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 (PROACC -1)

Study Intervention Number:	PF-06946860
Study Intervention Name:	ponsegromab
US IND Number:	139674
EudraCT/CTIS Number:	2022-003016-87
ClinicalTrials.gov ID:	NCT05546476
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3651003
Phase:	2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Phase 2 Study of the Efficacy and Safety of Ponsegromab in Patients with Cancer, Cachexia and Elevated GDF-15. (PROACC -1)

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Document History

Document	Version Date
Amendment 2	**24 May 2023**
Amendment 1	27 October 2022
Original protocol	17 June 2022

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

Protocol Amendment Summary of Changes Table

Amendment 2 (24 May 2023)

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate PK substudy, changes to eligibility criteria, and other clarifications.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Incorporated PK substudy design	Additional PK/PD samples included for a subset of participants in response to regulatory request.	1.1. Synopsis, 1.2 Schema, 1.3 Schedule of Activities, 3. Objectives, Endpoints and Estimands, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 8.1 Administrative Procedures, 8.1.3 Additional Visits for PK substudy, 8.1.4 Home Health Visits, 9.5 Sample Size Determination
Removed eGFR requirement	Ponsegromab is not excreted by the kidney. Insufficient rationale to support eGFR requirement.	1.1. Synopsis; 5.2. Exclusion Criteria (# 11)
Added exclusionary medications used for increasing	To minimize potential for confounding of primary endpoint.	6.9.1 Prohibited During the Study

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Description of Change	Brief Rationale	Section # and Name
appetite/body weight and weight loss.		
Clarified permitted medications	Clarification	6.9.2 Permitted During the Study
Removed Appendix 9 detailing France requirements	Decision made to not proceed with France	Appendix 9. Country Specific Requirements, 10.9.1 France
Added Appendix 12: list of platinum-based chemotherapy	Additional guidance since stratification at randomization is based upon participant being on platinum-based chemotherapy or not.	Appendix 12: List of Platinum-based Chemotherapy
Non-substantial Modification(s)		
Added ClinicalTrials.gov ID number	Information available	Title page and Section 1.1 synopsis
Separated SoA for Part A and Part B; removed visit numbers	Clarification	1.3. Schedule of Activities
Clarified text regarding SOC therapy timing	Clarification	1.1. Synopsis; 5.1. Inclusion Criteria (#2)
Clarified expectations of evaluation and timing of participation.	Clarification	1.1. Synopsis; 5.1 Inclusion Criteria (#5)
Clarified that participants previously dosed with IP are excluded	Clarification	1.1. Synopsis; 5.2. Exclusion Criteria (#9)
Consolidated exclusion criteria related to prior concomitant medications since information is covered in section 6.9 prior and concomitant therapy	Clarification	1.1. Synopsis; 5.2. Exclusion Criteria (# 7)
Updated to include “result may be confirmed by a single repeat test, if necessary” and “if there is liver involvement by the tumor”	Clarification	1.1. Synopsis; 5.2. Exclusion Criteria (#10)

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Description of Change	Brief Rationale	Section # and Name
Added exclusion criteria #12 to clarify participants cannot adhere to a calorie-restricted diet with the intention weight loss	Clarification	1.1. Synopsis; 5.2. Exclusion Criteria (#12)
Added examples for injection site combinations	Clarification	6.1.1 Administration
Editorial clarifications	To provide clarification, correct typos, and improve readability	1.1. Synopsis; 5.2. Exclusion Criteria (#s 1 & 4), 2.3.1 Risk Assessment, 2.3.3 Overall Benefit/Risk Conclusion, 4.1 Overall Design, 4.2 Scientific Rationale, 4.3 Justification for Dose, 4.4 End of study definition, 5.4 Screen Failures, 6.1.1 Administration, 6.5 Study Intervention Compliance, 6.9 Prior and Concomitant Therapy, 7.1 Discontinuation of Study Intervention, 7.3 Lost to Follow-up, 8.1.1 Screening Visit, 8.1.2 Week 5 Visit, 8.1.4 Home Health Visits, 8.2.2 Patient Reported Outcomes, 8.3.3.1 Blood Pressure and Pulse Rate, 8.3.4 Electrocardiograms, 8.3.7.1 Imaging Safety Assessment, 8.4.5.1 Exposure During Pregnancy, 8.5 Pharmacokinetics, 8.7.1 GDF-15, 9.3.2 Primary Endpoint analysis, 9.3.5 Other Analyses, 9.4.1 PK/PD Unblinding Plan, 10.4.2 Female Participant Reproductive Inclusion Criteria
• Updated visit windows for Part A and for Part B added contraception checks for follow up Part A and follow	Protocol Administrative Change Letter dated 13 Feb 2023	1.3 Schedule of Activities, 8.1.5 Transportation, 3. Objectives, Endpoints and Estimands, 8.4.1. Time Period

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Description of Change	Brief Rationale	Section # and Name
up Part B; added transportation allowance to footnote 'a'. • Added section for transportation. • Updated evaluation of safety and tolerability in Part B to also include vital signs and ECG abnormalities • Updated the time period for actively eliciting and collecting AEs and SAEs. • Updated the serum cystatin C (SCys) test to be performed at Screening to capture the baseline value		and Frequency for Collecting AE and SAE Information, 10.2 Appendix 2 Clinical Laboratory
Added updated clinical information	To include information from the latest IB update	2.2.1 Clinical Overview, 2.2.1.1 Phase 1b Body Weight Data, 2.2.1.3 Summary of Pharmacokinetics, 2.2.1.4 Summary of GDF-15 response, 2.2.1.5 Immunogenicity, 2.3.2 Benefit Assessment
Protocol template updates	Protocol template version 14 April 2023	Title page and Appendices

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LIST OF TABLES

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol 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.

Brief Title:

A Phase 2 Study of the Efficacy and Safety of Ponsegromab in Patients with Cancer, Cachexia and Elevated GDF-15. (PROACC -1)

Regulatory Agency Identification Number(s):

US IND Number:	139674
[EudraCT/CTIS] Number:	2022-003016-87
ClinicalTrials.gov ID:	NCT05546476
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3651003
Phase:	2

Rationale:

Patients with advanced cancer and elevated concentrations of GDF-15 frequently develop cachexia which impacts their quality of life and survival. Inhibiting the activity of GDF-15 in such patients may help reverse cachexia and improve their quality of life. This study will evaluate the efficacy, safety, and tolerability of ponsegromab, an inhibitor of GDF-15, compared to placebo, in patients with cancer, cachexia, and elevated concentrations of GDF-15.

This study is also known as PROACC -1, Patient Reported Outcomes and Activity in CanCer.

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Objectives, Endpoints, and Estimands:

Part A

Objectives	Endpoints	Estimands
Primary	**Primary**	**Primary**
• To evaluate the effect of ponsegromab compared with placebo on body weight in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline body weight at Week 12.	• Estimand 1 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in body weight at Week 12, in participants with cancer, cachexia and elevated concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• **Secondary**	• **Secondary**	• **Secondary**
• 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.	• Change from baseline in each of the 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.	• Estimand 2 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each of the physical activity and gait endpoints at Week 12, in participants with cancer, cachexia and elevated concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• To evaluate the effect of ponsegromab compared to placebo on the appetite-related symptoms as measured by FAACT in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline in FAACT sub-scale scores at Week 12: • FAACT-ACS; • FAACT-5IASS.	• Estimand 3 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each FAACT sub-scale score at Week 12, in participants with cancer, cachexia and elevated

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Objectives	Endpoints	Estimands
		concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• 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.	• Change from baseline score for the questions from the CRCSD at Week 12 related to: • Anorexia/appetite; • Nausea and vomiting; • Fatigue.	• Estimand 4 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each of the anorexia/appetite, nausea, vomiting, and fatigue questions from the CRCSD at Week 12, in participants with cancer, cachexia and elevated concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• 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.	• Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities*	• There are no defined estimands for the incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities, and these endpoints will be summarized using Pfizer data standards as applicable.

* Safety, tolerability and survival will also be characterized in Part B once all applicable participants have completed Part B of the study. These data will be reported as part of the supplemental CSR.

Overall Design:

This is a Phase 2, randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of three different doses of ponsegromab compared to placebo, administered for 12 weeks, in patients with NSCLC, PANC, or CRC who have elevated concentrations of GDF-15 and cachexia. The double-blind period is followed by an optional open-label (Part B) extension period.

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The Screening visit will occur no more than 28 days and no less than 7 days, prior to Randomization. The 7-day minimum duration between Screening and Randomization visits will ensure that the GDF-15 results are available to inform the investigator's assessment of eligibility and the 7-day collection of PRO and physical activity data. Following the Screening period to confirm eligibility, approximately 168 study participants, who meet the entry criteria, will be randomized to study intervention (one of 3 dose groups of ponsegromab or matching placebo) and will be stratified by treatment with or without platinum-based chemotherapy, which is known to induce GDF-15 and therefore may impact the response to ponsegromab treatment. The 12-week double-blind dosing period (Part A) will consist of a total of 3 doses administered Q4W SC.

A PK substudy will be conducted in approximately 36 of the approximately 168 participants (approximately 9 in each treatment group in Part A). Up to 3 additional PK and PD samples (two samples during Part A and one sample during Part B, if relevant), will be collected in these participants at timepoints during the study outlined in Sections 1.2 schema and 1.3 SoA.

On completion of Part A, participants will have the opportunity to enter an optional OLT period (Part B) consisting of ponsegromab 400 mg Q4W SC for up to 1 year. The investigator and participant must decide at the Week 8 visit if they wish to continue to the optional OLT period.

Participants opting to continue to the optional OLT period will receive their first dose of open-label ponsegromab 400 mg at the Week 12 visit, which is the last visit of the double-blind portion. Upon completion of the optional OLT period, there will be a follow-up visit (Week 72) which is to occur 56 to 63 days post last dose of study intervention.

Participants who do not proceed with the optional OLT period are to complete the Week 12 visit and a follow-up visit at Week 16.

Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

The optional OLT period will continue as currently planned, unless the following factors develop in which case the optional OLT period may be modified:

- Upon completion of the double-blind portion, the final analysis shows a lack of efficacy for the primary endpoint and/or inadequate safety and tolerability;
- An alternative method of study intervention delivery become available;
- A lower dose of ponsegromab is shown to be efficacious;
- The sponsor decides to terminate the study/clinical development program.

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- Participants may withdraw from the optional OLT period at any time, for reasons such as the following:

  - The study participant withdraws consent or dies;

    The study participant experiences an AE attributable to intervention;

    A change in study participant's medical condition that, in the investigator's judgment, makes it inappropriate to continue study participation.

  An independent oversight committee in the form of an IRC will monitor the safety, efficacy, and tolerability of the study participants and the study conduct. There will also be an Executive Steering Committee and an Operations Steering Committee.

Number of Participants:

Approximately 168 participants will be enrolled in the study, of which up to approximately 36 participants will be enrolled in the PK substudy.

Note: "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 and randomization to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after Screening. 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.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participants aged ≥18 years (or the minimum age of consent if > 18 in accordance with local regulations) at screening who have signed informed consent.

   a. A female participant is eligible to participate if she is not pregnant or breastfeeding.

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

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2. Documented histologic or cytologic active diagnosis of NSCLC, PANC, or CRC and are currently receiving, or have completed, standard of care treatment for this cancer (which may include systemic therapy).

3. Cachexia defined by Fearon criteria of weight loss as (See Section 8.1.1 for details if the participant's body weight is unavailable from medical record):

   - 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.

4. Serum GDF-15 concentrations of ≥1.5 ng/mL (as measured using the Investigational Use Only Roche Elecsys GDF-15 assay)[10] at Screening.

5. Participants who are assessed by the investigator to have:

   - an ECOG PS ≤3, and;

   - a life expectancy of at least 4 months to be able to complete Part A.

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

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

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

   - NCI CTCAE Grade 3 or 4 oral mucositis;

   - NCI CTCAE Grade 3 or 4 GI disorders [nausea, vomiting, diarrhea, and constipation];

   - mechanical obstructions interfering with the participant's ability to eat.

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

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3. Cachexia caused by other reasons, as determined by the investigator, including, but not limited to:

   - Severe COPD requiring use of home O2;
   - NYHA class III-IV heart failure;
   - AIDS.

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

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

6. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibody.

7. Current use of any prohibited concomitant medication(s) within 4 weeks prior to first dose of study intervention. Refer to Section 6.9.

8. Concurrent administration of investigational products (including drug, biologic agents, or vaccines) are not permitted within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) of the first dose of study intervention through the duration of the study (including both Part A and B). Refer to Section 6.9.

9. Enrollment and previously dosed in a prior study with ponsegromab.

10. History of severe liver disease or cirrhosis, unrelated to metastatic cancer. Potential study participants with the following liver function test abnormalities will be excluded; result may be confirmed by a single repeat test, if necessary:

    - Total bilirubin ≥1.5 × ULN (except for Gilbert's syndrome)
    - AST >3 × ULN (AST > 5X ULN if there is liver involvement by the tumor)
    - ALT >3 × ULN (ALT >5X ULN if there is liver involvement by the tumor)

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- Alkaline phosphatase >3 x ULN (Alkaline phosphatase >5X ULN if there is liver involvement by the tumor and/or in case of bone metastases, or if considered related to prior surgery e.g. pancreaticoduodenectomy).

11. Renal disease requiring dialysis.

12. Current adherence to a calorie-restricted diet with the intention of weight loss.

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

Study Arms and Duration:

Following a 28-day screening period to confirm eligibility, study participants who meet the entry criteria will be randomized to study intervention (one of 3 dose groups of ponsegromab or placebo). The 12-week double-blind dosing period (Part A) will consist of a total of 3 SC doses, administered Q4W. On completion of Part A, participants will have the opportunity to enter an optional open-label treatment period (Part B) consisting of ponsegromab 400 mg Q4W SC for up to 1 year.

	Study Intervention(s)			
Intervention Name	ponsegromab	ponsegromab	ponsegromab	placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	ponsegromab Double-Blind Treatment 100 mg	ponsegromab Double-Blind Treatment 200 mg	ponsegromab Double-Blind Treatment 400 mg	placebo Double-Blind Treatment
Dose Level	100 mg Q4W	200 mg Q4W	400 mg Q4W	placebo Q4W
Unit Dose Strength(s)	100 mg/ mL	100 mg/ mL	100 mg/ mL	placebo
Route of Administration	SC	SC	SC	SC
Use	experimental	experimental	experimental	placebo-active-comparator
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP

Statistical Methods:

The sample size in the ponsegromab and placebo arms is based on the primary efficacy endpoint, mean change from baseline in body weight at Week 12. Approximately 168 randomized participants are proposed, to ensure completion of approximately 120 participants, assuming a discontinuation rate of approximately 30%. 120 completing participants, in a 1:1:1:1 ratio, plus 39 participants from an informative meta-analytic

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predictive prior (based on historical results from internal and external studies, robustified by the inclusion of a weakly informative component to handle any possible prior-data conflict) gives acceptable Operating Characteristics in that the probability of achieving statistical significance (at the 5% significance level, using a 1-sided t-test), for a true difference between ponsegromab and placebo of 2.7 kg, is approximately 80% (with a conservative standard deviation of 4.9 kg).

The primary estimand will be the population level estimate of the difference between ponsegromab and placebo in the mean change from baseline in body weight at Week 12, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing. Data collected after a participant has discontinued study intervention, has undergone a prohibited procedure, received prohibited medications, or has inadequate compliance will be censored and treated as missing data.

