**Protocol C3651003**

# 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)

## Statistical Analysis Plan (SAP)

**Version:** 3

**Date:** 05 Apr 2024

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## APPENDICES

# 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 3<br>05 Apr 2024 | Amendment 2<br>24 May 2023 | Additional clarifications, definitions, and outputs required following BDR | • Header: Replaced compound number with compound name<br>• 2.2.1: for Estimand 1b - clarified intercurrent event<br>• 2.3: Added additional details about study design<br>• 3/3.4.10: Clarification of baseline definition<br>• 3: Clarification of efficacy data inclusion for Part A<br>• 3.2.1: Correction of definition of non-sedentary physical activity time<br>• 3.2.1: Further clarification of digital weekly average calculation and compliance definition<br>• 3.2.3: Clarification of CRCSD weekly average calculation<br>• 3.2.4.1/6.2.4.1: Details of Tier 1 events updated. Reference to Sampson criteria added<br>• 3.4.1: Updated "Cadence" to "Average Cadence"<br>• 3.4.13: Responder definition added for body weight<br>• 3.5: Definitions added for baseline BMI-adjusted weight loss category, sarcopenia and inflammation variables<br>• 5.2: Addition of 'Ponsegromab Combined' treatment group<br>• 5.2.1: Quartiles added to summaries<br>• 5.2.4: Clarification that Bayesian Emax model parameters not included in CSR<br>• 5.2.8/Appendix 4: Logistic regression details added for responder analysis<br>• 5.3.1: Multiple imputation details added for responder analysis<br>• 6.1.1.2: Additional supplementary analyses added for body weight<br>• 6.2.1/6.4.10: Removed boxplots for all endpoints<br>• 6.2.1: Additional summary of amount of available digital data<br>• 5.2/6.4.3/6.4.4/6.6.1: Clarification that separate PK substudy outputs may be reported in supplemental CSR<br>• 6.4.13: Responder analysis added for body weight<br>• 6.6.1: Additional endpoints for summary at baseline<br>• 6.6.5: Clarification that CRP may be included in CSR<br>• 8: Additional references<br>• Appendix 8: Abbreviations updated |
| 2<br>11 Dec 2023 | Amendment 2<br>24 May 2023 | Additional PK/PD samples included for a subset of participants (PK substudy) in response to regulatory request<br><br>Interim analysis details added | Applied new SAP template<br><br>General updates and clarification<br>• Study title updated<br>• 2.2.1/4: Clarified 'inadequate compliance' definition<br>• 2.2.2/3.2.3/6.2.3: changed wording of CRCSD endpoints<br>• 3.2.1: Definition of "compliant day" and weekly average calculations updated<br>• 3.2.4: Immunogenic AEs added |

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| | | | • 3.4.3/3.4.4: Protocol wording updated<br>• 3.4.10: Exclusion of radio-attenuation measurements; added formula for LSMI<br>• 3.5: Added definition for previous body weight loss<br>• 4: Added additional wording for 'actual' dose<br>• 5.1: Additional endpoints listed for testing<br>• 5.2.5: ANCOVA details added<br>• 6.1.1.1: Clarification of timepoints included in MMRM analysis<br>• 6.1.1.2: Clarification that only Bayesian analysis is being repeated for sensitivity analysis<br>• 6.2.4: Inclusion of ponsegromab combined and overall treatment groups; addition of ISR and immunogenic AE summaries<br>• 6.4.5: Cumulative percentage of ADA/NAb positive participants added; clarification changes made<br>• 6.4.6/6.4.7/6.4.10: Additional plots and analysis included<br>• 6.5: Additional subset analysis and scatterplot for GDF-15 levels<br>• 6.6.1: Additional baseline cancer details included<br>• 7.2: Interim analysis details added<br>• 8: Reference section added<br>• Appendix 4: Included ANCOVA code<br>• Appendix 5: Details of Bayesian Emax methodology updated<br><br>Updates for PK substudy<br>• 2.2/3.4.3/3.4.4/6.4.3/6.4.4: PK/PD endpoints updated to include extra timepoints<br>• 2.3: PK substudy description added; Figure 1 updated<br>• 3.4.3: Trough timepoints updated to include PK substudy<br>• 5.2 General note on reporting PK substudy as part of main study<br>• 6.4.3: PK endpoints updated and analysis for PK substudy added<br>• 6.4.4: PD endpoints updated and GDF-15 analysis for PK substudy added<br>• 6.6: Baseline summaries added for PK substudy |
| 1<br>09 Nov 2022 | Original<br>17 June 2022<br><br>Amendment 1<br>27 Oct 2022 | N/A | N/A |

## 2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in **Part A** of Study C3651003 (including follow-up for Part A if a participant does not continue to Part B of the study). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. The methodology for summary and statistical analyses of the data collected in Part B of the study will be detailed in a supplemental SAP.

## 2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

## 2.2. Study Objectives, Endpoints, and Estimands

| Type | Objectives | Endpoints | Estimands |
|---|---|---|---|
| **Primary:** | ***Primary:*** | ***Primary:*** | ***Primary:*** |
| Efficacy | • *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:*** | ***Secondary:*** |
| Efficacy | • *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:*<br>  • *Moderate to vigorous physical activity time;*<br>  • *Sedentary activity time;*<br>  • *Non-sedentary* physical *activity time*<br>  • *Total vector magnitude*<br>  • *Mean activity level during M6min* (maximum daily 6 minutes of activity);<br>  • *Mean gait speed;*<br>  • *95$^{th}$ 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.* |
| Efficacy | • *To evaluate the effect of ponsegromab compared to placebo on the appetite-related symptoms as measured by FAACT in participants with cancer,* | • *Change from baseline in FAACT sub-scale scores at Week 12:*<br>  • *FAACT-ACS;*<br>  • *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* |

