CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of Ponsegromab in Patients With Cancer, Cachexia, and Elevated Concentrations of GDF-15, Followed by An Optional Open-Label Treatment Period
Study Number:	C3651003
Study Phase:	2
Regulatory Agency or Public Disclosure Identifier Number:	National Clinical Trial (NCT) #: NCT05546476 European Union Clinical Trial (EU CT) #: 2023-510446-24-00
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Ponsegromab (PF-06946860)
Indication:	Cachexia
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (First Participant First Visit [FPFV]):	21 November 2022
Primary Completion Date (PCD):	13 March 2024
Presentation of data in this clinical study report (CSR) synopsis based on: **Study Completion (Last Participant Last Visit [LPLV]) Date:**	23 April 2025
Early Termination Status	This study was not terminated early and was completed as per protocol.

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CSR Version and Report Date:	Document Version	Report Date
	Interim PCD CSR Version 1.0	27 June 2024
	Final LPLV CSR Version 1.0	04 February 2026

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

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Number of Study Center(s) and Investigator(s):

A list of study centers and investigators involved in Part B of the study is provided in Appendix 16.1.4.1.

Publications:

Groarke JD, Crawford J, Collins SM, et al. Phase 2 study of the efficacy and safety of ponsegromab in patients with cancer cachexia: PROACC-1 study design. J Cachexia Sarcopenia Muscle. 2024 Jun;15(3):1054-1061.

Groarke JD, Crawford J, Collins SM, et al. Ponsegromab for the Treatment of Cancer Cachexia. N Engl J Med. 2024 Dec 19;391(24):2291-2303.

Brief Description of the Trial Design and Methodology:

Refer to the interim PCD CSR synopsis for the trail design and methodology.

Number of Participants (planned and analyzed):

Refer to the interim PCD CSR synopsis for number of participants planned and analyzed in Part A of the study.

Table S1. Number of Participants (Planned and Analyzed) in Part B

Population	N	Definition
Planned	NA	Participants who completed Part A had the opportunity to enter the optional OLT period (Part B).
Entered	117	Participants who completed Part A and opted into OLT period (Part B)
Safety analysis set	114	All participants randomly assigned to study intervention and who took at least 1 Part B dose of study intervention.
Complete Analysis Set	114	All participants randomly assigned to study intervention and who took at least 1 Part B dose of study intervention.
Censored Analysis Set	114	All participants randomly assigned to study intervention and who took at least 1 Part B dose of study intervention. For participants who missed a dose, or received an incomplete dose, all observations post missed/incomplete dose had been censored and treated as missing data until immediately after the participant resumed (complete) dosing.

Abbreviations: FAS=full analysis set; SAS=safety analysis set; NA=not applicable; OLT=open-label treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Refer to the interim PCD CSR synopsis for diagnosis and main criteria for inclusion and exclusion.

Study Intervention:

Refer to the interim PCD CSR synopsis for study interventions administered in Part A.

In Part B of the study, the study intervention refers to ponsegromab (PF-06946860, IMP), which was administered at a dose level of 400 mg every 4 weeks (Q4W) by subcutaneous (SC) injection. The manufacturing lot numbers for the study intervention(s) dispensed in Part B (OLT period) of the study are provided in Table S2.

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Table S2. Study Intervention(s) Administered During Part B

Study Intervention Description	Vendor Lot No.	Pfizer Lot No.	Dosage Form
PF-06946860 Solution for Injection	1-FIN-3807	21-DP-00435	Solution
PF-06946860 Solution for Injection	NA	22-DP-01303	Solution
PF-06946860 Solution for Injection	1-FIN-3460	19-003686	Solution
PF-06946860 Solution for Injection	1-FIN-3666	20-002056	Solution

Global Substantial Modifications

Table S3. Global Substantial Modifications

Date of Protocol Amendment	Amendment
24 May 2023	The overall rationale for this amendment was to incorporate PK substudy, changes to eligibility criteria, and other clarifications.
27 October 2022	The overall rationale for this amendment was to incorporate and clarify various protocol elements related to stopping criteria of the study intervention, assessment of weight change, CT scan regions and patient reported outcomes.