The primary endpoint analysis will be a Bayesian E_{max} model applied to results from an MMRM analysis. Change from baseline in body weight will be first analyzed using an MMRM model fitted to all post-treatment dosing timepoints up to Week 12 (ie, Weeks 4, 8, and 12). The primary analysis will include all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. The MMRM model will include participant as a random term, and baseline, time (as a factor), baseline-by-time interaction, treatment and treatment -by -time interaction as fixed terms in the model. Additional terms for type of therapy [ie, platinum or not] and type of cancer will be fitted in the model. An unstructured covariance matrix will be fitted to the repeated times within subject, and the Kenward Roger approximation will be used for estimating degrees of freedom. No adjustments will be made for multiplicity. A Bayesian E_{max} model will then be fitted to the Lsmeans and Ses from Week 12 only. The posterior medians and 90% credible intervals will be reported for each randomized dose (including placebo) and their differences relative to placebo.

Secondary endpoints of physical activity and gait, FAACT sub-scales and questions from the CRCSD, will be analyzed using an MMRM model with similar estimands to the primary estimand. Safety and tolerability data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations, as appropriate, in accordance with Pfizer Data Standards.

Ethical Considerations:

Considering all available clinical and nonclinical data, the benefit-risk profile of ponsegromab 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 ponsegromab may be found in the IB, which is the SRSD for this study.

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Taking into account the measures to minimize risk to study participants, the potential risks identified in association with ponsegromab are justified by the anticipated benefits that may be afforded to participants with cancer and cachexia.

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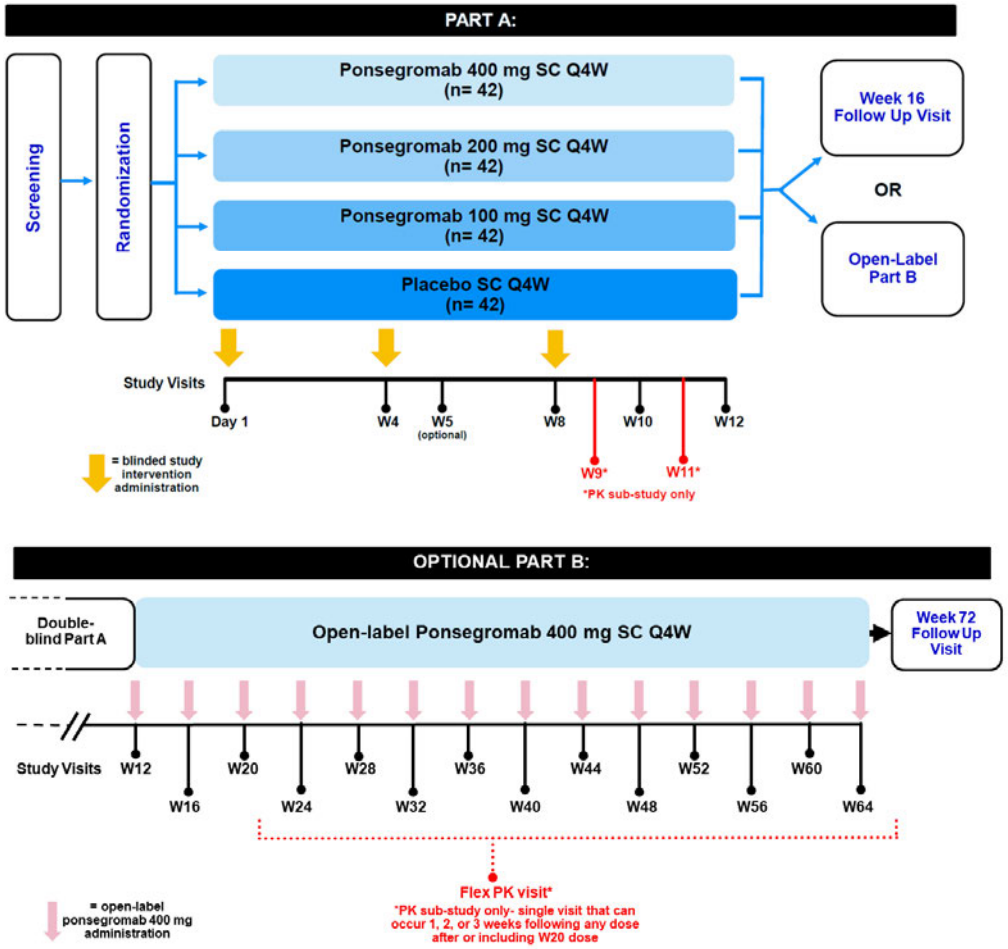
1.2. Schema



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1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the 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, to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Schedule of Activities for Part A Double-Blind

Visit Identifier Abbreviations used in this table may be found in Appendix 13	Screening			Part A: Double-Blind[a]						F/U Part A	ED Part A
Week #			4	5[b,c]	8[d]	9[c,e] (PK substudy only)	10[c,f]	11[c,e] (PK substudy only)	12	16	
Day -relative to start of study intervention (Day 1)	-28 to -7	1	29	36	57	64	71	78	85	113	
Visit Window (Days)			±3	-3/+7	±3	±2	±7/±3[f]	±2	±2	+7	
Informed consent	X										
Review eligibility criteria	X	X									
Medical History and Physical Examination											
Medical history	X										
Demography	X										
Full Physical examination (+ Height at Screening only)[g]	X								X		X
Abbreviated Physical examination[g]			X		X						
Vital signs	X		X		X				X		X
12-Lead ECG	X				X				X		X
ECOG PS	X								X		X
Contraception check	X	X	X		X				X	X	X
Laboratory Assessments											
Hematology	X				X				X		X
Blood chemistry	X				X				X		X
Pregnancy test[h]	X	X	X		X				X	X	X
Blood sample for GDF-15 (Roche Assay)	X										
Blood sample for GDF-15 (Pfizer Assay(s))[i]	X	X	X	X	X	X	X	X	X	X	X
Blood sample for ponsegromab PK[i]		X	X	X	X	X	X	X	X	X	X

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Table 1. Schedule of Activities for Part A Double-Blind

Visit Identifier Abbreviations used in this table may be found in Appendix 13	Screening			Part A: Double-Blind[a]						F/U Part A	ED Part A
Week #			**4**	**5[b,c]**	**8[d]**	**9 [c,e] (PK substudy only)**	**10[c,f]**	**11 [c,e] (PK substudy only)**	**12**	**16**	
Day -relative to start of study intervention (Day 1)	**-28 to -7**	**1**	**29**	**36**	**57**	**64**	**71**	**78**	**85**	**113**	
Visit Window (Days)			**±3**	**-3/+7**	**±3**	**±2**	**±7/±3[f]**	**±2**	**±2**	**+7**	
Blood sample for immunogenicity (ADA and Nab)[i]		X	X		X				X	X	X
Blood sample for albumin & pre-albumin		X							X		X
Study Intervention and Other Treatments											
Registration within IRT	X										
Randomization		X									
Study intervention administration		X	X		X				X[a]		
Prior/concomitant treatment(s)	X	X	X		X				X	X	X
Assessments											
Efficacy											
Weight[j]	X	X	X	X	X		X		X	X	X
PRO-CRCSD[k]	X	→	→	→	→	→	→	→	X		X
PRO-PROMIS (fatigue 7A & physical function 8c)[l]		X	X		X				X		X
PRO-FAACT[l]		X	X		X				X		X
PRO-PGI-S (appetite, fatigue and physical function)[l]		X	X		X				X		X
PRO-PGI-C (appetite, fatigue, and physical function)[l]			X		X				X		X
PRO-PGI-S (physical activity and walking)[m]	X				X		X		X		X
PRO-PGI-C (physical activity and walking)[m]					X		X		X		X
Digital Measures-physical activity and gait[n]	X→				X→		X→	→	X		X
Comfort and Wearability Questionnaire for Digital Measures (At clinic)									X		X
Qualitative Exit Interview[o]									X		X
Safety											
CT scan[p]	X								X		X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→
Retained Research Samples (not applicable for China)											
Retained research sample for genetics (Prep D1.5)[q,r]		X									

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Table 1. Schedule of Activities for Part A Double-Blind

Visit Identifier Abbreviations used in this table may be found in Appendix 13	Screening			Part A: Double-Blind[a]						F/U Part A	ED Part A
Week #			4	5[b,c]	8[d]	9 [c,e] (PK substudy only)	10[c,f]	11 [c,e] (PK substudy only)	12	16	
Day -relative to start of study intervention (Day 1)	-28 to -7	1	29	36	57	64	71	78	85	113	
Visit Window (Days)			±3	-3/+7	±3	±2	±7/±3[f]	±2	±2	+7	
Retained research samples for biomarkers (Prep B 1.5 & Prep B 2.5)[r]		X							X		X

a. All participants, regardless of proceeding with the optional OLT period (Part B), will complete the Week 12 visit. Participants proceeding with the optional OLT period (Part B) will complete all Week 12 study procedures before receiving the first dose of OLT study intervention. Transportation to and from the study site may be provided for study participants for Part A visits, as permitted by the country, study site, and participant.

b. The Week 5 visit is considered an optional visit to collect PK and GDF-15 samples as well as measurement of weight and SAE/AE monitoring based upon participant availability. It will not be considered a protocol deviation if the participant is unable to make this visit.

c. The PK and PD assessments at Week 5 and 10, as well as Week 9 and 11 in PK sub-study only may be conducted at participant's home or current residence if it is feasible to be performed by the site for flexibility of participant.

d. The investigator and participant must decide at the Week 8 visit if they wish to continue to the optional OLT (Part B).

e. Visits at Weeks 9 and 11 are only applicable for participants enrolled in PK sub-study.

f. For participants in PK substudy, visit window for Week 10 is ±3 days

g. All physical exams (full and abbreviated) will include an assessment for ascites and/or edema. In addition, ascites and/or edema will be captured as an AE on the AE CRF. See Section 8.3.1.

h. A serum pregnancy (b-hCG) test is only required at the screening visit and will be sent to the central lab. Following screening, a urine pregnancy test may be performed, and must have a sensitivity of at least 25 mIU/mL. The urine sample is to be tested at the site facility and results are to be confirmed negative and recorded in the database. Pregnancy test results must be reviewed and confirmed as negative in order to continue dosing with study intervention. Refer to Section 8.3.6.

i. On dosing days, blood samples for PK, GDF-15, and immunogenicity must be collected prior to study intervention administration. For any unplanned site visit, a PK and GDF-15 sample will be collected, if feasible, see Section 8.1.

j. Body weight does not need to be obtained if the visit is conducted offsite, see Section 8.2.1.

k. Data will be captured daily during Part A, including during the screening period, using the electronic PRO device at home. See Section 8.2.2.

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Table 1. Schedule of Activities for Part A Double-Blind

Visit Identifier Abbreviations used in this table may be found in Appendix 13	Screening			Part A: Double-Blind[a]						F/U Part A	ED Part A
Week #			4	5[b,c]	8[d]	9 [c,e] (PK substudy only)	10[c,f]	11 [c,e] (PK substudy only)	12	16	
Day -relative to start of study intervention (Day 1)	-28 to -7	1	29	36	57	64	71	78	85	113	
Visit Window (Days)			±3	-3/+7	±3	±2	±7/±3[f]	±2	±2	+7	

l. Data will be captured using the electronic PRO device at the clinic and should be completed by the participant at the beginning of the visit before any medical procedures or interactions with the medical staff takes place (as much as practically possible). See Section 8.2.2.

m. Data will be captured using the electronic PRO device either at home or at the clinic. Measured immediately at the end of the 7-day consecutive monitoring period for Screening (at home), Week 8 (approximately Day 63 at home), Week 10 (approximately Day 77 at home), and Week 12 (approximately Day 85 at the clinic). The Week 12 assessment is to be collected prior to the first dose of study intervention for participants proceeding with Part B OLT. See Section 8.2.2.

n. Measured during Screening, Week 8 (period of Week 8-9) and Week 12 (period of Week 10-12) for a minimum 7 days, using the electronic device at home. See Section 8.2.3.

o. Phone Interview will be conducted by the vendor within the 10 business days following the Week 12 visit, or at ED, if feasible. See Section 8.2.2.

p. All CT scans will need to include chest, abdomen, and pelvis to be acceptable for this study. If a SOC CT scan was performed within 3 weeks prior to the Screening visit, then a CT scan at screening is not needed. If a SOC CT scan is being performed at the Week 12 visit, between Weeks 10-12 or within 7 days after the Week 12 visit as part of SOC, then an additional CT scan is not needed. Similarly, if SOC CT scan is performed 2 weeks prior or 7 days after the ED visit, then an additional CT scan is not needed. The RECIST 1.1 categorization (Appendix 11) is to be entered in the CRF after each scan. See Section 8.3.7.

q. 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. On dosing days, retained research blood samples are to be collected prior to study intervention administration.

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Table 2. Schedule of Activities for Participants Enrolled in Optional Part B OLT

Visit Identifier Abbreviations used in this table may be found in Appendix 13	Part B: Open Label[a]													Flex PK/PD (PK substudy only)[b]	F/U Part B	ED Part B
Week #	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**		**72**	
Day -relative to start of study intervention (Day 1)	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**		**505**	
Visit Window (Days)	±7	±7	±3	±7	±7	±3	±7	±7	±3	±7	±7	±3	±7		+7	
Physical Examination																
Full Physical examination (+ Height at Screening only)[c]													X			X
Abbreviated Physical examination[c]			X			X			X			X				
Vital signs			X			X			X			X	X			X
12-Lead ECG													X			X
ECOG PS													X			X
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Laboratory Assessments																
Hematology			X			X			X			X	X			X
Blood chemistry			X			X			X			X	X			X
Pregnancy test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Blood sample for GDF-15 (Pfizer Assay(s))[e]	X		X			X			X				X	X	X	X
Blood sample for ponsegromab PK[e]	X		X			X			X				X	X	X	X
Blood sample for immunogenicity (ADA and Nab)[e]	X		X			X			X				X		X	X
Blood sample for albumin & pre-albumin													X			X
Study Intervention and Other Treatments																
Study intervention administration	X	X	X	X	X	X	X	X	X	X	X	X	X			
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

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Table 2. Schedule of Activities for Participants Enrolled in Optional Part B OLT

Visit Identifier Abbreviations used in this table may be found in Appendix 13	Part B: Open Label[a]													Flex PK/PD (PK substudy only)[b]	F/U Part B	ED Part B
Week #	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**		**72**	
Day -relative to start of study intervention (Day 1)	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**		**505**	
Visit Window (Days)	±7	±7	±3	±7	±7	±3	±7	±7	±3	±7	±7	±3	±7		+7	
Assessments																
Efficacy																
Weight[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety																
Serious and nonserious AE monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

a. All participants, regardless of proceeding with the optional OLT period (Part B), will complete the Week 12 visit. Participants proceeding with the optional OLT period Part B will complete all Week 12 study procedures before receiving the first dose of OLT study intervention.

b. PK sub-study only: one additional post-dose PK and PD sample collection can occur 1, 2 or 3 weeks following any dose after or including Week 20 and may be conducted at participant's home/current residence or at site, as per feasibility and preference. If conducted at the participant's home, body weight does not need to be obtained.

c. All physical exams (full and abbreviated) will include an assessment for ascites and/or edema. In addition, ascites and/or edema will be captured as an AE on the AE CRF. See Section 8.3.1.

d. Pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Refer to Section 8.3.6. The urine sample is to be tested at the site facility and results are to be confirmed negative and recorded in the database. Pregnancy test results must be reviewed and confirmed as negative in order to continue dosing with study intervention.

e. On dosing days, blood samples for PK, GDF-15, and immunogenicity must be collected prior to study intervention administration. For any unplanned site visit, a PK and GDF-15 sample will be collected, if feasible, see Section 8.1.

2. INTRODUCTION

Ponsegromab is an inhibitor of GDF-15 that is currently being investigated in participants with cancer, cachexia, and elevated concentrations of GDF-15. Ponsegromab is also being investigated in patients with heart failure and elevated concentrations of GDF-15.

2.1. Study Rationale

Patients with cancer suffer considerable morbidity related to both tumor progression and the side effects of therapies targeting the underlying malignancy. As cancers progress, patients frequently develop cachexia, a loss of weight due to the catabolism of muscle and fat tissue.[1,2] The progressive worsening of cachexia impacts a cancer patient's quality of life and contributes to poor survival.