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| | *cachexia, and elevated concentrations of GDF-15.* | | *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.* |
| Efficacy | • *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:*<br>  • *Anorexia/appetite;*<br>  • *Nausea and vomiting;*<br>  • *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.* |
| Safety | • *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:*** | ***Tertiary/Exploratory:*** |
| Efficacy | • *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 additional physical activity and gait endpoints measured with remote digital sensors at Week 12.* | • *Not Applicable.* |

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| Efficacy | • *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.* |
| Pharmacokinetics | • *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.* |
| Biomarkers | • *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.* |
| Immunogenicity | • *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.* |
| Efficacy | • *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.* |
| Efficacy | • *To evaluate the effect of ponsegromab compared to placebo on PROMIS Physical Function-Short Form 8c in participants with cancer, cachexia, and elevated concentrations of GDF-15.* | • *Change from baseline score for PROMIS-Physical Function at Week 12.* | • *Not Applicable.* |
| Efficacy | • *To evaluate the effect of ponsegromab compared to placebo on PGI-S and* | • *Change from baseline PGI-S at week 12;*<br>• *PGI-C at Week 12.* | • *Not Applicable.* |

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| | *PGI-C* (appetite, fatigue, physical function, physical activity and walking) *in participants with cancer, cachexia, and elevated concentrations of GDF-15.* | | |
| Efficacy | • *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.* |
| Efficacy | • *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;*<br>• *Percent change from baseline in skeletal muscle and adipose tissue measures derived from CT scans at Week 12.* | • *Not Applicable* |
| Biomarkers | • *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.* |
| Safety | • *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* in a separate CSR.

### 2.2.1. Primary Estimand(s)

*Estimands 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, prohibited medications or participants' non-compliance with dosing (ie, using the Censored analysis set, as defined in* Section 4).

- *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, or has received an incomplete 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.*

**Estimand 1b** (similar to "treatment policy") 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 regardless of discontinuation of study intervention, dosing compliance, prohibited procedures or prohibited medications (ie, using the Complete analysis set as defined in Section 4).

- Population: Participants with cancer, cachexia, and elevated concentrations of GDF-15.
- Endpoint: Change from baseline in body weight at Week 12.
- Intercurrent Events: There are no changes made based on intercurrent events. For participants who discontinue study intervention, receive a prohibited procedure, prohibited medication and/or miss a dose, or receive an incomplete dose, all observations post-discontinuation, post-procedure, post-medication or post-missed/incomplete dose will be included in the analysis set.
- Population-level summary: Difference in mean change from baseline body weight at Week 12 between ponsegromab and placebo.

### 2.2.2. Secondary Estimand(s)

*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* (maximum daily 6 mins of activity);
  - *Mean gait speed;*
  - *95$^{th}$ 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.*

*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;*
  - *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.*

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

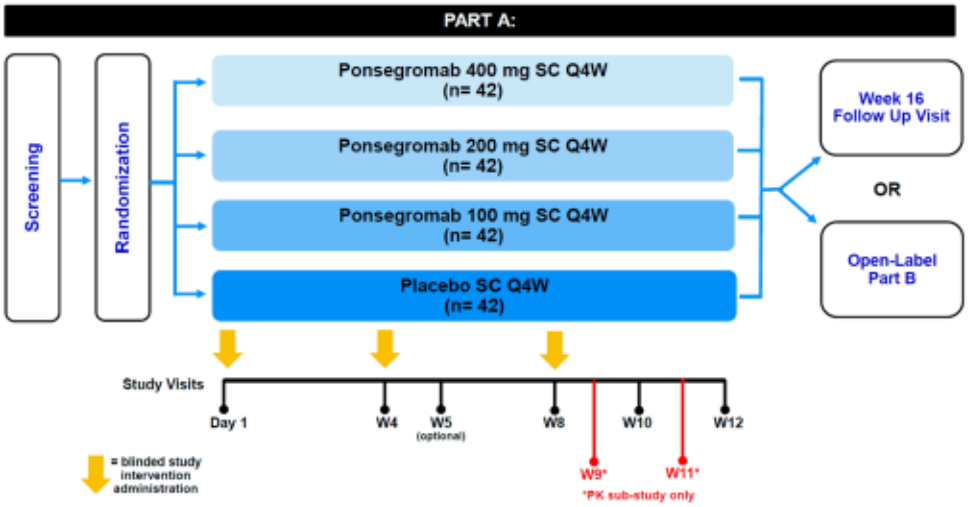
*Following the Screening period to confirm eligibility, approximately 168 study participants, who meet the entry criteria, will be randomized to study intervention (one of 3 dose groups of ponsegromab or matching placebo) and will be stratified by treatment with or without platinum-based chemotherapy, 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.*

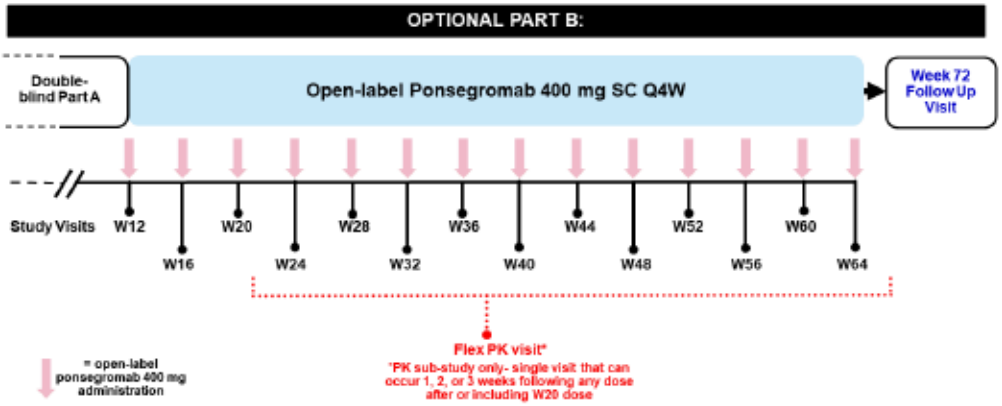
*A PK substudy will be conducted in approximately 36 of the approximately 168 participants (approximately 9 in each treatment group in Part A). Up to 3 additional PK and PD samples (two samples during Part A and one sample during Part B, if relevant), will be collected in these participants.*

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

Figure 1 lays out the structure of the study, including follow-up, for all participants depending on whether they enter the optional OLT period.