Abbreviations: CT=computed tomography; PK=pharmacokinetic(s).

Global Interruptions and re-starts

Not applicable

Endpoints and Statistical Methods:

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Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary	**Primary:**				
• Part A: To evaluate the effect of ponsegromab compared with placebo on body weight in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Part A: Change from baseline body weight at Week 12.	• Primary efficacy analysis	• Part A censored population	• For participants who discontinued study intervention, or received a prohibited procedure or prohibited medication during Part A, all observations post discontinuation or post procedure, were censored and treated as missing data. For participants who missed a dose in Part A, all observations post-missed dose were censored and treated as missing data.	• MMRM model followed by a Bayesian Emax model
Secondary	**Secondary:**				
• Part A: To evaluate the effect of ponsegromab compared to placebo on physical activity and gait as measured by wearable digital sensors in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Part A: Change from baseline in physical activity and gait endpoints measured with remote digital sensors at Week 12: • Moderate to vigorous physical activity time; • Sedentary activity time; • Non sedentary activity time; • Total vector magnitude; • Mean activity level during M6min; • Mean gait speed; • 95th percentile gait speed.	• Secondary efficacy analysis	• Part A censored population	• Same as the primary endpoints.	• MMRM model
• Part A: To evaluate the effect of ponsegromab compared to placebo on the appetite related symptoms as measured by	• Part A: Change from baseline in FAACT sub-scale scores at Week 12:	• Secondary efficacy analysis	• Part A censored population	• Same as the primary endpoints.	• MMRM model

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Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
FAACT in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• FAACT-ACS; • FAACT-5IASS.				
• Part A: To evaluate the effect of ponsegromab compared to placebo on anorexia/appetite nausea, vomiting, and fatigue measured by the CRCSD, Pfizer-developed instrument, in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Part A: Change from baseline score for the questions from the CRCSD at Week 12 related to: • Anorexia/appetite; • Nausea and vomiting; • Fatigue.	• Secondary efficacy analysis	• Part A censored population	• Same as the primary endpoints.	• MMRM model
• Part A: To characterize the safety and tolerability of repeated SC administrations of ponsegromab compared to placebo in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Part A: Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities.	• Secondary safety analysis	• Part A safety analysis set	• Data for all participants randomly assigned to study intervention and who took at least 1 dose of study intervention were included in the secondary safety analysis. The sponsor data standard rules for imputation were used for the analysis of safety endpoints.	• Descriptive summary

Abbreviations: ACS=Anorexia and Cachexia Subscale; CRCSD=cancer related cachexia symptom diary; ECG=electrocardiogram; Emax=maximal effect; FAACT=Functional Assessment of Anorexia-Cachexia Therapy; 5IASS=5-item Anorexia Symptom Scale; M6min=maximum daily 6 minutes of activity; MMRM=Mixed Model for Repeated Measures.

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SUMMARY OF RESULTS:

Participant Disposition

Part A: A total of 281 participants were screened across 74 centers in 11 countries, and 187 participants were enrolled and randomized at 62 centers in these 11 countries for participation in Part A of this study. All 187 participants were treated, of whom 50 (26.7%) participants discontinued the double-blind treatment period early and the remaining 137 (73.3%) participants completed the Week 12 visit. The most frequently reported reason for discontinuation from the double-blind treatment period was 'Death' (19 [10.2%] participants overall, with 4 [8.9%] in the placebo group and 15 [10.6%] across the ponsegromab groups combined). A total of 26 (13.9%) participants entered Part A follow-up period, of whom 9 (4.8%) participants discontinued early during the follow-up period and 17 (9.1%) participants completed the follow-up visit. The most frequently reported reason for early discontinuation during Part A follow-up period was 'Death', with 6 (4.2%) deaths occurring across the ponsegromab groups combined and no deaths in the placebo group.