The purpose of the study is to evaluate the efficacy, safety and tolerability of ponsegromab compared to placebo in the treatment of patients with cancer, cachexia, and elevated concentrations of GDF-15.

This study is also known as PROACC-1, Patient Reported Outcomes and Activity in CanCer.

2.2. Background

At the present time, treatments for cancer related cachexia are limited. Pharmacologic interventions associated with improvements in appetite improvement or body weight gain include progesterone analogues and corticosteroids.[1] The ASCO, in its 2020 *Management of Cachexia Guidelines*, stated that there is no recommended pharmacologic standard of care for patients with cancer associated cachexia.[2]

One of the biomarkers associated with cancer cachexia is the cytokine GDF-15.[3] GDF-15, also known as MIC-1, is a member of the TGFb 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.[4] GDF-15 is secreted by tumor cells and is associated with cachexia in cancer patients.[5,6,7]

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[8] 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, PANC, and CRC, 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 antitumor treatment that includes systemic platinum- based therapy, may be a specific population that could potentially gather additional- benefit from GDF-15 inhibition.[8]

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Ponsegromab is an anti-GDF-15 mAb that is currently being investigated in study participants with cancer who have elevated concentrations of GDF-15 and cachexia. The objective of this clinical study is to determine if ponsegromab administered at three different doses every 4-weeks over 12-weeks can reduce the study participants' cachexia related symptom burden and improve their quality of life compared to placebo during 12-weeks of treatment.

A summary of relevant, currently available data on ponsegromab is provided in this protocol. Additional detail, and further information for this compound, may be found in the IB, including its physical, chemical, pharmaceutical properties and formulation, non-clinical studies, and its known effects in humans.

2.2.1. Clinical Overview

To date, the safety of ponsegromab has been assessed in 2 completed Phase 1 clinical studies in healthy adult volunteers (C3651001 and C3651002) and in 2 completed Phase 1b studies in patients with elevated serum GDF-15 levels and cancer cachexia (C3651009) or cancer anorexia (C3651010). A total of 80 participants were exposed to this at least one dose of ponsegromab across these studies. A summary of the completed studies is presented in the table below.

Completed Clinical Studies with Ponsegromab

Study Identifier	Study Design and Type of Control	Dosing Regimen, Formulation, Dose	Number of Participants Randomized	Population	Treatment Duration
C3651001	Phase 1, double-blind, randomized, sponsor-open, placebo controlled, single ascending dose study.	Ponsegromab or placebo. Subcutaneously administered solution Dose: 0.1, 0.3, 1, 3, 10, 30, 100 and 300 mg	Total: 63 47 ponsegromab[a], 16 placebo	Eight sequential cohorts of healthy adult participants.	Single dose
C3651002	Phase 1, double-blind, randomized, sponsor-open, placebo controlled, single dose study.	Ponsegromab or placebo. Subcutaneously administered solution Dose: 100 mg	Total: 8 6 ponsegromab, 2 placebo	One cohort of healthy adult Japanese participants.	Single dose

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Completed Clinical Studies with Ponsegromab

Study Identifier	Study Design and Type of Control	Dosing Regimen, Formulation, Dose	Number of Participants Randomized	Population	Treatment Duration
C3651009	Phase 1b, open-label multiple dose study	Ponsegromab Subcutaneously administered solution Dose: 200 mg Q3W	Total: 11 10 ponsegromab[b]	Participants with cancer, cachexia, and serum GDF-15 levels ≥ 1500 pg/ml.	12 weeks
C3651010	Phase 1b, double-blind, randomized, placebo controlled followed by open-label extension	Ponsegromab or placebo Subcutaneously administered solution Dose: 200 mg Q3W	Total: 18 Double-blind period 12 ponsegromab 6 placebo Open-label period: 14 ponsegromab[c]	Participants with cancer, anorexia, and serum GDF-15 levels ≥ 1500 pg/ml.	6 weeks followed by 18 week open label extension.

a. N=6 per dose except for the 300 mg dose group where N=5.
b. 1 participant randomized and not dosed.
c. Of these 14, 5 received placebo and 9 received ponsegromab during the preceding double-blind period.

More detailed information for the completed studies may be found in the ponsegromab IB, which is the SRSD for this study.

2.2.1.1. Phase 1b Body Weight Data Summary

While the primary objective of Phase 1b C3651009 study was to evaluate the safety, tolerability, PK/PD, and immunogenicity of ponsegromab 200 mg Q3W (through 12 weeks/5 doses) in cancer patients with cachexia, change of body weight from baseline was also evaluated, as a signal of clinical efficacy. Mean increases from baseline in body weight were observed at all time points during the 12-week treatment period and 12-week follow-up period. The mean (SD) body weight increase from baseline was 4.46 (4.75) kg at Week 12, with a mean (SD) percent increase from baseline of 5.81 (5.87).

Body weight data are not presented for C3651010 study given that this study was terminated for non-safety reasons, with less than 50% of originally planned number of participants enrolled, precluding meaningful evaluation for changes in body weight.

2.2.1.2. Summary of Safety Data

In the single arm, open-label, Phase 1b C3651009 study of patients with cancer, cachexia, and elevated GDF-15 levels, there were 92 TEAEs reported for 10 participants dosed with ponsegromab 200 mg Q3W SC. None of these TEAEs were attributed to study intervention by the investigator or sponsor. Of these non-treatment related TEAEs, most were mild or moderate; 5 were serious, of which one was fatal due to neoplasm progression during the

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follow-up period (131 days after randomization). No deaths occurred during the treatment period.

In the Phase1B study C3651010 study in patients with cancer, anorexia and elevated GDF-15 levels, there were 58 TEAEs (including 8 SAEs) across 18 participants. Only 1 TEAE (myalgia) was considered treatment-related by the investigator. The incidence and severity of TEAEs were similar between the two treatment arms. In the double-blind treatment phase there were 3 deaths: one in a participant receiving placebo due to a cardiac arrest and 2 in the ponsegromab 200 mg Q3W treatment arm, one due to respiratory failure and one due to acute myocardial infarction. During the open label extension there were 3 deaths attributed due to disease progression. None of these deaths were considered treatment related.

2.2.1.3. Summary of Pharmacokinetics

Following single dose administration of ponsegromab to healthy non-Japanese participants, SC absorption of unbound ponsegromab for the 3 to 300 mg dose groups occurred with median T_{max} ranging from 2.25 to 7.00 days. In general, over the 10 to 300 mg dose range, increases in geometric mean unbound C_{max} in serum were approximately dose-proportional and increases in unbound AUC_{last} and AUC_{inf} in serum appeared to be greater than dose-proportional. The geometric mean CL/F appeared to decrease with increasing dose, and mean terminal $t_{½}$ increased with increasing dose, ranging from 3.52 to 11.1 days across the 10 to 300 mg dose groups.

Following single doses of SC ponsegromab in healthy participants, absorption of total ponsegromab occurred with median T_{max} ranging from 6.00 to 14.0 days across the 1 to 300 mg dose groups. In general, increases in geometric mean total C_{max}, AUC_{last}, and AUC_{inf} in serum appeared to be less than dose-proportional over the 10 to 100 mg dose range, while increases in exposure from 100 to 300 mg doses were largely dose proportional. The mean terminal $t_{½}$ values increased from 20.1 days for the 10 mg group to 30.9 days for the 300 mg group. The long terminal $t_{½}$ of total ponsegromab in serum is driven primarily by the half-life of bound ponsegromab (ponsegromab-GDF-15 complex), as the unbound ponsegromab terminal $t_{½}$ values observed over the same dose ranges were much shorter. Unbound ponsegromab (not total ponsegromab) is the active moiety that accounts for pharmacological activity of the drug.

At a single 100 mg SC dose, the geometric mean unbound ponsegromab C_{max}, AUC_{last}, and AUC_{inf} in Japanese participants were approximately 50%, 70%, and 71% higher, respectively, than those observed in non-Japanese participants. Similarly, the geometric mean total C_{max}, AUC_{last}, AUC_{inf} in Japanese participants were approximately 48%, 65%, and 66% higher, respectively.

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2.2.1.4. Summary of GDF-15 Response

In study C3651001, following single SC administration of 1 to 300 mg doses of ponsegromab to healthy non-Japanese adults, the median duration of serum unbound GDF-15 suppression (defined as last time post-dose with unbound GDF-15 concentration reported as below LLOQ which was 42.4 pg/mL) increased with increasing dose of ponsegromab, ranging from 0.17 day for the 1 mg dose group to 75.61 days for the 300 mg dose group. There was generally no change from baseline in measures of unbound GDF-15 in participants treated with placebo, ponsegromab 0.1 and 0.3 mg groups. Following a single SC administration of ponsegromab 100 mg in healthy Japanese adult participants in study C3651002, serum unbound GDF-15 concentrations were suppressed to below the LLOQ starting on Day 1, with the median duration of suppression of 40.49 days, ranging from 9.00-88.07 days in individual participants.

In study C3651009, following SC administration of ponsegromab at 200 mg Q3W through Week 12 (Day 85) in participants with cancer, cachexia and elevated serum GDF-15 concentrations, median unbound GDF-15 concentrations were suppressed from the baseline concentration of 2269 pg/mL to below the LLOQ at all visits between Day 1 and Week 15 (Day 106).

2.2.1.5. Immunogenicity

Based on the available ADA/Nab data from the Phase 1 C3651001 and C3651002 studies conducted in healthy participants (n=53), none of the 53 participants had pre-existing ADA at baseline and the overall incidence of treatment-induced ADA was 9.43% (5/53 participants). Nab was observed in 1 participant across the 2 studies. Overall, there was no apparent effect of ADA observed on the PK, PD and safety profile of ponsegromab.

In C3651009 and C3651010 studies, following SC administration of ponsegromab at 200 mg Q3W through 12 and 24 weeks, respectively, in participants with cancer, cachexia or anorexia, and elevated serum GDF-15 concentrations, the incidence of treatment-induced ADA was very low with overall incidence of treatment-induced ADA of 0 and 9.1% (1/11), respectively, and no incidence of Nab was observed in either study.

2.3. Benefit/Risk Assessment

Based on the available clinical data described in the IB, no safety concerns have been identified in the four clinical trials completed to date.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ponsegromab may be found in the IB which is the SRSD for this study.

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2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) ponsegromab		
SC injection site reactions and hypersensitivity reactions.	Although there were no injection site reactions or delayed hypersensitivity reactions observed in the completed clinical studies, as with all injectable mAbs, there is the potential for injection site reactions or delayed hypersensitivity reactions.	The following exclusion criteria is added: History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibody. Additionally, injection site reactions will be monitored, and injection sites rotated.
Use of a placebo arm.	Use of a placebo arm represents a risk of lack of benefit for those not receiving active therapy. As there are no data on efficacy yet, this risk cannot be assessed.	Participants will continue to receive standard of care throughout the study for their underlying cancer. The study has been designed with, a 3 active: 1 placebo randomization ratio, in order to increase participants' chances of receiving active therapy.
Study Procedure		
Challenges in collecting the requisite amount of blood required.	Participants may be anemic or have a concomitant condition that makes it difficult to collect requisite volume of bio-samples.	Effort to streamline bio sample collection in the SoA and reduce volume collected where feasible.
Additional CT scans.	Participants may undergo up to two additional CT scans beyond standard of care, thereby increasing exposure to radiation.	Participants will not be required to undergo additional CT scans if they had a SOC CT scan within 3 weeks prior to the Screening visit, between Weeks 10-12 or within 7 days after the Week 12 visit.
Use of ECG patches.	Mild skin reactions/irritations attributed to use of ECG patches were observed in completed studies with ponsegromab.	Sites will be reminded to clean and dry the study participant's skin before attaching the ECG electrodes; And after removing the electrodes, clean the study participant's skin with soap and water.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Sites will follow local guidelines to minimize risk of SARS-CoV-2 infection at a study facility. Non-dosing visits may be conducted by a qualified site staff member/phlebotomist at the participant's home, in order to reduce the risk of exposure at the site.

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2.3.2. Benefit Assessment

Clinical data on any potential benefit of ponsegromab in patients with cancer, cachexia, and elevated serum GDF-15 concentrations, are limited to observations from the single arm, open-label, Phase 1b C3651009 study of ponsegromab 200 mg Q3W. Mean increases from baseline in body weight were observed at all time points during the 12-week treatment period and 12-week follow-up period. In addition, median serum unbound GDF-15 concentrations were suppressed in these participants from elevated baseline concentrations to below the lower level of quantification at all visits from Day 1 through week 15, with last dose of ponsegromab 200 mg Q3W at 12 weeks (see Section 2.2.1.4). Similar suppression of serum unbound GDF-15 concentrations was observed throughout treatment with ponsegromab in patients with cancer, anorexia, and elevated serum GDF-15 concentrations enrolled in the Phase 1b C3651010 study. No safety concerns were identified in the 80 participants who received at least one dose of ponsegromab across four clinical trials completed to date.

Based upon these clinical data and nonclinical data, it is hypothesized that dosing with ponsegromab may improve participants appetite and support maintenance of body weight in participants enrolled in this study. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ponsegromab may be found in the IB, which is the SRSD for this study.

It is estimated that 50%-80%[9] of patients with advanced malignant cancer suffer with cachexia which results in worse outcomes. Therefore, the development of ponsegromab for the treatment of cachexia may satisfy an area of high unmet need.

2.3.3. Overall Benefit/Risk Conclusion

This study is designed primarily to assess efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of ponsegromab in participants with cancer who have cachexia and elevated concentrations of GDF-15.

Considering all available clinical and nonclinical data, the benefit-risk profile of ponsegromab is favorable and supports continued clinical development in patients with cancer, cachexia and elevated serum GDF-15 concentrations.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Part A

Objectives	Endpoints	Estimands
Primary	**Primary**	**Primary**
• To evaluate the effect of ponsegromab compared with placebo on body weight in participants with cancer,	• Change from baseline body weight at Week 12.	• Estimand 1 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change

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Objectives	Endpoints	Estimands
cachexia, and elevated concentrations of GDF-15.		from baseline in body weight at Week 12, in participants with cancer, cachexia and elevated concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• **Secondary**	• **Secondary**	• **Secondary**
• 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.	• 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.	• Estimand 2 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each of the physical activity and gait endpoints at Week 12, in participants with cancer, cachexia and elevated concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• To evaluate the effect of ponsegromab compared to placebo on the appetite-related symptoms as measured by FAACT in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline in FAACT sub-scale scores at Week 12: • FAACT-ACS; • FAACT-5IASS.	• Estimand 3 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each FAACT sub-scale score at Week 12, in participants with cancer, cachexia and elevated

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Objectives	Endpoints	Estimands
		concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• 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.	• Change from baseline score for the questions from the CRCSD at Week 12 related to: • Anorexia/appetite; • Nausea and vomiting; • Fatigue.	• Estimand 4 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each of the anorexia/appetite, nausea, vomiting, and fatigue questions from the CRCSD at Week 12, in participants with cancer, cachexia and elevated concentrations of GDF-15, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures, prohibited medications or participants' non-compliance with dosing.
• 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.	• Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities.*	• There are no defined estimands for the incidence of adverse events, safety laboratory tests, vital signs, and ECG abnormalities, and these endpoints will be summarized using Pfizer data standards as applicable.
• **Tertiary/Exploratory**	• **Tertiary/Exploratory**	• **Tertiary/Exploratory**
• To evaluate the effect of ponsegromab compared to	• Change from baseline in additional physical	• Not Applicable.