**Figure 1. Study Design**






## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

For all safety endpoints, unless otherwise stated, baseline is defined as the last-pre-dose measurement. For all efficacy endpoints, unless otherwise stated, baseline is defined as the last measurement prior to, or on, study day 1.

For those participants continuing into Part B of the study, safety data collected prior to dosing at Week 12 will be included in the summary and statistical analyses of Part A of the study. However, efficacy data collected up to and including Week 12 will be included, regardless of whether it is pre- or post-dose at Week 12.

### 3.1. Primary Endpoint(s)

#### 3.1.1. Change from baseline body weight at Week 12

*Body weight will be measured in duplicate. 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.* The average of the duplicate body weights collected at each assessment time will be calculated. If one of the two duplicates is missing, the non-missing value will be used for the average, and missing values will not be imputed.

Baseline is defined as the average of the duplicate measurements at the last pre-dose measurement time. Change from baseline and percent change from baseline in body weight will be calculated for all post-baseline averages.

### 3.2. Secondary Endpoint(s)

#### 3.2.1. Change from baseline in physical activity and gait endpoints measured with remote digital sensors at Week 12

Moderate to vigorous physical activity time (MVPA; mins/day)

- Sedentary activity time (mins/day)
- Non-sedentary physical activity time (mins/day)
- Total vector magnitude (vector magnitude of the activity counts X, Y, Z; au/day)
- Mean activity level during maximum daily 6 minutes of activity (M6mins; au/day)
- Mean gait speed (m/s)
- 95$^{th}$ percentile gait speed (m/s)

Note: au = arbitrary units

*Monitoring of physical activity and gait via accelerometry (wearable digital sensors) will be conducted in participants. Participants will be asked to wear the sensor on the wrist continuously, and the sensor on the lumbar* region *only during the day during the monitoring periods. 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.*

Raw data from both devices will be collected daily. Weekly averages (on Day 1 and at Weeks 8, 10 and 12) will be calculated as the mean taken over 8 days for each visit:

- Day 1 (screening):
  - If the PGI-S/C date falls within the screening device exposure period: Starting on the PGI-S/C date, or first non-zero wear day prior to the PGI-S/C date, and ending -7 days prior, or on the device exposure start date, whichever is sooner.
  - If the PGI-S/C date does not fall within the screening device exposure period:
    - Starting on the first non-zero wear day prior to the PGI-S/C date, within the screening device exposure period, and ending -7 days prior, or on the device exposure start date, whichever is sooner.
    - If no days are available: Starting on the first non-zero wear day after the PGI-S/C date, within the screening device exposure period, and ending +7 days later, or on the device exposure end date or Day -1, whichever is sooner.
  - If the PGI-S/C date is not reported: Starting on the first non-zero wear day closest to the device exposure end date, or on Day -1, whichever is sooner, and ending -7 days prior, or on the device exposure start date, whichever is sooner.
- Week 8: Starting on the Week 8 visit day and ending +7 days later or on the day before the next visit day, whichever is sooner (e.g. if the Week 8 visit date is Day 57, the Week 8 average will be taken over Days 57 to 64; however, if the Week 10 visit occurs on Day 64, the Week 8 average will be taken over Days 57 to 63 only)
- Week 10: Starting on the Week 10 visit day and ending +7 days later or on the day before the start day for the Week 12 average (e.g. if the Week 10 visit day is Day 71, the Week 10 average will be taken over Days 71 to 78; however, if the Week 12 start date is Day 77, the Week 10 average will be taken over Days 71 to 76 only)
- Week 12: Starting on the Week 12 visit day -8 days, and ending on the day before the Week 12 visit day (e.g. if the Week 12 visit occurs on Day 85, the Week 12 average will be taken over Days 77 to 84).

If fewer than 3 days of data are recorded on the lumbar device, the average should be treated as missing. If fewer than 3 compliant days of data are recorded on the wrist device, the average should be treated as missing (a day is defined as compliant if at least 7 hours of awake wear or 18 hours of total wear time are present).

Baseline is defined as the mean taken over the 8 days of wear during screening, i.e. Day 1 weekly average (as described above). Change from baseline will be calculated for all post-baseline weekly averages.

### 3.2.2. Change from baseline in FAACT sub-scale scores at Week-12

- FAACT-ACS
- FAACT-5IASS

*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.*

See Appendix 1 for FAACT scoring guidelines showing the calculation of FAACT subscales and total scores (including FAACT-ACS and -5IASS).

Change from baseline will be calculated at all post-baseline timepoints.

### 3.2.3. Change from baseline score for the questions from the Cancer Related Cachexia Symptom Diary (CRCSD) at Week 12 related to:

- Anorexia/appetite
- Nausea;
- Vomiting;
- Fatigue

*The CRCSD is a daily* (evening)*, self-reported questionnaire that measures severity of symptoms related to cancer cachexia: appetite, nausea, vomiting, and fatigue. 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*, apart from Vomiting which is measured on a numerical value from 0 to 30.

Weekly averages (on Day 1 and at Weeks 4, 8 and 12) will each be calculated as the mean taken over the 7 days immediately prior (e.g. if the Week 4 visit occurs on Day 29, the Week 4 average will be taken over Days 22 to 28; if the Week 8 visit occurs on Day 57, the Week 8 average will be taken over Days 50 to 56; and if the Week 12 visit occurs on Day 85, the Week 12 average will be taken over Days 78 to 84). If fewer than 4 days of scores are recorded, the mean should be treated as missing.