Part B: Of the 117 participants who entered Part B, 80 (68.4%) participants discontinued the open-label treatment (OLT) period early and the remaining 37 (31.6%) participants completed the OLT period. The most frequently reported reason for discontinuation from the OLT period was 'Progressive disease' (25 [21.4%] participants) followed by 'Death' (17 [14.5%] participants). A total of 59 (50.4%) participants entered Part B follow-up period, of whom 12 (10.3%) participants discontinued early during Part B follow-up period and 47 (40.2%) participants completed Part B follow-up period. The most frequently reported reason for early discontinuation during Part B follow-up period was 'Death' (7 [6.0%] participants). Six participants who died during Part B follow-up period had already discontinued the open-label treatment prior to completion of Part B due to 'Progressive disease' (4 participants) or 'Global deterioration of health status' (2 participants). Three participants that entered Part B did not receive any dose of open-label ponsegromab in Part B.

Demographic and Other Baseline Characteristics:

Part A: A total of 79 participants were enrolled in EU countries (14 in Spain, 36 in Bulgaria, 10 in Poland, and 19 in Slovakia), 30 participants were enrolled in the US, and 78 participants were enrolled in other countries (6 in Australia, 4 in Canada, 3 in Hungary, 37 in Japan, 20 in China, and 8 in Taiwan). Of the 187 participants who entered Part A of the study, 76 (40.6%) were 18-64 years old, 108 (57.8%) were 65-84 years old, and 3 (1.6%) were ≥85 years old. Refer to the interim PCD CSR synopsis for more details on demographic and other baseline characteristics for Part A.

Part B: Demographic and other baseline characteristics for Part B participants (ie, participants who entered Part B) are based on assessments performed prior to first dose of blinded study intervention in Part A.

- The median age was 68 years. The majority of Part B participants were ≥65 years old (61.5%) and male (64.1%); 59.8% of Part B participants were White and 40.2% were Asian.

- The median body weight was 54.70 kg at baseline and 58 (49.6%) had a BMI <20 kg/m^2.

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- Of the 117 Part B participants, 52 (44.4%) participants were diagnosed with non-small cell lung cancer (NSCLC), 34 (29.1%) participants were diagnosed with colorectal cancer (CRC), and 31 (26.5%) participants were diagnosed with pancreatic cancer (PANC), at baseline.

- The majority of Part B participants had tumour, node, metastasis (TNM) Stage IV cancer at baseline (70.9%). There was an imbalance in the frequency of Stage IV disease among Part B participants based on treatment assignment in Part A, ranging from 53.8% of Part B participants assigned to placebo in Part A versus 86.2% assigned to ponsegromab 400 mg in Part A.

- The majority of Part B participants (94.0%) were actively receiving systemic anticancer therapy during the study (during Part A and/or Part B).

- The median (range) interval from cancer diagnosis to the randomization of Part A was 11.4 (4.1, 26.8) months for Part B participants.

- Baseline concomitant use of platinum-based chemotherapy was reported in 38.5% of Part B participants. Baseline treatment with any systemic anti-cancer therapies was reported in 92.3% of Part B participants.

- The median baseline GDF-15 concentration was 3581.0 pg/mL (ranging from 2259.0 to 7125.0 pg/mL).

- The majority of Part B participants had either an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 (17.9% of participants) or 1 (66.7% of participants).

Exposure:

Refer to the interim PCD CSR synopsis for exposure of study interventions in Part A of the study. For Part B, of the 117 participants who entered Part B, 114 (97.4%) participants received at least 1 dose of study intervention during Part B.