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Objectives	Endpoints	Estimands
placebo on physical activity and gait as measured by wearable digital sensors in participants with cancer, cachexia, and elevated concentrations of GDF-15.	activity and gait endpoints measured with remote digital sensors at Week 12.	
• To evaluate the effect of ponsegromab compared to placebo on HRQoL as measured by FAACT in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline in additional FAACT total and sub-scale scores at Week 12.	• Not Applicable.
• To evaluate PK of ponsegromab following repeated SC administration to participants with cancer cachexia and elevated concentrations of GDF-15.	• Serum unbound and total concentrations of ponsegromab on Day 1, Week 4, 5, 8, 10, 12, and 16, plus Week 9 and 11 in PK substudy only	• Not Applicable.
• To evaluate the effect of repeated SC administration of ponsegromab on circulating GDF-15 concentrations in participants with cancer cachexia, and elevated concentrations of GDF-15.	• Serum unbound and total concentrations of GDF-15 on Day 1, Week 4, 5, 8, 10, 12, and 16, plus Week 9 and 11 in PK substudy only	• Not Applicable.
• To evaluate the immunogenicity profile of ponsegromab following repeated SC administration in participants with cancer cachexia, and elevated concentrations of GDF-15.	• Incidence of ADA and NAb.	• Not Applicable.
• To evaluate the effect of ponsegromab compared to placebo on Patient-Reported Outcomes Version PROMIS-Fatigue questionnaire in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline score for PROMIS-Fatigue at Week 12.	• Not Applicable.
• To evaluate the effect of ponsegromab compared to placebo on PROMIS Physical Function-Short Form 8c in	• Change from baseline score for PROMIS-Physical Function at Week 12.	• Not Applicable.

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Objectives	Endpoints	Estimands
participants with cancer, cachexia, and elevated concentrations of GDF-15.		
• To evaluate the effect of ponsegromab compared to placebo on PGI-S and PGI-C in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline PGI-S at week 12; • PGI-C at Week 12.	• Not Applicable.
• To evaluate the effect of ponsegromab compared to placebo on tumor burden and tumor status in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Tumor status according to RECIST 1.1 guidelines using CT scan at Week 12.	• Not Applicable.
• To evaluate the effect of ponsegromab compared to placebo on body composition as measured by CT scan in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline in LSMI derived from CT scans at Week 12. • Percent change from baseline in skeletal muscle and adipose tissue measures derived from CT scans at Week 12.	• Not applicable
• To evaluate the effect of ponsegromab compared to placebo on albumin and pre-albumin levels in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline albumin and pre-albumin levels at Week 12.	• Not Applicable.
• To evaluate the effect of ponsegromab compared to placebo on survival in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Survival status at end of Part A.*	• Not Applicable.

* Safety, tolerability and survival will also be characterized in Part B once all applicable participants have completed Part B of the study. These data will be reported as part of the supplemental CSR.

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Part B

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

Objectives	Endpoints	Estimands
Tertiary/Exploratory	**Tertiary/Exploratory**	**Tertiary/Exploratory**
• To evaluate the effect of ponsegromab on body weight in participants with cancer, cachexia, and elevated concentrations of GDF-15.	• Change from baseline body weight, in Part B of the study.	• Not Applicable.
• To characterize the safety and tolerability of repeated SC administrations of ponsegromab in participants with cancer cachexia, and elevated concentrations of GDF-15, during the open-label treatment period.	• Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities, in Part B of the study.	• Not Applicable.
• To evaluate the PK of ponsegromab following repeated SC administration in participants with cancer cachexia, and elevated concentrations of GDF-15, during the open-label treatment period.	• Serum unbound and total concentrations of ponsegromab at Weeks 16, 24, 36, 48, 64, and 72 plus flexible PK timepoint in PK substudy.	• Not Applicable.
• To evaluate the effect of repeated SC administration of ponsegromab on circulating GDF-15 concentrations in participants with cancer cachexia, and elevated concentrations of GDF-15, during the open-label treatment period.	• Serum unbound and total concentrations of GDF-15 at Weeks 16, 24, 36, 48, 64, and 72, plus flexible PD timepoint in PK substudy.	• Not Applicable.
• To assess the immunogenicity of ponsegromab following repeated SC administration in participants with cancer cachexia, and elevated concentrations of GDF-15, during the open-label treatment period.	• Incidence of ADA and Nab.	• Not Applicable.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, double blind, placebo-controlled study of the efficacy, safety, and tolerability of three different doses of ponsegromab compared to matching placebo in patients with NSCLC, CRC, or PANC, receiving standard of care (which may include

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systemic therapy), who have elevated levels of GDF-15 and cachexia. The double-blind period is followed by an optional open-label extension period.

The Screening visit will occur no more than 28 days and no less than 7 days, prior to Randomization. The 7-day minimum duration between Screening and Randomization visits will ensure that the GDF-15 results are available to inform the investigator's assessment of eligibility and the 7-day collection of PRO and physical activity data. Following the Screening period to confirm eligibility, approximately 168 study participants, who meet the entry criteria, will be randomized to study intervention (one of 3 dose groups of ponsegromab or matching placebo) and will be stratified by treatment with or without platinum-based chemotherapy (see Appendix 12), which is known to induce GDF-15 and therefore may impact the response to ponsegromab treatment. The 12-week double-blind dosing period (Part A) will consist of a total of 3 doses administered Q4W SC.

A PK substudy will be conducted in approximately 36 of the approximately 168 participants (approximately 9 in each treatment group in Part A). Up to 3 additional PK and PD samples (two samples during Part A and one sample during Part B, if relevant), will be collected in these participants at timepoints during the study outlined in Sections 1.2 schema and 1.3 SoA.

On completion of Part A, participants will have the opportunity to enter an optional OLT period (Part B) consisting of ponsegromab 400 mg Q4W SC for up to 1 year. The investigator and participant must decide at the Week 8 visit if they wish to continue to the optional OLT period.

Participants opting to continue to the OLT period will receive their first dose of open-label ponsegromab 400 mg at the Week 12 visit, which is the last visit of the double-blind portion. Upon completion of the OLT period, there will be a follow-up visit (Week 72) which is to occur 56 to 63 days post last dose of study intervention.

Participants who do not proceed with the optional OLT period are to complete the Week 12 visit and a follow-up visit at Week 16.

Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

The optional OLT period will continue as currently planned, unless the following factors develop in which case the open-label extension may be modified:

- Upon completion of the double-blind portion, the final analysis shows a lack of efficacy for the primary endpoint and/or inadequate safety and tolerability;
- An alternative method of study intervention delivery become available;
- A lower dose of ponsegromab is shown to be efficacious;

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- The sponsor decides to terminate the study/clinical development program.

- Participants may withdraw from the optional OLT period at any time, for reasons such as the following:
  - The study participant withdraws consent or dies;
  - The study participant experiences an AE attributable to study intervention.
  - A change in study participant's medical condition that, in the investigator's judgment, makes it inappropriate to continue study participation.

An independent oversight committee in the form of an IRC will monitor the safety, efficacy, and tolerability of the study participants and the study conduct. There will also be an Executive Steering Committee and an Operation Steering Committee.

Study design aspects have been informed by feedback obtained during the conduct of the ponsegromab Phase 1b studies to enhance recruitment, reduce participant dropout and reduce the likelihood of missing data.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the efficacy, safety, and tolerability of ponsegromab, an inhibitor of GDF-15, compared to placebo, in patients with cancer, cachexia, and elevated concentrations of GDF-15.

Elevated concentrations of circulating GDF-15 have been reported in literature[5,6,7] in patients experiencing weight loss with a variety of tumor types and a greater magnitude of elevation was associated with worse survival. Biospecimens from healthy adults[10] (n=739) 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. Analysis of both the cancer and healthy sample sets using the Roche Elecsys assay,[10] confirmed literature reported elevations in GDF-15 concentrations in NSCLC, PANC, and CRC 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 GDF-15 inclusion criteria for this study to be the 95th percentile of GDF-15 concentrations reported in these healthy subjects (≥1.5 ng/mL).

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[8] model data 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.

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Therefore, it is hypothesized that cachexia in many types of cancer, including NSCLC, PANC and CRC, 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. Therefore, randomization will be stratified by presence/absence of background platinum therapy due to this association of platinum and GDF-15 levels.

The primary endpoint is the change in body weight from baseline. The study will also assess secondary and exploratory endpoints including physical activity, safety, fatigue, appetite, immunogenicity, PK and PD.

Patient safety will be monitored primarily via clinical laboratory tests, vital signs, ECG and adverse event monitoring. To supplement the standard clinical safety laboratory tests assessed at this stage of development, albumin and pre-albumin will be included as measures of nutritional status. Additionally, CT scans will be performed for evaluation of tumor burden by the investigator and measurement of the skeletal muscle area and adipose tissue area at the 3rd lumbar vertebral level by a central imaging laboratory.

Assessment of the impact of ponsegromab on other aspects of cachexia, such as anorexia, nausea, vomiting and fatigue, will be studied. These will be measured through the use of ePRO instruments administered to patients at home and during clinic visits.

Another characteristic of cachexia is a decline in performance status with impairment in the patients' ability to carry out desired activities. Assessment of the potential impact of ponsegromab on activity measures (eg, gait speed, activity time) via wearable digital sensors will be included in this study to better understand the effects of PF-06946860 on patients' physical function.

Sparse unbound and total ponsegromab and GDF-15 concentrations will be measured in this study to (1) characterize ponsegromab PK in this population; (2) assess the range of baseline GDF-15 values and variability in this population; (3) characterize the dose/exposure-GDF-15 response after ponsegromab treatment in this population, and (4) evaluate GDF-15 suppression effect on body weight response. Participants enrolled in the PK substudy will have additional PK and PD assessments to enhance PK/PD characterization. As ponsegromab is a monoclonal antibody, immunogenicity samples will be collected for the determination of ADA and NAb.

4.2.1. Patient Input Into Design

Previously patients and caregivers were interviewed in order to better understand what symptoms are most burdensome to patients and what might impact their decision to participate in a clinical study. All patients had cancer (prostate, non-small cell lung,

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colorectal or pancreatic cancer) and had experienced significant unintentional weight loss and other symptoms of cachexia.

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

- Decision to maintain a dosing frequency that aligns with SOC treatment visits.
- Option for home/tele-visits with physician or in-person physician appointments where feasible.
- Confirmed the importance to patients of including the option to receive open-label treatment following double-blind period.
- Patients emphasized the significance of having their overall experiences with the study treatment heard by the Sponsor. This led to the incorporation of phone interviews in order to facilitate a more holistic assessment.
- Highlighted the value of appropriate training, including to home HCPs, on important aspects of the disease and the potential social and psychological impact.

4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants that are representative of the patient population that will be treated with ponsegromab in clinical practice. The team will follow best practices for diverse study population enrollment and retention. The following strategies may be explored in support of diverse recruitment efforts:

- Inclusion of diversity questions into the Feasibility Survey and Pre-Trial Assessment to identify sites with access to diverse patient populations.
- Discussion with investigator sites ahead of selection to assess preparedness, mitigation strategies for reaching diversity goals, and active inclusion.
- Encouragement of investigator sites to complete the Investigator Site Recruitment Plan.
- Provide investigator sites with site kit materials designed for use with diverse patient populations.
- Implement as needed targeted digital outreach to diverse patient groups.
- Have proactive discussions with investigator sites throughout the enrollment period to assess and reevaluate site specific strategies as needed to best position each site for the most diverse representation enrollment outcomes.

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- Monitor diverse enrollment to identify potential opportunities to include diverse populations.

4.2.3. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of ponsegromab have not been conducted. However, based upon the calculated safety margins, no contraception methods are required for male participants, and the use of a highly effective method of contraception is required for female participants (see Appendix 4).

4.2.4. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

In the part A of this study, ponsegromab will be administered with 100, 200, or 400 mg Q4W SC for a total of 3 doses. The proposed doses were determined based on all relevant information obtained from nonclinical safety studies and clinical data (including safety, tolerability, PK and PD) available. These clinical data included data from 2 completed studies in healthy participants (C3651001 and C3651002, see IB), clinical data (including safety, tolerability, PK, and PD) from the phase 1b study in cancer cachexia patients (C3651009), and the expected duration of GDF-15 suppression, defined as the time it suppress GDF-15 to below the median observed in healthy subjects (0.71 ng/mL).

The median baseline GDF-15 in NSCLC, PANC, and CRC patients are expected to be approximately 3.02, 3.32, and 3.50 ng/mL, respectively, and the 95th percentile are expected to be 8.69, 9.35, and 13.4 ng/mL, respectively. It is assumed that the composition of the cancer types will be similar to that observed in study C3651009, which is 4:4:3 for NSCLC, CRC, and PANC, respectively. Based on preliminary population PK/PD simulations, the proposed 100 mg Q4W SC dose is expected to suppress the unbound GDF-15 concentration in ~64%, and ~28% of the assumed cancer cachexia patients for 2, and 4 weeks, respectively. The proposed 200 mg Q4W SC dose is expected to suppress the unbound GDF-15 concentration in ~92%, and ~72% of the cancer cachexia patients for 2, and 4 weeks, respectively. The proposed high dose of 400 mg Q4W SC dose is expected to suppress the unbound GDF-15 concentration in >90% of the cancer cachexia patients for 4 weeks.

Based on these preliminary PK/PD simulations, the predicted steady state total ponsegromab C_{max}, AUC_{tau}, and C_{avg}, following 100, 200, and 400 mg Q4W SC doses, along with the corresponding safety margins calculated using exposure data from the 6-month toxicology study in monkeys (See IB), and exposure multiples calculated using total exposure data following a single 300 mg SC dose to healthy participants in study C3651001 are summarized in Table 3. The corresponding steady state unbound ponsegromab exposures and exposure multiples calculated using unbound exposure data from study C3651001, are summarized in Table 4.

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Table 3. Summary of Predicted Steady State Total ponsegromab Exposures and Associated Safety Margins and Exposure Multiples Following Q4W SC Doses

Dose (mg, Q4W SC)	C_{max} (µg/mL)	AUC_{tau} (µg•day/mL)	C_{avg} (µg/mL)	Safety Margin[a]		Exposure Multiple[b]	
				C_{max}	C_{avg}	C_{max}	AUC_{tau}
100	16.4	413	14.8	57	53	0.85	0.54
200	29.5	739	26.4	32	30	1.5	0.96
400	52.8	1302	46.5	18	17	2.7	1.7

a. Based on the predicted steady state total C_{max} and C_{avg} following Q4W SC doses of ponsegromab at 100, 200, and 400 mg relative to the NOAEL total C_{max} (934 µg /mL) and C_{avg} (786 µg /mL) observed in the 6-month toxicology study in monkey (IB).

b. Based on the predicted steady state total C_{max} and AUC_{tau} following Q4W SC doses of ponsegromab at 100, 200, and 400 mg relative to the total C_{max} (19.2 µg /mL), and AUC_{inf} (766 µg•day /mL) observed following the 300 mg single SC dose from C3651001.

Table 4. Summary of Predicted Steady State Unbound ponsegromab Exposures and Associated Exposure Multiples Following Q4W SC Doses

Dose (mg, Q4W SC)	C_{max} (µg/mL)	AUC_{tau} (µg•day/mL)	C_{avg} (µg/mL)	Exposure Multiple[a]	
				C_{max}	AUC_{tau}
100	3.14	51.9	1.85	0.15	0.08
200	11.5	238	8.50	0.55	0.38
400	32.1	726	25.9	1.5	1.1

a. Based on the predicted steady state unbound C_{max} and AUC_{tau} following Q4W SC doses of ponsegromab at 100, 200, and 400 mg relative to the unbound C_{max} (20.9 µg /mL)and AUC_{inf} (632 µg•day /mL) observed following the 300 mg single dose from study C3651001.

Given the safety margins, the observed safety data in healthy participants from studies C3651001 and C3651002, with up to ponsegromab 300 mg SC single doses, and the observed safety data in participants with cancer, cachexia or anorexia, and elevated serum GDF-15 concentrations from studies C3651009 and C3651010, with repeated doses of ponsegromab 200 mg SC Q3W, the proposed 100, 200, and 400 mg Q4W SC doses are expected to have an acceptable safety and tolerability profile.

Upon completion of Part A, participants will have the opportunity to enter an optional open-label treatment period (Part B) and receive the high dose of 400 mg Q4W SC as a no-regret approach until a lower efficacious dose is identified either at the interim analysis or the end of Part A.