Baseline is defined as the mean taken over the 7 days prior to Day 1 (e.g. Days -7 to -1). Change from baseline will be calculated for all post-baseline weekly averages.

### 3.2.4. Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities

#### 3.2.4.1. Adverse Events

An adverse event (AE) is considered a Treatment Emergent Adverse Event (TEAE), relative to a given treatment, if the event starts during the effective duration of treatment, i.e. starting on, or after, the date and time of the first dose, but before the end of Part A (i.e. Week 12 for participants continuing to Part B; or follow-up contact [28-35 days after last dose], for those participants not continuing to Part B of the study).

A Treatment-Emergent Serious Adverse Event (TESAE) is a TEAE which also meets the definition of a Serious Adverse Event (SAE)

A 3-tier approach will be used to summarize TEAEs. Under this approach, TEAEs are classified into 1 of 3 tiers: -

> Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan (or similar, e.g. Safety Surveillance Review Plan). Appendix 2
>
> Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 5% of participants reporting the event in any treatment group.
>
> Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

Potential immunogenic AEs will be medically evaluated and categorized as per guidances as: 1) Hypersensitivity, 2) Anaphylaxis, 3) Angioedema, 4) Delayed I-AE response and / or 5) Cytokine Release syndrome. See Appendix 2 for Sampson Criteria.

#### 3.2.4.2. Laboratory Data

Safety laboratory tests (hematology, chemistry, and other clinical laboratory tests) will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the safety laboratory tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

#### 3.2.4.3. Vital Signs

A single measurement of pulse rate and supine systolic and diastolic blood pressure (BP) will be taken at the times specified in the protocol.

Change from baseline will be calculated for all post-baseline timepoints.

#### 3.2.4.4. Electrocardiograms (ECGs)

*A single standard 12-lead ECG* will *be collected at times specified in the* protocol.

Change from baseline for ECGs (heart rate, QT, QTcF, PR and QRS interval) will be calculated for all post-baseline timepoints.

### 3.3. Other Safety Endpoint(s)

See Section 3.2.4.

### 3.4. Other Endpoints/ Exploratory Endpoints

#### 3.4.1. Change from baseline in additional physical activity and gait endpoints measured with remote digital sensors at Week 12

See Section 3.2.1.

The additional physical activity and gait endpoints are:

From the wrist device:

- Light, Moderate, Vigorous Activity Time (mins/day)
- Number of Steps per Day (steps/day)
- Sleep Time (mins/day)
- Calories (cal)
- Max 15/60 mins of activity level (M15mins, M60mins; au/day)
- Average activity counts for the most active 10 hours of the day (M10hr; au/day)
- Average activity counts for the least active 5 hours of the day (L5hr; au/day)

From the lumbar device:

- Stride Duration (s)
- Double Support Duration (s)
- Single Limb Support Duration (s)
- Stance Duration (s)
- Swing Duration (s)
- Stride Lengths (m)
- Number of Steps (Average Cadence) (steps/min)
- Total Number of Steps per Day (steps/day)

#### 3.4.2. Change from baseline in additional FAACT total and sub-scale scores at Week 12

See Section 3.2.2.

The additional FAACT total and sub-scale scores are:

- Physical Well-being (PWB)
- Social/Family Well-being (SWB)
- Emotional Well-being (EWB)
- Functional Well-being (FWB)
- FACT-G Total score
- FAACT Total score

#### 3.4.3. Serum unbound and total concentrations of ponsegromab on Day 1, Weeks 4, 5, 8, 10, 12, and 16 (follow-up), plus Week 9 and 11 in PK substudy only

*Blood samples will be collected for measurement of serum unbound and total concentrations of ponsegromab as specified in the* protocol. *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.*

Trough concentrations ($C_{trough}$) are defined as the samples measured pre-dose at Weeks 4, 8, and 12.

### 3.4.4. Serum unbound and total concentrations of GDF-15 on Day 1, Weeks 4, 5, 8, 10, 12, and 16 (follow-up), plus Week 9 and 11 in PK substudy only

*Blood samples will be collected for measurement of serum concentrations of total and unbound GDF-15 at time points specified in the* protocol. *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.*

Change from baseline and fold change from baseline (i.e. post-dose / baseline), for total and unbound GDF-15, will be calculated for all post-baseline timepoints.

Additionally, the unbound GDF-15 will be compared to the median healthy volunteer level, at all timepoints, to create an endpoint with two levels ('Yes' and 'No') indicating whether the concentration is below the estimated healthy volunteer median level (< 0.3ng/mL) or not (≥ 0.3ng/mL).

### 3.4.5. Incidence of ADA and NAb

*Blood samples will be collected for determination of ADA and NAb as specified in the* protocol. See Appendix 7 for immunogenicity terms and definitions.

### 3.4.6. Change from baseline score for PROMIS-Fatigue at Week 12

*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 to 5. *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* Fatigue 7a Short Form score conversion table, provided in Appendix 3.

Change from baseline for PROMIS-Fatigue T-score will be calculated for all post baseline timepoints.

### 3.4.7. Change from baseline score for PROMIS-Physical Function at Week 12

*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* Physical Function Short Form 8c score conversion table, provided in Appendix 3.

Change from baseline for PROMIS-Physical Function T-score will be calculated for all post baseline timepoints.

### 3.4.8. Patient's Global Impression of Change (PGI-C) at Week 12; Change from baseline in Patient's Global Impression of Severity (PGI-S) at Week 12

#### 3.4.8.1. PGI-C

The PGI-C consists of 5 questions that ask the study participants to rate the overall change in their level of appetite, fatigue, physical function, 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 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.*

#### 3.4.8.2. PGI-S

The PGI-S consists of 5 questions that ask the study participants to evaluate the severity of their appetite loss, fatigue, physical function, 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 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.*

The change from baseline in PGI-S will be calculated for all post-baseline timepoints.

