10.19. Appendix 19: Proposed Chronology of Procedures

Other procedures listed in the SoA may be conducted after the procedures listed below as per site discretion to allow for flexibility of participant care. For the procedures described below, where multiple procedures are scheduled at the same timepoint(s) relative to dosing, the below chronology of events should be adhered to, where possible.

Note: All samples collected are to be processed and shipped according to the lab manual.

Screening:

- Patient signature on current IRB/RC approved informed consent form MUST be obtained prior to performing any study-related procedures, see Section 10.1.3.
- Patient Reported Outcomes (see Section 8.1.3 (Cohort 1 only).
- Supine standard 12-lead ECG: obtain prior to vital signs assessment (see Section 8.2.3 and Section 8.2.4).
- Blood samples for safety (see Section 8.2.5) and PD (GDF-15, Section 8.6) are to be collected after assessment of supine standard 12-lead ECG and vital signs.

Day 1:

- Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).
- Supine standard 12-lead ECG: obtain prior to vital signs assessment, and, where applicable, prior to dosing (see Section 8.2.3 and Section 8.2.4).
- **Pre-dose** blood samples for safety (see Section 8.2.5), PK (see Section 8.5), PD (GDF-15, see Section 8.6), immunogenicity (see Section 8.9), and banked biospecimens (see Section 8.7.2 and Section 8.8.1) are to be collected after assessment of supine standard 12-lead ECG and vital signs.
- Dosing: Administration of Investigational Product (PF-06946860) must be given at least 0.5h prior to administration of SoC anti-tumor therapy.
- **Post-dose** blood samples for PK (see Section 8.5) and PD (GDF-15, see Section 8.6) will be collected at a minimum of 3h post PF-06946860 administration or at a maximum by the end of the clinic visit.

Weeks 1 and 13:

Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).

Blood samples for PK (see Section 8.5), PD (GDF-15, see Section 8.6) and banked biospecimens (see Section 8.8.1).

Week 2:

Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).

Blood samples for PK (see Section 8.5), PD (GDF-15, see Section 8.6) and immunogenicity (see Section 8.9).

Weeks 3, 6 and 9:

- Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).
- Supine standard 12-lead ECG: obtain prior to vital signs assessment and, where applicable, prior to dosing (see Section 8.2.3 and Section 8.2.4).
- **Pre-dose** blood samples for safety (see Section 8.2.5), PK (see Section 8.5), PD (GDF-15, See Section 8.6), immunogenicity (see Section 8.9) and banked biospecimens (see Section 8.8.1) are to be collected after assessment of supine standard 12-lead ECG and vital signs.
- Dosing: Administration of Investigational Product (PF-06946860) must be given at least 0.5h prior to administration of standard of care anti-tumor therapy.

Weeks 4, 5 and 14:

- Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).
- Blood samples for PK (see Section 8.5) and PD (GDF-15, see Section 8.6).

Week 12:

- Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).
- Supine standard 12-lead ECG: obtain prior to vital signs assessment and, where applicable, prior to dosing (see Section 8.2.3 and Section 8.2.4).
- **Pre-dose** blood samples for safety (see Section 8.2.5), PK (see Section 8.5), PD (GDF-15, See Section 8.6), immunogenicity (see Section 8.9) and banked biospecimens (see Section 8.8.1), are to be collected after assessment of supine standard 12-lead ECG and vital signs.
- Dosing: Administration of Investigational Product (PF-06946860) must be given at least 0.5h prior to administration of standard of care anti-tumor therapy.

- **Post-dose** blood samples for PK (see Section 8.5) and PD (GDF-15, see Section 8.6), will be collected at a minimum of 3h post PF-06946860 administration or at a maximum by the end of the clinic visit.

Weeks 15, 18 and 24:

- Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).
- Supine standard 12-lead ECG: obtain prior to vital signs assessment and, where applicable, prior to dosing (see Section 8.2.3 and Section 8.2.4).
- PK (see Section 8.5), PD (GDF-15, see Section 8.6), immunogenicity (see Section 8.9) and banked biospecimens (see Section 8.8.1) are to be collected after assessment of supine standard 12-lead ECG and vital signs.

- **Early Termination**
  - Patient Reported Outcomes (see Section 8.1.3) (Cohort 1 only).
  - Supine standard 12-lead ECG: obtain prior to vital signs assessment and, where applicable, prior to dosing (see Section 8.2.3 and Section 8.2.4).
  - Blood samples for safety (see Section 8.2.5), PK (see Section 8.5), PD (GDF-15, see Section 8.6), immunogenicity (see Section 8.9) and banked biospecimens (see Section 8.8.1) are to be collected after assessment of supine standard 12-lead ECG and vital signs.

10.20. Appendix 20: 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).

10.20.1. 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 viral test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2.

10.20.2. Home Health Visits

A home health care service will 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. The following may be performed during a home health visit:

- The use of the home-health visit could be extended to include specimen collection for PK, PD and ADA during the follow-up visits.

10.20.3. 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 events (SAE) and appropriate medical intervention provided.

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.

If a participant is confirmed to have active SARS-CoV2 infection and if alteration of the planned anti-tumor regimen is deemed necessary, the study medical monitor should be consulted regarding how to manage the study treatment, including potential temporary or permanent discontinuation of the study treatment.

10.21. Appendix 21: Abbreviations

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

Abbreviation	Term
Abs	Absolute
ACS	anorexia and cachexia subscale
ADA	antidrug antibodies
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC168H	area under the curve from the time of dose administration up to 168 hours
AUC_{inf}	area under the serum concentration time profile from time zero extrapolated to infinite time
AUC_{last}	area under the serum concentration time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the serum concentration-time curve over the dosing interval tau
AV	atrioventricular
BBS	Biospecimen Banking System
β-hCG	beta human chorionic gonadotropin
BLQ	Below the limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Cav	average concentration
CDC	complement dependent cytotoxicity
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CL/F	apparent clearance of drug from eg, plasma
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COPD	Chronic obstructive pulmonary disease
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein

Abbreviation	Term
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CT scan	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDP	exposure during pregnancy
EMA	European Medicines Agency
E_{max}	maximal effect
EOT	End of Treatment
ePRO	electronic Patient Reported Outcome
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials Database
FAACT	Functional Assessment of Anorexia-Cachexia Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
Fcγ	fragment crystallizable gamma
FDA	Food and Drug Administration
FIH	first in human
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	glial cell-derived neurotrophic factor (GDNF) family receptor alpha- like
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HRQoL	Health Related Quality of Life

Abbreviation	Term
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG1	immunoglobulin gamma-1
IgG1κ	immunoglobulin gamma-1 with kappa light chains
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUO	Investigational Use Only
IUS	Intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
LBBB	left bundle branch block
LFT	liver function test
LSMI	Lumbar Skeletal Muscle Index
LSLV	last subject last visit
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
MRI	magnetic resonance imaging
MSD	Meso Scale Discovery
MSI-H	metastatic microsatellite instability-high
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NRS	numerical rating scale
NSCLC	non-small cell lung cancer
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
PCD	primary completion date
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change

Abbreviation	Term
PGI-S	Patient Global Impression of Severity
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	prothrombin time
PVCs	premature ventricular complexes
Q1W	administered every week
Q2W	administered every 2 weeks
Q3W	administered every 3 weeks
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SMP	study monitoring plan
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TBili	total bilirubin
TEAE	treatment emergent adverse event
TGFβ	transforming growth factor beta
T_{max}	time for C_{max}
TMDD	target-mediated drug disposition
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential

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