Summary of Efficacy/Immunogenicity/PK/Safety Results

Table S5. Study C3651003 Efficacy/Safety Results

Endpoints	Results
Efficacy:	
• Part A: Change from baseline body weight at Week 12 (primary endpoint) • Part B: Change from baseline body weight, in Part B of the study.	• Refer to the interim PCD CSR synopsis for the final results of the primary endpoint. • During the 12-week double-blind Part A of this study, all ponsegromab-treatment groups demonstrated statistically significant, dose-responsive increases in body weight relative to placebo. Participants who then entered the optional open-label extension (Part B) received ponsegromab 400 mg Q4W SC from Week 12 through Week 64 and showed sustained and/or gradual body weight gains through the open-label extension period, with a mean (standard deviation [SD]) increase from

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Table S5. Study C3651003 Efficacy/Safety Results

Endpoints	Results
	baseline in body weight at Week 64 of 5.18 (5.924) kg. Participants assigned to placebo in Part A showed improvement of body weight after Week 12 during the open-label extension, but overall body weight gain was less than observed for patients who received ponsegromab during Part A. Least-squares (LS) means showed a similar body weight trajectory up to Week 52, with LS mean confidence intervals (CIs) becoming wider due to small n numbers beyond that timepoint.

• Part A: Change from baseline in physical activity and gait endpoints measured with remote digital sensors at Week 12 (secondary endpoint):
  • Moderate to vigorous physical activity time;
  • Sedentary activity time;
  • Non sedentary activity time;
  • Total vector magnitude;
  • Mean activity level during M6min;
  • Mean gait speed;
  • 95th percentile gait speed.
	• Refer to the interim PCD CSR synopsis for the final results of these secondary endpoints.

• Part A: Change from baseline in FAACT sub-scale scores at Week 12 (secondary endpoint):
  • FAACT-ACS;
  • FAACT-5IASS.
	• Refer to the interim PCD CSR synopsis for the final results of these secondary endpoints.

• Part A: Change from baseline score for the questions from the CRCSD at Week 12 related to (secondary endpoint):
  • Anorexia/appetite;
  • Nausea and vomiting;
  • Fatigue.
	• Refer to the interim PCD CSR synopsis for the final results of these secondary endpoints.

Safety	
• Part A: Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities (secondary endpoint).	• Refer to the interim PCD CSR synopsis for more details on the interim results of safety secondary endpoints.
• Part B: Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities, in Part B of the study.	• A total of 538 all-causality treatment-emergent adverse events (TEAEs) were reported across 96 (84.2%) participants during Part B of the study (from Week 12 through Week 72). The majority were either mild (206 Grade 1 TEAEs) or moderate (205 Grade 2 TEAEs). • There were 6 treatment-related TEAEs across 5 (4.4%) participants in Part B. • Overall, 79 all-causality TESAEs were reported across 50 (43.9%) participants. No treatment-related TESAEs were reported in Part B.

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Table S5. Study C3651003 Efficacy/Safety Results

Endpoints	Results
• Overall	• During Part B of the study, of the 114 participants who received at least 1 dose of study intervention, Grade 5 all-causality TEAEs (deaths) were reported in 23 (20.2%) participants. • There were no clinically significant findings in the frequency of laboratory abnormalities, or vital sign or ECG abnormalities by categorical analysis observed during Part B of the study. • A total of 154 (82.4%) participants (38 [84.4%] in the placebo group, 40 [87.0%], 39 [84.8%], and 37 [74.0%] in the ponsegromab 100, 200, and 400 mg groups, respectively, based on the treatment assignment in Part A) experienced non-serious TEAEs in Parts A and B.

CONCLUSIONS:

Refer to the interim PCD CSR synopsis for conclusions in Part A of the study.

Part B Efficacy:

- Participants who entered the optional open-label extension (Part B) received ponsegromab 400 mg Q4W SC from Week 12 through Week 64 and showed sustained and/or gradual body weight gains through the open-label extension period.

- Participants assigned to placebo in Part A demonstrated stabilization of body weight during Part B, but weight gain was less than for participants who received ponsegromab during Part A.

Part B Safety:

- No new safety signals were observed with longer exposure to ponsegromab 400 mg Q4W in Part B, the overall safety conclusions derived from Part A safety data at PCD remained unchanged with the safety updates in Part B.

- Ponsegromab at multiple doses up to 400 mg Q4W by SC administration for up to 64 weeks was considered safe and well-tolerated, with an adverse event profile consistent with advanced malignancy and high rates (≥86.0%) of concomitant use of systemic anticancer therapies.