### 3.4.9. Tumor status according to RECIST 1.1 guidelines using CT scan at Week 12

*CT scans will be acquired during the study to monitor the tumor burden. Monitoring of the tumor burden will be performed by the site following standard RECIST 1.1 criteria* (outlined in Appendix 11 of the protocol).

### 3.4.10. 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

CT scans will also be submitted to a central imaging vendor for the measurement of body composition (skeletal muscle area and adipose tissue areas at the 3rd lumbar vertebral level).

The endpoints are:

- LSMI ($cm^2/m^2$): LSMI = skeletal muscle area ($cm^2$) / height $(m)^2$
- Skeletal muscle area ($cm^2$)
- Subcutaneous adipose area ($cm^2$)
- Visceral adipose area ($cm^2$)
- Intramuscular adipose area ($cm^2$)
- Skeletal muscle radio-attenuation (Hounsfield Units, HU)
- Subcutaneous adipose radio-attenuation (Hounsfield Units, HU)
- Visceral adipose radio-attenuation (Hounsfield Units, HU)

- Intramuscular adipose radio-attenuation (Hounsfield Units, HU)

Baseline is defined as the last measurement prior to, or on, study day 8. Change from baseline for LSMI will be calculated for all post baseline timepoints.

Percent change from baseline for the remaining skeletal muscle and adipose tissue measures will be calculated for all post baseline timepoints.

Percent change from baseline in radio-attenuation measurements at post baseline timepoints will be excluded for a participant if the IV contrast used at that timepoint is different to that used at baseline.

*Additional exploratory body composition measurements may be performed but may not be reported in the CSR.*

### 3.4.11. Change from baseline albumin and pre-albumin levels at Week 12

*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* Protocol.

The fold change from baseline in albumin and pre-albumin will be calculated for all post-baseline timepoints.

### 3.4.12. Survival status at end of Part A

The survival status at the end of Part A will be recorded for each participant. End of Part A is considered Week 12 for all participants (regardless of whether they enter the optional Part B or not).

The time (days) to death during Part A (up to Week 12) will also be calculated for each participant.

### 3.4.13. Response as defined by a ≥3.5% increase from baseline in body weight at Week 12

Additionally, response, as defined by a ≥3.5% increase from baseline in body weight at Week 12, will be defined as having two levels: 'Response' and 'Non-response'. The former will be based on participants having a ≥3.5% increase from baseline in body weight at Week 12. Otherwise, participants will be classed as having a 'Non-response'. Participants with an intercurrent event of premature discontinuation of study intervention, prohibited procedure/medication or inadequate compliance prior to Week 12 will have their Week 12 value censored (if not missing). Missing or censored values at Week 12 will be imputed as described in Section 5.3.1. Participants who die during the study will be classed as having a 'Non-response' after imputation. This endpoint will be calculated similarly for Week 4 and Week 8.

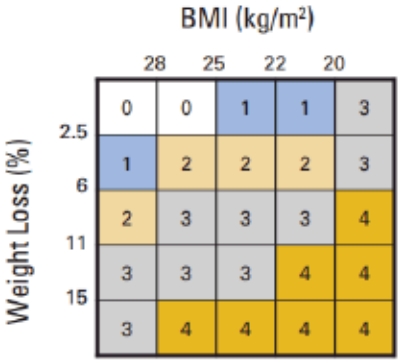
## 3.5. Baseline Variables

Percent weight loss in the 6 months prior to screening visit (SV) will be calculated as:

$$\frac{weight\ from\ 6\ months\ prior\ to\ SV\ [kg] - SV\ weight\ [kg]}{weight\ from\ 6\ months\ prior\ to\ SV\ [kg]} \times 100$$

If weight from 6 months prior to SV is missing, weight from the closest timepoint after 6 months should be used, e.g. if a participant has a weight available from 8 months, 6 months, and 4 months prior to SV, the weight from 6 months prior to SV should be used. If a participant has a weight available for 9 months, 4 months, and 2 months prior to SV, the weight from 4 months prior to SV should be used.

BMI-adjusted weight loss category (0/1/2/3/4) will be determined based on the percent weight loss in the 6 months prior to screening visit and the BMI at screening using the following grading system developed by Martin (2015)[1]:




Sarcopenia status at baseline will be determined. Participants with baseline lumbar skeletal muscle index (LSMI) ≤ 38.5 $cm^2/m^2$ in women, and ≤ 52.4 $cm^2/m^2$ in men, will be defined as having sarcopenia.

The following baseline inflammation variables will be determined for participants, if possible (note that the recorded units may differ from the units required in calculations):

- C-reactive protein (CRP) (mg/dL): from Retained Research Samples on Day 1
- CRP-albumin ratio: CRP on Day 1 (mg/dL) / albumin (mg/dL) on Day 1

  [Note: CRP concentrations below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLQ) prior to calculation of the ratio]
- Modified Glasgow Prognostic Score on Day 1:

  0: if CRP ≤ 1 mg/dL
  1: if CRP > 1 mg/dL
  2: if CRP > 1 mg/dL and albumin < 3.5 g/dL
- Neutrophil-lymphocyte ratio (NLR): neutrophil count at screening / lymphocyte count at screening
- Platelet-lymphocyte ratio (PLR): platelet count at screening / lymphocyte count at screening

## 4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

| ***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 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.* This will be the study intervention received by the participant for the majority of the timepoints during the relevant part of the study. If a participant receives an equal number of different doses, then the lowest of those doses will be used. If a participant receives an equal number of placebo and a given dose of ponsegromab, the ponsegromab dose will be used. |

| ***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*, or receive an incomplete dose, *all observations post-missed/*incomplete *dose will be censored and treated as missing data.* |
| Complete | All evaluable participants. For participants who discontinue study intervention, receive a prohibited procedure or prohibited medication, and/or miss a dose, |

| *Defined Analysis Set* | *Description* |
|---|---|
| | or receive an incomplete dose, all observations post-discontinuation, post-procedure or post-missed/incomplete dose will be included in the analysis set. |
| *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.* |

For participants who discontinue study intervention, the date of discontinuation of study intervention is defined as the date of last dose of IP + 29 days.