4.4. End of Study Definition

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

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A participant is considered to have completed the study if they have either completed Part A (including follow-up), or has completed Part A and has entered, and completed, the OLT extension Part B, as described in the SoA.

The PCD is the date of the last visit for Part A (Week 12,) for the last participant.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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. Participants aged ≥18 years (or the minimum age of consent if >18 in accordance with local regulations) at Screening who have signed informed consent.

    a. A female participant is eligible to participate if she is not pregnant or breastfeeding.

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

Disease Characteristics:

2. Documented histologic or cytologic active diagnosis of NSCLC, PANC, or CRC and are currently receiving, or have completed, SOC treatment for this cancer (which may include systemic therapy).

3. Cachexia defined by Fearon criteria of weight loss as (See Section 8.1.1 for details if the participant's body weight is unavailable from medical record):

    - BMI <20 kg/m^2 with involuntary weight loss of >2% within 6 months prior to Screening;

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or

- involuntary weight loss of >5% within 6 months prior to screening irrespective of BMI.

4. Serum GDF-15 concentrations of ≥1.5 ng/mL (as measured using the Investigational Use Only Roche Elecsys GDF 15 assay)[10] at Screening.

5. Participants who are assessed by the investigator to have:

   - an ECOG PS ≤3, and,

   - a life expectancy of at least 4 months to be able to complete Part A.

Other Inclusion Criteria:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

   - NCI CTCAE Grade 3 or 4 oral mucositis;

   - NCI CTCAE Grade 3 or 4 GI disorders (nausea, vomiting, diarrhea, and constipation);

   - Mechanical obstructions interfering with the participant's ability to eat.

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

3. Cachexia caused by other reasons, as determined by the investigator, including, but not limited to:

   - Severe COPD requiring use of home O2;

   - NYHA class III-IV heart failure;

   - AIDS.

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4. Undergoing major surgery (central venous access placement and tumor biopsies are not considered major surgery) within 4 weeks prior to randomization. Patient must have recovered from acute effects of surgery prior to Screening. Patient should not have plans to undergo major surgical procedures during the study.

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

6. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibody.

Prior/Concurrent Therapy:

7. Current use of any prohibited concomitant medication(s) within 4 weeks prior to first dose of study intervention. Refer to Section 6.9.

Prior/Concurrent Clinical Study Experience:

8. Concurrent administration of investigational products (including drug, biologic agents, or vaccines) are not permitted within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) of the first dose of study intervention. Refer to Section 6.9 .

9. Enrollment and previously dosed in a prior study with ponsegromab.

Diagnostic Assessments:

10. History of severe liver disease or cirrhosis, unrelated to metastatic cancer. Potential study participants with the following liver function test abnormalities will also be excluded; result may be confirmed by a single repeat test, if necessary:

    - Total bilirubin ≥1.5 × ULN (except for Gilbert's syndrome)
    - AST >3 × ULN (AST > 5X ULN if there is liver involvement by the tumor)
    - ALT >3 × ULN (ALT >5X ULN if there is liver involvement by the tumor)
    - Alkaline phosphatase >3 x ULN (Alkaline phosphatase >5X ULN if there is liver involvement by the tumor and/or in case of bone metastases, or if considered related to prior surgery e.g. pancreaticoduodenectomy).

11. Renal disease requiring dialysis.

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Other Exclusion Criteria:

12. Current adherence to a calorie-restricted diet with the intention weight loss.

13. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, 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 enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who qualify for this study but are not randomized for administrative reasons, may be rescreened. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened **once with sponsor notification** if, in the judgement of the investigator, the reason for initial ineligibility is considered to be resolved, or there has been a change in eligibility status.

For individuals who are rescreened for any reason, all screening procedures must be repeated, unless discussed with, and agreed by, the Sponsor in advance, and the participant assigned a new SSID.

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6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational interventions, marketed products, placebo and medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to ponsegromab (PF-06946860, IMP) and placebo (IMP).

6.1. Study Intervention(s) Administered

Intervention Name	ponsegromab **(PF-06946860)**	placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	ponsegromab Double-Blind Treatment	placebo Double-Blind Treatment
Type	biologic	placebo
Unit Dose Strength(s)	100 mg/mL	placebo
Dosage Level(s)	100 mg, 200 mg, and 400 mg Q4W	Matching placebo Q4W
Route of Administration	SC	SC
Use	experimental	experimental
IMP or NIMP/AxMP	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)	ponsegromab	placebo

6.1.1. Administration

Each dose of investigational product must be administered by appropriately qualified health care personnel in a clinic setting. During the double blind portion (Part A) of the study, investigational product will be administered at a dose of 100 mg, 200 mg, 400 mg, or matching placebo Q4W SC for a total of 3 doses. On completion of Part A, participants will have the opportunity to enter an optional OLT period (Part B) consisting of ponsegromab 400 mg Q4W SC for up to 1 year. For participants who are receiving standard of care (which may include systemic therapy), premedication is permitted consistent with institutional guidelines, and, may include an antihistamine, anti-inflammatory agent, or pain reliever. In such cases, ponsegromab is to be administered first, followed by any required

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premedications. If the standard of care systemic antineoplastic treatment is to be administered on the same day of dosing with study intervention (ponsegromab or matching placebo in Part A or ponsegromab in Part B), where feasible, the study intervention will be administered prior to the standard of care treatment.

Study intervention will be administered in a divided dose requiring 2 separate SC injections given in rapid succession every 4 weeks. The permitted injection sites are the abdomen, upper arm (right or left) and the thigh (right or left). The following combination of injection sites are provided as examples:

- Two injections in abdomen (each injection should be administered into a different quadrant and separated by at least 3 cm)
- One injection into each upper arm
- One injection into each thigh
- One injection in the arm (right or left) and one injection in the leg (right or left) or
- One injection in arm or leg (left or right) and one in the abdomen.

The injections can be rotated with each administration for participant comfort. If participants are receiving other, non-study intervention injectable agents, those interventions should be administered in a quadrant different from where the study intervention was administered. Additionally, areas with scarring, redness, tattoos, or other visible marks should be avoided.

Refer to the IP manual for additional details regarding the preparation, injection site administration, handling, storage and accountability.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

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

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

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

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

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention 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. A second staff member will verify the dispensing.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using a central randomization list. Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and

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DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

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

6.4. Blinding

This is a double-blind study with blinding of ponsegromab versus placebo for each dose level.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

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

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention.

6.4.4. Breaking the Blind

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

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

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6.5. Study Intervention Compliance

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

Deviation(s) from the protocol-specified dosage regimen should be recorded in the CRF. In exceptional circumstances and with agreement from the Sponsor, the study intervention may be administered outside of the window for a given dosing visit; in such circumstances, the rationale should be recorded in the CRF.

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

6.6. Dose Modification

There is no dose modification of study intervention anticipated for a given participant in this study.

6.7. Continued Access to Study Intervention After the End of the Study

The study design includes an optional open-label treatment period for up to 1 year (Part B) as described in Section 4.1. An expanded access program may be available after the open label treatment period.

6.8. Treatment of Overdose

Given the allowed visit window, an overdose will be defined as more than 2 doses of ponsegromab 400 mg administered in a period of 4 weeks, eg, any dose of ponsegromab greater than 900 mg within a 4-week period will be considered an overdose.

There is no specific treatment for an overdose.

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate for at least 5 half-lives or 28 calendar days after the overdose of ponsegromab (whichever is longer). The duration of monitoring required will be provided by the sponsor.

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

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

5. Obtain a blood sample for PK analysis within 5-7 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

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

6.9. Prior and Concomitant Therapy

Details on all concomitant treatment (including antitumor treatments and steroid usage) will be determined from participant and/or medical records, at each visit from Screening until the end of study visit and will be recorded on the CRF. Investigators should specify reasons for modifications to or discontinuations of prescribed antitumor treatments. At the Screening visit and each clinic visit, details of previous and current treatment with a platinum-based therapy will be determined from participant and/or medical records. The information will be recorded on the CRF at each visit. Specifically at the Screening visit, current treatment with or without platinum-based chemotherapy will be utilized for stratification of study participants who meet the entry criteria at the Randomization visit. (see Appendix 12)

6.9.1. Prohibited During the Study

- Initiation of new treatment with systemic glucocorticoids within the 4 weeks prior to the first dose of study intervention through Week 16; Stable (ie, no significant change to dosage or frequency of administration in prior 4 weeks) steroid therapy eg, dexamethasone as part of pre-medication or daily oral prednisone is permissible. Initiation of steroid therapy following randomization (eg, for management of immune-related AEs that occur as a consequence of immunotherapy) may be permitted following discussion with Sponsor

- Concurrent administration of anamorelin hydrochloride is not permitted within 30 days prior to first dose of study intervention through Week 16.

- Concurrent administration of megestrol acetate, olanzapine, cannabinoids, or mirtazapine, if prescribed for purpose of increasing appetite/body weight, are not permitted within 30 days prior to first dose of study intervention through Week 16. Use of these medications on a short-term, as required basis, for management of symptoms (eg, chemotherapy-induced nausea and vomiting) is permitted.

- Concurrent administration of a GLP-1 receptor agonist-based therapy (eg, semaglutide, liraglutide, tirzepatide), if prescribed specifically to promote weight

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loss, is not permitted within 30 days prior to first dose of study intervention through Week 16. Use of such therapies for indication of diabetes mellitus is permitted.

- Investigational products (including drug, biologic agents, or vaccines) are not permitted within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) of the first dose of study intervention through the duration of the study (including both Part A and B).

6.9.2. Permitted During the Study

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

- All standard of care (which may include systemic therapy) including required premedications (see Section 6.1.1).

- Background biologics are permitted as indicated by the label (not contra-indicated for combination with an investigational mAb).

Participants in this study will be allowed to be on concomitant medications that have been prescribed according to their label and monitored as per local standard of care.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention may include the following:

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

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

- If a participant experiences Grade 3 AEs judged by the Investigator as related to randomized study intervention, the study intervention will be temporarily discontinued until the treatment-related AEs return to Grade 2 (or less). If the treatment-related AEs return to Grade 2 (or less) or resolve within 4 weeks, continuation of dosing with study intervention may be considered. If these AEs do not return to Grade 2 (or less) within 4 weeks, and after discussion with the sponsor, the participant will be permanently discontinued from the study intervention.

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- If a participant experiences Grade 4 AEs judged by the Investigator as related to randomized study intervention, the participant will be permanently discontinued from the study intervention.
- Severe allergic reaction to study intervention.
- Intent to become pregnant or pregnancy confirmed by b-hCG testing.
- Drug-induced liver injury as described in Section 10.6, Appendix 6.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for follow up. All cases of planned or potential discontinuation of study intervention should be discussed with Sponsor before classifying a subject as 'Discontinued from Study Intervention' and completing an Early Termination visit. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

Participants will undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related AEs through approximately 56 days following discontinuation of study intervention. Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If the unresolved AE is considered by the investigator as possibly related to or associated with ADA formation, the participant will be asked to return for drug concentration and ADA blood sampling at up to 3-month intervals, until the last follow-up of the AE.

7.1.1. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) 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.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

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7.2. Participant Discontinuation/Withdrawal From the Study

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

- Participant 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.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

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

7.2.1. Withdrawal of Consent

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

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7.3. Lost to Follow-Up

To prevent participants being lost to follow-up, their contact details, including next of kin contacts should be collected initially, if permitted, and updated regularly by the site staff or representative. The Investigator should educate the participant on the importance of contact with the Investigator throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for participants who are potentially lost to follow up.

If a participant fails to return to the clinic for/attend a required study visitthe site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.

Where permissible by local regulations, the ICD will include language to grant the option to employ patient locator agencies to assist in obtaining updated contact information or ascertainment of vital status of lost participants using publicly available source.

A participant will be classified as lost to follow up only if they have failed to return for the required study visits and their visit status remains unknown despite multiple attempts to contact them via telephone, fax, email, certified letter or through patient locator agencies (if allowed by local regulations). These contact attempts should be documented in the participant's medical record. The participant will then be considered lost to follow-up and discontinuation of study will be documented in source data and CRF as the date of last contact.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and

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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 they have 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.

Safety/laboratory/analyte results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 each part of the study is estimated as follows for individual participants:

- Part A, where participants are not enrolled in the PK substudy = 145 mL
- Part A, where participants are enrolled in the PK substudy = 165 mL
- Optional Part B, where participants are not enrolled in the PK substudy = 125 mL
- Optional Part B. where participants are enrolled in the PK substudy = 135 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 56 consecutive days. In addition, if a participant has an unplanned site visit for any reason (chemotherapy, radiology, other doctor appointments, etc.), collect an unplanned PK and GDF-15 sample during this visit, if feasible, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Screening Visit

The Screening visit will occur no more than 28 days and no less than 7 days, prior to Randomization. The 7-day minimum duration between Screening and Randomization visits will ensure that the GDF-15 results and the 7-day collection of PRO and physical activity data are available to inform the investigator's assessment of eligibility.

At the Screening visit only, the evaluation of the Fearon Criteria eligibility criteria is to be assessed using the participant's body weight from their medical record. If the participant's body weight is unavailable from medical record, the participant's weight is to be captured utilizing question 1 of the PG-SGA questionnaire.[11]

8.1.2. Week 5 Visit

The Week 5 visit is considered an optional visit to collect PK and GDF-15 samples as well as measurement of weight and SAE/AE monitoring based upon participant availability. It will not be considered a protocol deviation if the participant is unable to make this visit.

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8.1.3. Additional Visits for PK Substudy

Participants enrolled in the PK substudy will have an additional visit, as per SoA, at Week 9 and Week 11 in Part A, and one flexible visit in Part B that can occur 1, 2 or 3 weeks following any dose after or including the Week 20 dose. The purpose of these additional PK visits is to obtain blood samples for PK and PD assessment. These visits may be performed at the participant's home rather than at the study site if feasible and permitted by country, study site, and participant.

8.1.4. Home Health Visits

A home health care service/phlebotomist may be utilized to facilitate the Week 5, Week 9 (PK substudy only), Week 10, and Week 11 (PK substudy only) visits. 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 (see the SoA):

- PK and PD sample collection.

Note: Body weight does not need to be obtained if the visit is conducted offsite.

8.1.5. Transportation

Transportation to and from the study site may be provided for study participants for Part A visits, as permitted by the country, study site and participant.

8.2. Efficacy Assessments

8.2.1. Body Weight

Body weight will be measured in duplicate as indicated in the SoA. The second weight measurement should be obtained at least 1-2 minutes apart from the first measurement. Weight will be recorded using a calibrated scale (with the same scale used if possible for the duration of the study) reporting weight in kg, and accuracy to the nearest 0.1 kg; ie, the device must be able to distinguish a difference between 68.4 kg versus 68.3 kg. The scale must be placed on a stable, flat surface. Body weight does not need to be obtained if the visit is conducted offsite.

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

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

8.2.2. Patient Reported Outcomes

Patient Reported Outcome (PRO) Measure	Frequency	Completion location	Number of Questions	Completion Time
FAACT	Baseline, Week 4, Week 8, Week 12 or ED Part A	At clinic	39	~15 minutes
PGI-S of appetite, fatigue, and physical function	Baseline, Week 4, Week 8, Week 12 or ED Part A	At clinic	3	
PGI-C of appetite, fatigue, and physical function	Week 4, Week 8, Week 12 or ED Part A	At clinic	3	
PROMIS-Fatigue 7a ("Past 7 days" recall version)	Baseline, Week 4, Week 8, Week 12 or ED Part A	At clinic	7	
PROMIS-Physical Function 8c (no recall version)	Baseline, Week 4, Week 8, Week 12 or ED Part A	At clinic	8	
Cancer-Related Cachexia Symptom Diary 2.0 (appetite, fatigue, nausea, and vomiting)	Daily including the Screening period (minimum of 7 consecutive days) to Week 12 or ED Part A	At home	4	~2 minutes
Qualitative Exit Interview	Week 12 or ED Part A	Via phone	N/A	Up to 60 minutes
PGI-S of physical activity and walking	At the end of the 7-day consecutive monitoring period/wearing the digital sensors for Screening (at home), Week 8 (approximately Day 63 at home), Week 10 (approximately Day 77 at home), at Week 12 (approximately Day 85 at the clinic) or ED Part A	At home/in clinic	2	~2 minutes
PGI-C of physical activity and walking	At the end of the 7-day consecutive monitoring period for Week 8 (approximately Day 63 at home), Week 10 (approximately Day 77 at home) and at Week 12 (approximately Day 85 at the clinic), or ED Part A	At home/in clinic	2	~2 minutes

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All PRO assessments, with the exception of the Exit Qualitative Interview, are implemented using a sponsor-provided ePRO device and completed by study participants at home (handheld device), or at the clinic (tablet), as per the SoA.