Listings of non-drug treatment(s)/procedure(s) and concomitant medication(s) will be provided (see Section 6.6.3). These will be blinded tables and will be reviewed prior to database lock to determine which procedures and medications would be classed as "prohibited".

Participants who are randomized to the wrong stratum, in error, will have the incorrect stratum assignment remain in IMPALA but the clinical database will include the correct stratum. The latter will subsequently be used for all relevant analyses, as appropriate.

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

*The null hypothesis of no difference between ponsegromab and placebo will be tested for each primary, and selected secondary* (physical activity, FAACT and CRCSD) *and tertiary* (PROMIS-fatigue, PROMIS-physical function, LSMI and survival status) *endpoints. The alternative hypothesis is that ponsegromab is superior to placebo.* The Type I error rate (α-level) used for the statistical inference will be 5% (1-sided). Each dose of ponsegromab will be compared separately with placebo. No adjustment for multiple comparisons will be made.

For all other endpoints, the results of any statistical analyses are for exploratory purposes only and there is no formal hypothesis testing.

### 5.2. General Methods

Unless otherwise stated, the main cohort and PK substudy will be reported together. Note that the separate presentations for the participants in the PK substudy may be reported in a supplemental CSR rather than the main CSR.

The analyses related to the primary, secondary and exploratory endpoints will be based on the appropriate population for analysis (see Section 4).

Unless otherwise stated, all summaries and plots will be presented by treatment group. The following treatment group labels (or similar) will be used:

- Placebo
- Ponsegromab 100mg
- Ponsegromab 200mg
- Ponsegromab 400mg

A 'Ponsegromab Combined' group will also be presented for safety summaries.

### 5.2.1. Summaries for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation (SD), median and Q1, Q3 and/or range (minimum and maximum) values. For endpoints to be analyzed on the natural log scale ($\log_e$), the geometric mean and geometric coefficient of variation (CV) will additionally be calculated.

### 5.2.2. Summaries for Categorical Endpoints

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

### 5.2.3. Mixed Models Repeated Measures (MMRM) Analysis

*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.*

Least-squares (LS) means (and 90% CIs) and LS mean differences versus placebo (and 90% CIs, and p-values for primary and selected secondary/tertiary endpoints), at each timepoint, will be provided. No adjustments will be made for multiplicity. In addition, profile plots of the LS means and differences (and 90% CIs for both) will be produced over time, with a separate line for each treatment group.

Standard SAS output will be provided to support the statistical summary table for the analysis model but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

Statistical Model Diagnostics

The presence of outliers will be investigated for this model. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than 3. A listing will be presented of any participants meeting these criteria and will be included with standard SAS output. The assumptions of normality will be verified graphically using

residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, quartile-quartile (QQ) plot and summary of fit statistics. The residual plots will not be included in the CSR.

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

### 5.2.4. 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* as described in Appendix 5.

Estimates of the model parameters of $E_0$, $E_{max}$, $ED_{50}$ and *Hill* and their 95% credible intervals will be produced to support the statistical summary table for the analysis model but will not be included in the CSR.

*The posterior medians and 90% credible intervals ($5^{th}$ and $95^{th}$ percentiles of the relevant posterior distribution) will be reported for each randomized dose (including placebo) and their differences relative to placebo.* Plots of the posterior medians and differences (including credible intervals for both) will be produced versus dose. *No adjustments will be made for multiplicity.*

*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.*

### 5.2.5. Analysis of Covariance (ANCOVA)

The ANCOVA model will include baseline and treatment as fixed terms in the model. Additional terms may be fitted in the model (eg, type of therapy [ie, platinum or not], type of cancer), as appropriate. LS means (and 90% CIs) and LS mean differences versus placebo (and 90% CIs) will be provided. No adjustments will be made for multiplicity. In addition, plots of the LS means and differences (and 90% CIs for both) will be produced.

Standard SAS output will be provided to support the statistical summary table for the analysis model but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

Statistical model diagnostics will be assessed in a similar way to that described in Section 5.2.3.

### 5.2.6. Cumulative Incidence Plots

Cumulative incidence plots will be produced based on the time to the event of interest (starting from the time of start of dosing on Day 1) for each treatment group separately, all treatments on the same plot. This will be based on plotting the cumulative incidence function (with no competing risks), which will be presented as a percentage on the y-axis. Participants who discontinue from the study or from study intervention will be censored at the associated discontinuation date. The number of participants at risk at each timepoint may be included.

Example SAS code is provided in Appendix 4.

### 5.2.7. Cox Proportional Hazards Model

The Cox proportional hazards model will include treatment as a fixed term in the model. Additional terms will be fitted in the model (eg, type of therapy [ie, platinum or not], type of cancer), as appropriate. Hazard ratios versus placebo (and 90% CIs and p-value) will be provided. No adjustments will be made for multiplicity. If the model is deemed inappropriate (e.g. the assumption of proportional hazards is not met), the analysis may not be performed.

Standard SAS output will be provided to support the statistical summary table for the analysis model.

Example SAS code is provided in Appendix 4.

### 5.2.8. Logistic Regression

The logistic regression model will include baseline and treatment as fixed terms in the model. Additional terms may be fitted in the model (eg, type of therapy [i.e. platinum or not] and type of cancer), as appropriate. Missing values (e.g. due to censoring) will be imputed for missing data using a multiple imputation method as described in Section 5.3.1. Odds (and 90% CIs) and odds ratios versus placebo (and 90% CIs and p-values) will be provided. No adjustments will be made for multiplicity.

Standard SAS output will be provided to support the statistical summary table for the analysis model and multiple imputation approach but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

## 5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

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

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

In listings, BLQ values (for PK or PD) will be reported as "<LLQ", where LLQ will be replaced with the value for the LLQ.