Every effort should be made to have the study participant complete all PRO assessments as per the SoA. Site-based PRO assessments should be completed by the participant at the beginning of the visit before any medical procedures or interactions with the medical staff (as much as practically possible) take place.

Additional details are provided in the ePRO/eCOA User Manual

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

The FAACT combines the FACT-G core instrument and 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 FAACT. Higher scores are associated with a higher health-related quality of life. For additional details regarding scoring refer to FACIT User's Manual.

8.2.2.2. Patient's Global Impression of Severity (PGI-S) of Appetite, Fatigue, and Physical Function

The PGI-S consists of 3 questions that ask the study participants to evaluate the severity of their appetite loss, fatigue, and physical function over the past 7 days, on a 5-point verbal response scale that ranges from "None" to "Very severe".

The PGI-S 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.

8.2.2.3. Patient's Global Impression of Change (PGI-C) of Appetite, Fatigue, and Physical Function

The PGI-C consists of 3 questions that ask the study participants to rate the overall change in their level of appetite, fatigue, and physical function since they started taking the study intervention on a 5-point verbal rating scale 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.

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8.2.2.4. PROMIS – Fatigue (version 7a)

The PROMIS Fatigue 7a 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.

8.2.2.5. PROMIS – Physical Function (version 8c)

The PROMIS Physical Function short form 8C 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.

8.2.2.6. Cancer-Related Cachexia Symptom Diary 2.0

The CRCSD is a daily, self-reported questionnaire that measures severity of symptoms related to cancer cachexia: appetite, nausea, vomiting, and fatigue. It was developed based on qualitative research with patients as well as review of literature and other existing relevant measures. The measure consists of 4 questions that ask study participants to rate the severity of their symptoms over the past 24 hours on an 11 point NRS.

8.2.2.7. Qualitative Exit Interviews

Qualitative exit interviews with a selected group of English-speaking participants (up to 40) at selected sites will be conducted by telephone at the end of Part A, as indicated in the SoA. The interviews will be conducted by trained moderators, that are not part of study site staff, will be audio recorded and transcribed, and are anticipated to be approximately 60 minutes in duration.

The transcripts and interviewer field notes will be used to examine changes in symptoms and impacts experienced over the period of study duration, to describe treatment experience, and the importance of any improvement reported by the study participants. Following the analysis of the qualitative data, a summary report that describes the study objectives, methods, participants, and results of the qualitative interviews will be reported separately from the CSR.

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8.2.2.8. Patient's Global Impression of Severity (PGI-S) of Physical Activity and Walking

The PGI-S of physical activity and walking consists of 2 questions that ask the study participants to evaluate the severity of limitations of physical activity and walking over the past 7 days, on a 5-point verbal response scale that ranges from "None" to "Very severe". **The PGI-S is to be administered at the end of the 7-day monitoring period** for Screening (+1) (at home), Week 8 (approximately Day 63 +1 at home), Week 10 (approximately Day 77 +1 at home), and at the Week 12 visit (approximately Day 85 at the clinic).

8.2.2.9. Patient's Global Impression of Change (PGI-C) of Physical Activity and Walking

The PGI-C of physical activity and walking consists of 2 questions that ask the study participants to rate the overall change in their level of physical activity and walking since they started taking the study intervention on a 5-point verbal rating scale that ranges from "Much better" to "Much worse". **The PGI-C is to be administered at the end of the 7-day monitoring period** for Week 8 (approximately Day 63 +1 at home), Week 10 (approximately Day 77 +1 at home) and at the Week 12 visit (approximately Day 85 at the clinic).

8.2.3. Physical Activity

Monitoring of physical activity and gait via accelerometry (wearable digital sensors) will be conducted in participants during the following 3 periods: Screening (with a target of at least 1 consecutive week of monitoring prior to first dose of IP), Week 8 (from Week 8 to Week 9) and from Week 10 to Week 12. The digital sensors will be worn continuously for one week during Screening and Week 8; and will be worn continuously for two weeks between Week 10 and Week 12.

Placement of the sensors: one sensor will be placed on the lumbar region and one sensor will be placed on the non-dominant wrist. Participants will be asked to wear the sensor on the wrist continuously (approximately 24/day; can remove for short periods of time as needed). the sensor worn on the lumbar only needs to be worn while awake during the monitoring periods.

The participant is able to remove the activity monitors for charging or other activities without it being considered a protocol deviation. Please refer to the activity monitoring manual for detailed instructions.

8.2.3.1. Comfort and Wearability Questionnaire for Digital Measures

To measure comfort and wearability of the wearable digital sensors, the participant will be asked to complete a Comfort and Wearability Questionnaire at Week 12 or at Early discontinuation visit. Data will be captured on the CRF. See Appendix 9.

The Digital Sensors technical training guide will be provided separately.

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8.3. Safety Assessments

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

Although not observed so far with ponsegromab, injection site reactions and delayed hypersensitivity reactions are theoretically possible in response to injected monoclonal antibodies. Participants should be monitored after receiving injections for clinical signs of systemic immune reactions, and any such reactions assessed and reported as part of standard safety/AE monitoring, including adverse events that are manifestations of injection site reactions. Additional assessments may be conducted at investigator discretion and/or until any symptoms resolve. 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. As part of the safety analysis, any cases of potential anaphylaxis will be assessed by the sponsor against the Sampson criteria.[12]

8.3.1. 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. Height and weight will also be measured and recorded. Height will be measured at Screening only, in cm and accuracy to the nearest 0.1 cm. Body weight will be measured in duplicate at each visit, in kg, and accuracy to the nearest 0.1 kg. Please refer to Section 8.2.1 for additional details regarding collection of body weight.

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

Physical examinations (full and abbreviated) will be conducted as detailed in the SoA, however full exams may be performed for findings during previous exam, new/open AEs, or at investigator discretion.

All physical exams (full and abbreviated) will include an assessment for ascites and/or edema. In addition, ascites and/or edema will be captured as an AE on the AE CRF.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the

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definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

The assessment of ECOG performance status may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. See Appendix 10.

8.3.3. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Single BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a supine position, in a quiet setting without distractions (eg, television, cell phones) and the results recorded in the CRF.

Vital signs will be taken before collection for laboratory tests, if feasible, but it would not be considered a protocol deviation if collected after laboratory tests. .

8.3.4. Electrocardiograms

A single standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. At all visits, a single standard 12-lead ECG will be collected.

If the site does not have an ECG machine that performs automated calculations, the investigator is permitted to calculate the standard intervals.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.5. Clinical Safety Laboratory Assessments

All laboratory samples are to be sent to the central lab.

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

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The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or within 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 study medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.6. Pregnancy Testing

A serum pregnancy test is only required at Screening and will be sent to the central lab. Following Screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. For urine samples collected after the screening visit, the urine sample should be tested at the site facility and results are to be confirmed negative and recorded in the database. Pregnancy test results must be reviewed and confirmed as negative in order to continue dosing with study intervention.

8.3.7. Imaging Assessment-CT Scan

8.3.7.1. Imaging Safety Assessment

CT scans will be acquired during the study to monitor the tumor burden. All CT scans will need to include chest, abdomen, and pelvis to be acceptable for this study.

If SOC CT scan with chest, abdomen, and pelvis was performed within 3 weeks prior to the Screening the visit, then a CT scan at Screening is not needed. If a SOC CT scan is being performed at the Week 12 visit, between Weeks 10-12 or within 7 days after the Week 12

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visit as part of SOC, then an additional CT scan is not needed. Similarly, if SOC CT scan is performed 2 weeks prior or 7 days after the ED visit, then an additional CT scan is not needed.

Monitoring of the tumor burden will be performed by the site following standard RECIST 1.1 criteria (outlined in Appendix 11). The RECIST 1.1 categorization is to be entered in the CRF after each scan.

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.

8.3.7.2. Imaging Efficacy Assessment

CT scans are to include the chest, abdomen and pelvis. All CT scans will be collected for the RECIST assessment by the study site. The CT scans will then need to be submitted to a central imaging vendor for the measurement of body composition. The central imaging assessments will be performed solely for the analysis of the skeletal muscle area and adipose tissue areas at the 3rd lumbar vertebral level. Additional exploratory body composition measurements may be performed, but may not be reported in the CSR. The analyses from the central review of the CT scans for body composition will not be shared with the site or study participant. The central imaging laboratory will not be performing a clinical assessment of the images and no incidental findings will be shared with the principal investigator, site staff or participant. All medical reviews of CT scan images will be the sole responsibility of the site staff.

Instructions for central image upload will be provided in a separate manual. In addition to submitting all CT scans to a central repository, sites will still be required to save all participants' radiologic images for source verification and for potential questions.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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

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During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of the time of the final planned follow-up visit, except as indicated below, after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

If a participant permanently 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 information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

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8.4.1.2. 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 8.4.1, 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward 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

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sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

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

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

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

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should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose (ie, at least 8 weeks).

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

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

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure 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 about the occupational exposure 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 must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

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8.4.8. Adverse Events of Special Interest

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 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.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL serum, will be collected for measurement of serum unbound and total concentrations of ponsegromab as specified in the SoA. The PK sample collection at the Week 5 visit is considered an optional sample and it will not be considered a protocol deviation if the participant is unable to make this visit. In addition, if a participant has an unplanned site visit for any reason, (chemotherapy, radiology, other doctor appointments, etc), a PK sample may be collected, if feasible, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

The actual times may change, but the number of samples will remain the same. Collection of samples within the protocol-allowed visit window, as defined in SoA or noted above will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of ponsegromab. Samples collected for analyses of ponsegromab serum concentrations 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 the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of serum concentrations of ponsegromab (unbound and total) will be analyzed using a validated analytical method(s) in compliance with applicable SOPs.

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

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

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

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If the sample is unable to be collected during F/U part A and F/U part B, it will not be considered a protocol deviation.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

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

Retained Research Samples may be used for research related to the study intervention(s) and cancer cachexia. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained 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.

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study, see Section 8.7.6.

8.7.1. GDF-15

Blood samples of approximately 6 mL, to provide a minimum of 2 mL serum, will be collected for measurement of serum concentrations of total and unbound GDF-15 at time points specified in the SoA. The GDF-15 sample collection at the Week 5 visit is considered an optional sample. It will not be considered a protocol deviation if the participant is unable to make this visit. In addition, if a participant has an unplanned site visit for any reason, (chemotherapy, radiology, other doctor appointments, etc.), a GDF-15 sample may be collected, if feasible, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

At the Screening visit, two GDF-15 samples will be collected (6-mL for each). One GDF-15 (Roche) sample will be analyzed using the IUO Roche Elecsys GDF-15 assay, for determination of enrollment eligibility. In addition, this sample may be used to help support development of a potential companion diagnostic test for ponsegromab. This screening assay will be validated in a CLIA accredited central laboratory. The second Screening GDF-15 (Pfizer) sample, as well as the GDF-15 samples collected at the other time points specified in the SoA, will be analyzed for unbound and total GDF-15 using validated Pfizer assays in compliance with applicable SOPs.

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.

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The actual times may change, but the number of samples will remain the same. Collection of samples within the protocol-allowed visit window, as defined in the SoA or above will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

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

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

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

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

If the sample is unable to be collected during F/U part A and F/U part B, it will not be considered a protocol deviation.

8.7.2. Circulating Biomarkers

Albumin and pre-albumin will be assessed as a biomarker for nutritional status. A serum sample of approximately 6 mL will be collected for measurement of albumin and pre-albumin as specified in the SoA.

Laboratory/analyte results for albumin and pre-albumin collected from baseline through EOT of Part A, that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

8.7.3. Specified Gene Expression (RNA) Research

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

8.7.4. Specified Protein Research

Specified protein research is not included in this study.

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8.7.5. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.6. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study according to the SoA:

- A 2-mL whole blood (Prep B 1.5 optimized for plasma).
- A 2-mL whole blood (Prep B 2.5 optimized for serum).

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention(s) and cancer cachexia. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained 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. Immunogenicity Assessments

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL serum, will be collected for determination of ADA and NAb as specified in the SoA.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

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

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

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

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and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

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

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

If the sample is unable to be collected during F/U Part A and F/U Part B, it will not be considered a protocol deviation.

8.9. 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 the 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. Statistical Hypotheses

The null hypothesis of no difference between ponsegromab and placebo will be tested for each primary and selected secondary and tertiary endpoints. The alternative hypothesis is that ponsegromab is superior to placebo.

9.1.1. Estimands

9.1.1.1. Primary Estimand

Estimand related to the **body weight** primary objective:

Estimand 1 (similar to "hypothetical") is intended to provide a population level estimate of the treatment effect on the change from baseline in body weight for ponsegromab compared with placebo in all evaluable participants under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures,

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prohibited medications or participants' non-compliance with dosing (ie, using the Censored analysis set, as defined in Section 9.2).

- Population: Participants with cancer, cachexia, and elevated concentrations of GDF-15.
- Endpoint: Change from baseline in body weight at Week 12.
- Intercurrent Events:
    a. Discontinuation of study intervention: Data collected after a participant has discontinued study intervention will be censored and treated as missing data.
    b. Prohibited procedures: Data collected after a participant has undergone prohibited procedures, that would modulate the primary endpoint will be censored and treated as missing data. Any procedures will be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.
    c. Prohibited medications: Data collected after a participant has received prohibited medications, that would modulate the primary endpoint, will be censored and treated as missing data. The list of concomitant medications will be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.
    d. Inadequate compliance: Data collected after a participant has missed a dose will be censored and treated as missing data.

    Missing data due to censoring, study withdrawal or other reasons, are assumed to be missing at random in the analysis.
- Population-level summary: Difference in mean change from baseline body weight at Week 12 between ponsegromab and placebo.

Alternative estimands (eg, one similar to "treatment policy", using a complete analysis set where all observations post-discontinuation, prohibited procedure, prohibited medications or inadequate compliance, will be included) for the primary objective may be used in order to examine the robustness of the results and will be detailed in the SAP.

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9.1.1.2. Secondary Estimands

Estimand related to the **physical activity and gait** secondary objective:

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

- Endpoint: Change from baseline in each of the physical activity and gait endpoints 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.
- Population-level summary: Difference in mean change from baseline for the physical activity and gait endpoints at Week 12 between ponsegromab and placebo.

Estimand related to the **appetite-related symptoms as measured by FAACT** secondary objective:

Estimand 3 will be similar to Estimand 1, except for the following:

- Endpoint: Change from baseline in each FAACT sub-scale score at Week 12:
  - FAACT-ACS;
  - FAACT-5IASS.
- Population-level summary: Difference in mean change from baseline for the FAACT sub-scale scores at Week 12 between ponsegromab and placebo.

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Estimand related to the anorexia/appetite, nausea, vomiting and fatigue measured by the CRCSD secondary objective:

Estimand 4 will be similar to Estimand 1, except for the following:

- Endpoint: Change from baseline score for each of the questions from the CRCSD at Week 12:
  - Anorexia/appetite;
  - Nausea and vomiting;
  - Fatigue.
- Population-level summary: Difference in mean change from baseline in each of the questions from the CRCSD at Week 12 between ponsegromab and placebo.