For PK and PD summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

#### 5.3.1. Multiple Imputation

For summarizing the proportion of responses (e.g. response as defined by a ≥3.5% increase from baseline in body weight at Week 12), all percent change from baseline data from the censored analysis set will be included (all timepoints up to and including Week 12, i.e. Weeks 4, 8 and 12). A multiple imputation method will be implemented, using a multivariate imputation method by chained equations, which is still valid with an arbitrary missing data pattern. The model will include baseline and treatment. Additional terms for type of therapy [i.e. platinum or not] and type of cancer will also be included, as appropriate. Twenty sets of imputations of each missing value will be constructed from the multiple imputation method and the proportion of responses by treatment will be determined with associated standard errors utilizing a normal approximation and will be combined using standard multiple imputation techniques proposed by Rubin[2] to yield overall estimates and CIs. If there is more missing data in the study than anticipated, the number of imputation sets may be increased as required. Note that data for participants who die during the study will be included in the imputation but will then be classed as having a 'Non-response' after imputation.

For logistic regression, all percent change from baseline data from the censored analysis set will be included (all timepoints up to and including Week 12, i.e. Weeks 4, 8 and 12). The same imputed datasets as produced for the proportion of responses above will be utilized, where a Logistic Regression model (as described in Section 5.2.8) will be applied to each of the 20 imputed datasets separately. Parameter estimates, of the log odds for each treatment and log odds ratios for each dose relative to placebo, will be combined using standard multiple imputation techniques proposed by Rubin[2] to yield overall estimates of the log odds and log odds ratios and their associated standard errors and will be used to create 90% CIs on the log-odds scale. The log odds (and CIs) and log odds ratios (and CIs) will be back transformed into odds and odds ratios (and CIs) for final reporting.

## 6. ANALYSES AND SUMMARIES

Unless otherwise specified, all analyses will be carried out using the Censored Analysis Set as defined in Section 4.

### 6.1. Primary Endpoint(s)

#### 6.1.1. Change from baseline body weight at Week 12

##### 6.1.1.1. Main Analysis

Absolute values, changes from baseline and percent changes from baseline in body weight will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1. Tables will include baseline and all post-baseline timepoints. Box and whisker plots (or similar) of absolute values, changes from baseline and percent changes from baseline over time will also be produced, with all treatments on the same plot.

Change from baseline in body weight will be analyzed using an MMRM model as described in Section 5.2.3. All *post-treatment dosing timepoints up to Week 12 (ie. Weeks 4, 8 and 12)* will be included in the model. *Additional terms for type of therapy [i.e. platinum or not] and type of cancer will be fitted in the model*. Additional plots of LS means and differences (including 90% CIs for both), for Week 12 only, will be produced over treatment.

*A Bayesian $E_{max}$ model*, as described in Section 5.2.4, *will then be fitted to the Week 12 LSmeans and SEs from the MMRM analysis*. This will be used to estimate the treatment effect related to the primary Estimand 1 (as described in Section 2.2.1). If the $E_{max}$ model analysis is not performed, *the primary results for the study will be based on the MMRM results at Week 12*.

#### 6.1.1.2. Sensitivity/Supplementary Analyses

A sensitivity analysis will be performed for the Bayesian Emax model on the primary endpoint. The same Bayesian Emax model analysis as in Section 6.1.1.1 will be performed and reported, applied to the Censored Analysis Set (as described in Section 4), but using a vague prior for the placebo change from baseline at Week 12 ($E_0$). This will be a t-distribution with a mean of 0 and a standard deviation equal to 10 times the predicted standard deviation, i.e. t(Mean = 0, SD = 49, df=5).

An exploratory analysis for the primary endpoint, will be performed to estimate the treatment effect related to Estimand 1b (as described in Section 2.2.1). The same summaries and analysis as in Section 6.1.1.1 (except the additional week 12 only plots of LS means and differences) will be performed and reported, but applied to the Complete Analysis Set (as described in Section 4).

A supplementary analysis will be performed for the percent change from baseline in body weight, using an MMRM model as described in Section 5.2.3. All post-treatment dosing timepoints up to Week 12 (ie. Weeks 4, 8 and 12) will be included in the model. Additional terms for type of therapy [i.e. platinum or not] and type of cancer will be fitted in the model.

An additional supplementary analysis will be performed for the percent change from baseline in body weight at Week 12 only, by summarizing descriptively by treatment group (as described in Section 5.2.2) based on the following categories:

| 3-Categories | |
|---|---|
| ≥ 1% loss: | %CFB ≤ -1 |
| Stable: | -1 > %CFB < 1 |
| ≥ 1% gain: | %CFB ≥1 |

| 5-Categories | |
|---|---|
| ≥ 3.5% loss: | %CFB ≤ -3.5 |
| ≥ 1% loss: | -3.5 > %CFB ≤ -1 |
| Stable: | -1 > %CFB < 1 |
| ≥ 1% gain: | 1 ≤ %CFB < 3.5 |
| ≥ 3.5% gain: | %CFB ≥3.5 |

Barcharts of these percentages of participants in each category at Week 12 will also be produced, with all treatments on the same plot (one plot for the 3-category definition and one for the 5-category definition).

## 6.2. Secondary Endpoint(s)

### 6.2.1. Change from baseline in physical activity and gait endpoints measured with remote digital sensors at Week 12

Absolute values and changes from baseline in the physical activity and gait endpoints (listed in Section 3.2.1) will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1. Tables will include baseline and all post-baseline timepoints.

Change from baseline in the physical activity and gait endpoints will be analyzed using an MMRM model as described in Section 5.2.3. All timepoints up to Week 12 will be included in the model. Additional terms for type of therapy [i.e. platinum or not] and type of cancer will be fitted in the model. This will be used to estimate the treatment effect related to Estimand 2 (as described in Section 0).