Estimands related to the **safety and tolerability** secondary objective:

There are no defined estimands for the incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities, and these endpoints will be summarized using Pfizer data standards as applicable.

Estimands related to **tertiary/exploratory** objectives:

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

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

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"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 and randomization to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in

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Participant Analysis Set	Description
	the study, are not considered enrolled, unless otherwise specified by the protocol.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized intervention.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

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

9.3. Statistical Analyses

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

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9.3.1. General Considerations

Part A and Part B of the study will be presented separately. For objectives relating to Part A of the study, each treatment arm will be reported separately through the 12-week double-blind treatment period only (including follow-up for any participants not continuing onto Part B of the study).

9.3.1.1. Analyses for Continuous Endpoints

MMRM Model

The MMRM model will include participant as a random term, and baseline, time (as a factor), baseline-by-time interaction, treatment and treatment-by-time interaction as fixed terms in the model. An unstructured covariance matrix will be fitted to the repeated times within subject (other covariance matrices will be considered if necessary), and the Kenward Roger approximation will be used for estimating degrees of freedom. Additional terms may be fitted in the model (eg, type of therapy [ie, platinum or not], type of cancer), as appropriate.

Bayesian Emax Model

The Bayesian four-parameter Emax model will use dose as a continuous variable. The model structure will take the form:

$$CFB = E_0 + \frac{E_{max} * dose^{Hill}}{ED_{50}{}^{Hill} + dose^{Hill}}$$

E_0 is the placebo response, *dose* is the randomized dose (placebo dose = 0), E_{max} is the maximum effect, ED_{50} is the dose producing 50% of the maximum effect and *Hill* is the slope parameter. The model will utilize a Bayesian methodology approach.

The default prior distributions for the *Hill* parameter and the ED_{50} are based on a meta-analysis of clinical dose response data[13,14,15] and are listed below. These default distributions will be updated if the meta-data, and their analysis, are updated before the completion of the current study.

Parameter	Prior
$log(ED_{50})$	$log(P_{50})$ + t(Mean=0, SD=1.73, df=5)
log(Hill)	t(Mean = 0, SD =0.85, df=5)

The correlation between these two parameters is currently -0.45 based on the analysis of the meta-data, which also would be updated if the historical analysis is updated.

The predicted ED_{50} for the compound (P_{50}), and prior distributions for the placebo response (E_0), the difference in response (*difTarget*) between the highest dose (400 mg) and placebo,

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and the residual standard deviation (*sigma*) will be specified for the analysis endpoint. Note that E_{max} is derived from other parameters and is thus not explicitly supplied.

9.3.2. Primary Endpoint Analysis

The primary endpoint analysis will be a Bayesian E_{max} model applied to results from an MMRM analysis.

Change from baseline in body weight at Week 12 will first be analyzed using Estimand 1 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment dosing timepoints up to Week 12 (ie, Weeks 4, 8, and 12) using the Censored analysis set. Additional terms for type of therapy [ie, platinum or not] and type of cancer will be fitted in the model. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p-values) will be provided.

A Bayesian E_{max} model will then be fitted to the Week 12 LSmeans and SEs from the MMRM analysis. The predicted ED_{50} for the compound (P_{50}) is currently ~150 mg Q4W dose, based on latest data for the compound (this may be updated as new data become available). Prior distributions for the placebo response (E_0), the difference in response (*difTarget*) between the highest dose (400 mg) and placebo, and the residual standard deviation (*sigma*) are:

> E_0: An informative meta-analytic predictive[16,17] prior, based on historical results from internal and external studies, robustified by the inclusion of a weakly informative component to handle any possible prior-data conflict, will be used for the placebo change from baseline at Week 12. This will be approximated by a t-distribution with a mean of -0.58 kg, an SD of 1.84 kg and 3 degrees of freedom. If additional relevant data become available during the study, a sensitivity analysis may be performed by incorporating the new data, using the same approach as above. Further details on the prior derivation will be given in the statistical analysis plan (SAP).
>
> *difTarget*: A vague t-distribution will be used for the 400 mg placebo-corrected change from baseline at Week 12 with a mean of 0, a SD equal to 10 times the predicted standard deviation (ie, 49 kg) and 5 degrees of freedom.
>
> *sigma*: A uniform prior will be used, with a range we are confident will include the population value. A lower bound of 0.49 kg and an upper bound of 49 kg will be used.

The posterior medians and 90% credible intervals (5th and 95th percentiles of the relevant posterior distribution) will be reported for each randomized dose (including placebo) and their differences relative to placebo. If the E_{max} model cannot be fitted to the data, or the data do not support a dose-response, the model may be simplified, or the analysis may not be performed and the primary results for the study will be based on the MMRM results at Week 12. More details on how this will be assessed will be described in the SAP. No adjustments will be made for multiplicity.

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9.3.3. Secondary Endpoints Analysis

Endpoint	Statistical Analysis Methods
Change from baseline in each of the physical activity and gait endpoints 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.	Change from baseline in physical activity and gait endpoints will be analyzed separately using Estimand 2 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 12 using the Censored analysis set. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p values) will be provided. No adjustments will be made for multiplicity.
Change from baseline in each of the FAACT sub-scale scores at Week 12: • FAACT-ACS; • FAACT-5IASS.	Change from baseline in FAACT sub-scale scores will be analyzed separately using Estimand 3 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 12 using the Censored analysis set. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p values) will be provided. No adjustments will be made for multiplicity.
Change from baseline for each of the questions from the CRCSD at Week 12: • Anorexia/appetite; • Nausea and vomiting; • Fatigue.	Change from baseline in questions from the CRCSD will be analyzed separately using Estimand 4 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline weekly averages at all post-treatment timepoints up to Week 12 using the Censored analysis set. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p values) will be provided. No adjustments will be made for multiplicity.
Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities.	All safety analyses will be performed on the safety population. The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations, as appropriate. Part B safety data will be reported once all applicable participants have completed Part B of the study. More details will be provided in the SAP.

9.3.4. Tertiary/Exploratory Endpoints Analysis

The analysis of exploratory endpoints will be detailed in the SAP.

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9.3.5. Other Analyses

Selected data collected at Screening may be reported. These data may include demographic data, concomitant medications, GDF-15 concentrations, height, weight, BMI, and ECOG PS. In addition, a subset of medical history data will be reported; this may include type and stage of cancer, where feasible. Other data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, will be considered source data, and will not be required to be reported, unless otherwise noted.

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

Up to 40 exit interviews will be conducted by telephone at Week 12 or early discontinuation. Interviews will be conducted by trained moderators and are anticipated to be approximately 60 minutes in duration. Using the transcripts and interviewer field notes, dominant trends will be identified in each interview and compared across all the interviews to describe the participant experience with a focus on the themes or patterns in the way the treatment experience is described, and the importance of any improvements reported. Following the analysis, a comprehensive summary report that fully describes the study objectives, methods, participants and results of the qualitative interviews will be prepared and reported separately from the CSR.

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

CT scans will be collected, retained, analyzed for tumor burden, skeletal muscle, adipose tissue, and may be used for additional research related to the study intervention(s) and cancer cachexia. The results of such additional research analyses may not be included in the CSR.

9.4. Interim Analyses

Interim analyses may be performed to assess efficacy and/or safety after at least approximately 25% of the planned participants, ie, approximately 30 participants, complete their study participation through Week 12 of the study. Interim analysis results may be used for decisions regarding stopping for futility, stopping for early success, conducting a sample size re-estimation, or adapting the study after the interim analysis. Participants may be discontinued from the study intervention/study as a result of the interim analysis, as described in Section 7.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per Pfizer's SOPs will be documented and approved in an IRC charter. In addition, the analysis details will be documented and approved in the SAP.

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Following completion of Part A (PCD), the data will be analyzed and reported in the main CSR. The results for Part B will be reported separately at the end of Part B.

9.4.1. PK/PD Unblinding Plan

If needed, a PK/PD unblinding plan will be developed to safeguard the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind. Under this plan, a limited number of individuals, not on the study team, will be unblinded, with the purpose of composing PK/PD and/or immunogenicity analysis sets and conducting PK/PD analysis that will not be made available to the study team until after database lock.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve a total of approximately 168 participants, with 42 participants randomly assigned to ponsegromab 100, 200 or 400 mg and placebo in approximately a 1:1:1:1 ratio. This is expected to ensure completion through Week 12 of the study of approximately 120 completing participants (30 in each of ponsegromab 100, 200 or 400 mg and placebo), assuming a discontinuation rate of approximately 30% (if this rate is higher, or there is a high rate of non-compliance, more participants may be randomized to ensure the required number of completing participants).

The sample size in the ponsegromab and placebo arms is based on the primary efficacy endpoint, mean change from baseline in body weight at Week 12. An informative meta-analytic predictive prior, based on historical results from internal and external studies, robustified by the inclusion of a weakly informative component to handle any possible prior-data conflict, will be used for the placebo response and is expected to equate to an effective sample size of 39 placebo participants. Further details on the prior derivation will be given in the statistical analysis plan SAP.

120 completing participants, in a 1:1:1:1 ratio, plus 39 participants from the placebo prior, gives acceptable Operating Characteristics in that:

- The probability of achieving statistical significance (at the 5% significance level, using a 1-sided t-test), for a true difference between ponsegromab and placebo of 2.7 kg, is approximately 80%.
- An observed difference between ponsegromab and placebo of 1.8 kg is expected to achieve statistical significance (at the 5% significance level, using a 1-sided t-test).

A conservative estimate of the standard deviation, for the change from baseline in body weight at 12 weeks of 4.9 has been used.

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The sample size determination has been performed using pairwise comparisons. This is considered to be a conservative approach since the primary analysis will utilize a Bayesian E_{max} dose-response model, which would be anticipated to best describe the dose-response in the presence of an effective compound.[15]

Evaluable participants are defined as in Section 9.2. Participants who withdraw from the study will not be replaced.

Of the approximately 168 planned randomized participants, up to approximately 36 are planned to be randomized (to ponsegromab 100, 200 or 400 mg and placebo in approximately a 1:1:1:1 ratio) into the additional PK substudy. This sample size has been chosen empirically to provide sufficient data to adequately characterize ponsegromab PK and GDF-15 effect and PK/PD relationship in cancer patients with cachexia and elevated concentrations of GDF-15.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

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

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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 the ICH GCP guidelines 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

The investigator must ensure that each participant or their 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 or their legally authorized representative must be informed that their 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 or their legally authorized representative.

The participant or their legally authorized representative must be informed that their 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 their legally authorized representative is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

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

Participants or their legally authorized representative must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

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

10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

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10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The IRC will conduct an initial review of the unblinded safety data once the first 20 randomized participants have safety data through at least 6 weeks after randomization. Thereafter, the IRC will review safety data approximately every 3 months to ascertain whether there is a ponsegromab-related safety concern by evaluating treatment emergent AEs, including those related to study intervention, using the NCI CTCAE grading system, and by reviewing the AEs in both the active treatment arms and placebo. The IRC will also review data collected on the administration of anti-cancer therapy, to ascertain if there is an imbalance in the rates of discontinuation of anti-cancer therapies across the treatment arms. The IRC will issue periodic recommendations to the study team, based on its periodic review of the unblinded study data. Such recommendations may include modification to or discontinuation of a study treatment arm or termination of the study. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.5.2. Executive Steering Committee

The Executive Steering Committee will be responsible for reviewing the protocol and may make suggestions on protocol design and amendments. This committee will with work jointly with the Operations Steering Committee to provide guidance regarding identified issues with study conduct. They will also lead authorship and provide oversight of study publications in collaboration with the sponsor. The charter describes the role of the Executive Steering Committee in more detail.

10.1.5.3. Operations Steering Committee

The Operations Steering Committee comprised of medical representatives from each country or region, Pfizer clinical colleagues and Pfizer operations colleagues, will oversee recruitment, retention, and quality issues within the country or region. This committee will work jointly with the Executive Steering Committee to ensure that identified issues are effectively addressed at each participating site. The charter describes the role of the Operations Steering Committee in more detail.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local

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laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

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10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and 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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

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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.

10.1.8. Source Documents

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

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

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

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

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or

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Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

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10.2. Appendix 2: Clinical Laboratory Tests

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

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count	Urea and creatinine, SCys (at Screening only) Sodium Potassium AST, ALT Total bilirubin Alkaline phosphatase Total protein Glucose (non-fasting)	At Screening only: • FSH[a] Per SoA or as needed: • Pregnancy test (b-hCG or urine test)[b] For potential DILI: AST/ALT T bili, direct and indirect bili Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) For potential DICI/DIKI: Creatinine (Scr) CystatinC (Scys) eGFR (Scr only and combined Scr+Scys) Spot (dipstick) UACR

a. For confirmation of postmenopausal status only.
b. Serum b-hCG will be collected at Screening for female participants of childbearing potential. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC.

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.

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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 Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  ◦ Is associated with accompanying symptoms.
 	
  ◦ Requires additional diagnostic testing or medical/surgical intervention.
 	
  ◦ Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition 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 or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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.

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

d. Results in persistent or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant 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.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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

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leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**

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Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or 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 listed below (as defined by the NCI CTCAE version 5.0):

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.

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GRADE	Clinical Description of Severity
1	MILD; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	MODERATE; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	SEVERE or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

- *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- 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.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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**

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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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

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10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT 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 DCT 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 the 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, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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.

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10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100 fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

- 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 definition in Section 10.4.3).

    OR

  - Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 8 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

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- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

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

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

2. Postmenopausal female:

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.

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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

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*;
    - Intravaginal + barrier*;
    - Transdermal + barrier*.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral + barrier*;
    - Injectable + barrier*.

Sexual Abstinence

8. 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.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to 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 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:

    - Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples 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.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN or if the value reaches ≥3 × ULN (whichever is smaller).

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Rises in AST/ALT and T bili 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.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

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10.7. Appendix 7: Kidney Safety Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)-2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if >0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	if ≤0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ≤0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49.[18]

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE criteria.

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10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants 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 participants 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).

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- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >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 SAEs

- 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: Comfort and Wearability Questionnaire

Participant ID	
1. Date of Assessment (dd-MMM-yyyy)	
2. Device Placement	**WRIST JOINT**
Name of the person completing this form	

	Questions					
		Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
3.a	The device is comfortable to wear	◯	◯	◯	◯	◯
3.b	The device is easy to put on	◯	◯	◯	◯	◯
3.c	The device is easy to take off	◯	◯	◯	◯	◯
3.d	The device is easy to wear	◯	◯	◯	◯	◯
3.e	The device changes the way I move (e.g., walking)	◯	◯	◯	◯	◯
3.f	The device changes the way I behave	◯	◯	◯	◯	◯
3.g	I am willing to wear the device for 4 to 7 days	◯	◯	◯	◯	◯
3.h	I am willing to wear the device for more than 7 days	◯	◯	◯	◯	◯
3.i	If the device could follow change in my activity levels during treatment, I would wear it	◯	◯	◯	◯	◯
3.j	If the device could follow change in my activity levels, I would want my doctor to have access to my results	◯	◯	◯	◯	◯

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Participant ID	
1. Date of Assessment (dd-MMM-yyyy)	
2. Device Placement	**LUMBAR REGION**
Name of the person completing this form	

Questions						
		Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
3.a	The device is comfortable to wear	◯	◯	◯	◯	◯
3.b	The device is easy to put on	◯	◯	◯	◯	◯
3.c	The device is easy to take off	◯	◯	◯	◯	◯
3.d	The device is easy to wear	◯	◯	◯	◯	◯
3.e	The device changes the way I move (e.g., walking)	◯	◯	◯	◯	◯
3.f	The device changes the way I behave	◯	◯	◯	◯	◯
3.g	I am willing to wear the device for 4 to 7 days	◯	◯	◯	◯	◯
3.h	I am willing to wear the device for more than 7 days	◯	◯	◯	◯	◯
3.i	If the device could follow change in my activity levels during treatment, I would wear it	◯	◯	◯	◯	◯
3.j	If the device could follow change in my activity levels, I would want my doctor to have access to my results	◯	◯	◯	◯	◯

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10.10. Appendix 10: ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
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, eg, 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

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10.11. Appendix 11: RECIST 1.1 Tumor Assessment Criteria RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from Eisenhauer E.A., et al.[19]

*Since MRIs are not included in this study, the RECIST criteria only applies to CT scans.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

- 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).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- 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.

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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

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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.

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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.

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Table 5. 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 6 will be used:

Table 6. 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

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10.12. Appendix 12: List of Platinum-Based Chemotherapies

Platinum-based chemotherapies include the following:

Cisplatin

Oxaliplatin

Carboplatin

Nedaplatin

Lobaplatin

Heptaplatin

Miriplatin

Satraplatin

Picoplatin

Phenanthriplatin

The list above is non-exhaustive and please review list of chemotherapies carefully with your pharmacist and/or Pfizer study team to determine if any should be considered as platinum-based. Please note agents are listed above using generic terms and trade names are not included.

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10.13. Appendix 13: Abbreviations

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

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ACS	anorexia and cachexia subscale
ADA	anti-drug antibodies
ADE	adverse device effect
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AIDS	Acquired Immunodeficiency Syndrome
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
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
AxMP	auxiliary medicinal product
BA	bioavailability
BE	bioequivalence
b-hCG	b-human chorionic gonadotropin
BioMeT	biometric monitoring technology
BMI	Body Mass Index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
C_{avg}	average concentration
CFR	Code of Federal Regulations
CL/F	apparent clearance for oral dosing
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology

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Abbreviation	Term
CLIA	clinical laboratory improvement amendments
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing and Controls
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRC	colorectal cancer
CRCSD	Cancer related cachexia symptom diary
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DHT	digital health technology
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
eCOA	electronic clinical outcome assessment
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
ED	Early discontinuation
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency

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Abbreviation	Term
Emax	maximal effect
EOT	end of treatment
ePRO	electronic Patient Reported Outcome
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAACT	Functional Assessment of Anorexia-Cachexia Therapy
FAACT-5IASS	Functional Assessment of Anorexia/Cachexia Therapy 5-item Anorexia Symptom Scale
FAACT-ACS	Functional Assessment of Anorexia-Cachexia Therapy- anorexia and cachexia subscale
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GDF-15	growth differentiation factor 15
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	Glucagon-like peptide-1
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCP	health care professional
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HRU	healthcare resource utilization
hs-CRP	high-sensitivity C-reactive protein
Ht	height
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Abbreviation	Term
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	Investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
ISO	International Organization for Standardization
IUO	Investigational Use Only
IWR	Interactive Web-based Response
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LLOQ	lower limit of quantification
LPD	local product document
LSmeans	Least-Squares Means
LSMI	Lumbar Skeletal Muscle Index
M6min	Maximum daily 6 minutes of activity
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MQI	medically qualified individual
MRI	magnetic resonance imaging
NA	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NRS	numerical rating scale
NSCLC	non-small cell lung cancer
NT-pro-BNP	N-terminal-pro hormone B-type natriuretic peptide
NYHA	New York Heart Association

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Abbreviation	Term
OLT	Open-label treatment
PBMC	peripheral blood mononuclear cell
PANC	pancreatic cancer
PCD	Primary completion date
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PG-SGA	Patient Generated-Subjective Global Assessment
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PRO	Patient Reported Outcomes
PROACC-1	Patient Reported Outcomes and Activity in CanCer
PROMIS	Patient-Reported Outcomes Measurement Information System
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTH	parathormone
PVC	premature ventricular contraction
Q3W	administered every 3 weeks
Q4W	administered every 4 weeks
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia’s formula
QTL	quality tolerance limit
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
Scr	serum creatinine
Scys	serum cystatin C
SD	Standard deviation
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	Single Reference Safety Document

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Abbreviation	Term
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
T^3	total triiodothyronine
T^4	total thyroxine
TB	tuberculosis
T bili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time for Cmax
TOC	table of contents
TSH	thyroid-stimulating hormone
UACR	urine albumin/creatinine ratio
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States Prescribing Information
UTI	urinary tract infection
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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10.14. Appendix 14: Protocol Amendment History

Amendment 1 (27 October 2022)

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate and clarify various protocol elements related to stopping criteria of the study invention, assessment of weight change, CT scan regions and patient reported outcomes. The details are described below.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.1. Synopsis; 3. Objectives, Endpoints, and Estimands	moved CRCSD from tertiary to secondary.	To support validation of CRCSD	Substantial
1.3. Schedule of Activities	Added vital signs, physical exams, chemistry and hematology assessments every 3 months in Part B; also expanded Part B visits such that all visits are visualized in the table rather than one column for visits 16-60; added ECOG PS to Part B (visit 20 and ED).	Additional timepoints for procedures added for evaluation of safety	Substantial
1.3. Schedule of Activities; 8.3.1. Physical Examination	• Updated physical exam plan: • updated SoA footnote ‘e’ to include evaluation of ascites and edema and reporting as an AE; • Added a separate line for abbreviated physical exam to clarify which visits should be full physical exam	added for evaluation of weight change and clarified which type of type of physical exam would be required for specific visits	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	versus abbreviated physical exam; • Updated Week 8 physical exam from full physical exam to abbreviated physical exam; • Added abbreviated physical exam at Week 4, 24, 36, 48, and 60; • Added text to include evaluation of ascites and edema and reporting as an AE.		
1.3. Schedule of Activities; 3. Objectives, Endpoints and Estimands; 4.2 Scientific Rationale for Study Design; 8.3.7. Imaging Assessment-CT scan; 9.3.5 Other Analyses	• Clarified specific required body regions for CT scans in SoA footnote 'o'; • Clarified specific body regions for CT scans and added text to clarify that all CT scans will be collected centrally to allow for a central review of body composition measures; • Added an exploratory/tertiary objective for evaluation of LSMI and skeletal muscle	Added for LSMI and skeletal muscle and adipose tissue measures evaluation and analysis	substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	and adipose tissue measures derived from CT scans.		
1.3. Schedule of Activities; 8.2.2. Patient Reported Outcomes	Added an additional question related to physical activity to PGI-S and PGI-C.	Added for anchoring of physical function assessments	Substantial
7.1. Discontinuation of Study Intervention	added stopping criteria for participants experiencing Grade 3 or 4 AEs.	stopping rules added to assess toxicity associated with PF-06946860 leading to discontinuation or delay in administration of anti-cancer therapy	Substantial
1.1. Synopsis; 5.1. Inclusion Criteria (criterion #5)	updated to reflect inclusion of ECOG PS≤3 and removal of sponsor discussion of ECOG PS of 4.	updated to allow meaningful interpretation of results	Substantial
1.1. Synopsis; 5.2. Exclusion Criteria (criterion # 11)	Added specific criteria for exclusion due to liver enzyme lab abnormalities.	Added specific values to quantify threshold	Substantial
6.9. Prior and Concomitant Therapy	Added text to clarify that reasons for discontinuing and modifying SOC therapies will be recorded on a CRF.	Added for evaluation of SOC therapies	Substantial
1.1 Synopsis and 2.1 Study Rationale	Added study name and description.	Modification to incorporate study name	nonsubstantial
1.1. Synopsis and 3. Objectives,	Updated objectives for FAACT.	Modification	nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Endpoints and Estimands			
1.1 Synopsis and 5.1 Inclusion Criteria	Updated Inclusion Criterion #3 to clarify the Fearon criteria of weight loss.	Clarification	nonsubstantial
Title page and Section 1.1 synopsis	Updated Eudra CT number.	Changed submission from CTR to National route	nonsubstantial
1.1 Synopsis and 3. Objectives, Endpoints and Estimands and 9.1.1.1. Primary Estimand	Updated Estimands to include prohibited medications.	Clarification	nonsubstantial
1.1. Synopsis; 3. Objectives, Endpoints, and Estimands	Updated physical function endpoints.	Clarification	nonsubstantial
1.3 Schedule of Activities	Expanded the visit windows for part B from ±1 to ±3.	Updated to allow for additional flexibility	nonsubstantial
1.3 Schedule of Activities and 8.3.6 Pregnancy Testing	Updated footnote f. to clarify that following the Screening visit, a urine pregnancy test may be performed; removed duplicative text.	Clarification	nonsubstantial
1.3 Schedule of Activities	Clarified that retained samples will not be collected for China.	Clarification	nonsubstantial
1.3. Schedule of Activities; 8.2.2.	Modified SoA footnotes ‘k’ and ‘l’ to clarify physical	Clarification	nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Patient Reported Outcomes	activity collection period description; Clarified in table and text for physical activity collection period.		
2.2.1.3 Summary of Pharmacokinetics	The following sentence was corrected to describe information regarding ponsegromab rather than GDF-15: "The mean terminal t½ increased with increasing dose, ranging from 3.52~11.1 days and 20.1~30.9 days for the unbound and total ponsegromab, respectively, across the 10 to 300 mg dose groups."	Update	nonsubstantial
2.2.1.5 Immunogenicity	Added immunogenicity data based upon completion of the C3651009 CSR.	Update	nonsubstantial
2.3.1 Risk Assessment	Corrected text in the sentence related to injection site reactions in Phase 1 studies in healthy participants and added use of ECG patches.	Clarification	nonsubstantial
3 Objectives, Endpoints, and Estimands	Modified objectives table to include prohibited medications to estimands; modified physical activity endpoints.	Clarification	nonsubstantial
4.4 End of Study Definition	Updated the end of study definition and defined primary completion date.	Clarification	nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
6.9.2 Permitted During the Study	Removed duplicative text regarding the collection of all concomitant therapies since already stated in 6.9 Prior and Concomitant Therapy.	Clarification	nonsubstantial
8.1. Administrative Procedures; 8.5. Pharmacokinetics ;8.7.1. GDF-15	Added text to collect PK and GDF-15 samples at any unplanned site visit when feasible.	Clarification	nonsubstantial
8.2.2 Patient Reported Outcomes	Clarified text for physical activity collection period language in table.	Clarification	nonsubstantial
8.2.3 Physical Activity	Clarified description of physical activity collection period.	Clarification	nonsubstantial
8.3.6 Pregnancy Testing	Clarified test is only required at Screening and will be sent to central lab.	Clarification	nonsubstantial
8.5 Pharmacokinetic; 8.7.1 GDF-15	To align with Section 8, clarified blood volume does not exceed 550 mL during any period of 56 consecutive days.	Clarification	nonsubstantial
8.7.1 GDF-15	Added rationale for sample collection for potential companion diagnostic test for ponsegromab.	Clarification	nonsubstantial
9.1.1.1 Primary Estimands	• Added text to clarify the management of data collected after a participant has received prohibited medications that	Clarification	nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	would modulate the primary endpoint; • Updated text to provide clarity on prohibited procedures and inadequate compliance.		
9.1.1.2 Secondary Estimands and 9.3.3 Secondary Endpoints Analysis	Modified text to correspond to the updates made to the FAACT, physical activity and CRCSD objectives and endpoints.	Clarification	nonsubstantial
9.2 Analysis Sets	Added "prohibited medications" to censored analysis set.	Clarification	Nonsubstantial
9.4 Interim Analysis	Added text to describe end of study data reporting.	Update	Nonsubstantial
10.1.5.1. Data Monitoring Committee	Included additional details related to the IRC data review.	added to incorporate details of IRC review and timelines	Nonsubstantial
10.2. Appendix 2. Clinical Laboratory Tests	• Clarified that glucose sample is collected non-fasting; • Moved potential DILI lab tests under other; • Added potential DICI/DIKI lab test under other.	Update	Nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs During the Active Collection Period	Added severity grading table and descriptions to align with CTCAE v5.	To align with safety reporting of adverse events	Nonsubstantial
10.13. Appendix 13. RECIST 1.1 Tumor Assessment Criteria RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines	Added note to specify that the RECIST criteria only applies to CT scans in this study.	Clarification	nonsubstantial
1.3. Schedule of Activities	The PROMIS (fatigue 7A & physical function 8c) assessment corrected to be linked with footnote 'j' rather than '.	Protocol Administrative Change Letter dated 28 July 2022	Nonsubstantial
4.3. Justification for Dose	The titles and corresponding footnotes for Table 1 and 2 corrected to reflect that the predicted total and unbound C_{max} , AUC_{tau}, and C_{avg} are steady-state exposures.	Protocol Administrative Change Letter dated 28 July 2022	Nonsubstantial
6.1.1. Administration	Specific instructions added to describe injection sites of administration of ponsegromab and placebo.	Protocol Administrative Change Letter dated 28 July 2022	Nonsubstantial

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11. REFERENCES

[1] Arends J, Strasser F, Gonella S, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines. ESMO Open. 2021;6(3):100092.

[2] Roeland EJ, Bohlke K, Baracos VE, et al. Management of Cancer Cachexia: ASCO Guideline. J Clin Oncol. 2020;38(21):2438-2453.

[3] Ahmed DS, Isnard S, Lin J, et al. GDF15/GFRAL Pathway as a Metabolic Signature for Cachexia in Patients with Cancer. J Cancer. 2021;12(4):1125-1132.

[4] Tsai VW, Husaini Y, Manandhar R, et al. Anorexia/cachexia of chronic diseases: a role for the TGF-b family cytokine MIC-1/GDF15. J Cachexia Sarcopenia Muscle. 2012;3(4):239-43.

[5] Lu ZH, Yang L, Yu JW, et al. Weight loss correlates with macrophage inhibitory cytokine-1 expression and might influence outcome in patients with advanced esophageal squamous cell carcinoma. Asian Pac J Cancer Prev. 2014;15(15):6047-52.

[6] Lerner L, Hayes TG, Tao N, et al. Plasma growth differentiation factor 15 is associated with weight loss and mortality in cancer patients. J Cachexia Sarcopenia Muscle. 2015;6(4):317-324.

[7] Lerner L, Tao J, Liu Q, et al. MAP3K11/GDF15 axis is a critical driver of cancer cachexia. J Cachexia Sarcopenia Muscle. 2016;7(4):467-482.

[8] Altena, R, Fehrmann RSN, Boer, H., et al. Growth differentiation factor 15 (GDF-15) plasma levels increase during bleomycin-and cisplatin-based treatment of testicular cancer patients and relate to endothelial damage. PLoS One. 2015;10(1): e0115372.

[9] Von Haeling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. J Cachexia Sarcopenia Muscle. 2016; 7(5): 507–509.

[10] Elecsys® GDF-15 package insert (2017). Documentation Roche Diagnostics, Bâle.

[11] Jager-Wittenaara H, Ottery F. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. Clinical nutrition. 2017;20(5):322-329.

090177e19da07ca7\Approved\Approved On: 02-Jun-2023 06:15 (GMT)

[12] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391-7.

[13] Thomas, N., Sweeney, K., and Somayaji, V. (2014). Meta-analysis of clinical dose response in a large drug development portfolio. Stat Biopharm Res. 2014;6(4):302-317.

[14] Thomas, N., and Roy, D. (2016). Analysis of clinical dose-response in small-molecule drug development: 2009-2014. Stat Biopharm Res. 2017;9(2):137-146.

[15] Wu J, Banerjee A, Jin B, et al. Clinical dose-response for a broad set of biological products: A model-based meta-analysis. Stat Methods Med Res. 2018 Sep;27(9):2694-2721.

[16] Neuenschwander B, Capkun-Niggli G, Branson M, et al. Summarizing historical information on controls in clinical trials. Clinical Trials 2010;7(1):5–18.

[17] Schmidli H, Gsteiger S, Roychoudhury S, et al. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics 2014;70(4):1023–32.

[18] Inker LA et al. N Engl J Med. 2021;385:1737-49.

[19] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J of Cancer 2009; 45(2): 228-47.

090177e19da07ca7\Approved\Approved On: 02-Jun-2023 06:15 (GMT)