Additionally, the amount of available physical activity and gait data will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.2. If it is deemed that the amount of available data is insufficient or too imbalanced across the treatment groups, the results of the MMRM analysis may not be included in the CSR.

### 6.2.2. Change from baseline in FAACT sub-scale scores at Week 12

FAACT-ACS and FAACT-5IASS will be summarized and analyzed in a similar way to the secondary endpoint described in Section 6.2.1, These analyses will estimate the treatment effect related to Estimand 3 (as described in Section 0).

### 6.2.3. Change from baseline score for each of the questions from the CRCSD at Week 12

- Anorexia/appetite;
- Nausea;
- Vomiting;
- Fatigue

Weekly average data for each of the CRCSD endpoints will be summarized and analyzed in a similar way to the secondary endpoint described in Section 6.2.1. These analyses will estimate the treatment effect related to Estimand 4 (as described in Section 0).

### 6.2.4. Incidence of adverse events, safety laboratory tests, vital signs and ECG abnormalities

Analysis of adverse events, laboratory abnormalities, vital signs and ECG abnormalities will use the Safety Analysis Set defined in Section 4.

#### 6.2.4.1. Adverse Events

Adverse events (Tier 1, 2 and 3 AEs as described in Section 3.2.4.1) will be summarized by treatment group (including ponsegromab combined) and overall, in accordance with sponsor reporting standards. The adverse events will be sorted in descending frequency within a system organ class. If applicable, subject discontinuations due to adverse events will be detailed and summarized.

Incidence and severity of TEAE and TESAE tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment group (including ponsegromab combined) and overall.

TEAEs classed as Tier 2 events will each be tabulated by treatment group (including ponsegromab combined). The number and percentage of participants will be presented, along with the risk difference (and 95% confidence interval) between each dose of ponsegromab and placebo. No adjustment for multiplicity will be used.

Tier 2 TEAEs will also be presented graphically in two-panel plots; the left panel will present the proportions of TEAEs observed in a dose group of (including ponsegromab combined) and separately placebo, while the right panel will display the 95% confidence interval for the risk differences for each TEAE. A vertical line corresponding to the value of 0 will be added to the right-hand plot. Each panel will be paged by dose of ponsegromab.

Tier 2 TEAE outputs will be ordered in descending point estimate of risk difference within System Organ Class. If two or more events have the same frequency, they will be sorted alphabetically by preferred term. Footnotes will be included on the tables to provide proper interpretation of confidence intervals and to describe how the comparison was conducted, e.g. "Confidence intervals are not adjusted for multiplicity and should be used for screening purposes only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference is computed as ponsegromab versus placebo."

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

TEAEs classed as Tier 1 events will be tabulated by treatment group (including ponsegromab combined). Note that Tier 1 events are not planned to be presented graphically due to the small number of expected events.

Injection site reactions (ISR) will also be summarized by treatment group (including ponsegromab combined) and overall, in accordance with sponsor reporting standards. The ISRs will be sorted in descending frequency within a system organ class. Incidence and severity of ISR tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarize the total number of ISR by preferred term, which will be reported by treatment group (including ponsegromab combined) and overall.

Potential immunogenic AEs will be summarized by medical evaluation category and treatment groups (including ponsegromab combined) and overall. The number and percentage of participants, judged to have met the immune reaction criteria (injection site reactions, potential cases of angioedema, anaphylaxis, hypersensitivity, delayed hypersensitivity reactions and events potentially meeting the Sampson criteria), will be tabulated by treatment group (and with ponsegromab treatment groups combined only) and overall, and by severity.

#### 6.2.4.2. Laboratory Data

Laboratory data will be listed and summarized by treatment group (including ponsegromab combined) and overall, in accordance with the sponsor reporting standards.

#### 6.2.4.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic BP, and pulse rate will be summarized by treatment group (including ponsegromab combined) and overall, and timepoint, according to sponsor reporting standards. Tables will be paged by parameter.

In addition, changes from baseline will be analyzed using an MMRM model, as described in Section 5.2.3. The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 12 using the safety analysis set (as defined in Section 4). Additional terms will be fitted in the model (eg, type of therapy [ie, platinum or not], type of cancer), as appropriate.

Maximum decrease from baseline for supine systolic and diastolic blood pressures and maximum increase from baseline for supine pulse rate will be summarized by treatment group (including ponsegromab combined) and overall, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment group (including ponsegromab combined) and overall, using categories as defined in Appendix 6. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post dose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

#### 6.2.4.4. ECGs

Absolute values and changes from baseline for the ECG parameters (ie, HR, PR interval, QT interval, QTcF and QRS complex) will be summarized by treatment group (including ponsegromab combined) and overall, and timepoint according to sponsor reporting standards. Tables will be paged by parameter.

In addition, changes from baseline will be analyzed using an MMRM model, as described in Section 5.2.3. The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 12 using the safety analysis set (as defined in Section 4). Additional terms will be fitted in the model (eg, type of therapy [ie, platinum or not], type of cancer), as appropriate.

Maximum increase from baseline for QTcF will be summarized by treatment group (including ponsegromab combined) and overall, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for QTcF, PR and QRS will also be summarized descriptively by treatment group (including ponsegromab combined) and overall, using categories as defined in Appendix 6. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

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

### 6.3. Other Safety Summaries and Analyses Endpoint(s)

See Section 6.2.4.

### 6.4. Other Endpoints/Exploratory Endpoints

#### 6.4.1. Change from baseline in additional physical activity and gait endpoints measured with remote digital sensors at Week 12

Absolute values and changes from baseline in the additional physical activity and gait endpoints (listed in Section 3.4.1) will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

#### 6.4.2. Change from baseline in additional FAACT total and sub-scale scores at Week 12

Absolute values and changes from baseline in the additional FAACT total and sub-scale scores (listed in Section 3.4.2) will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

#### 6.4.3. Serum unbound and total concentrations of ponsegromab on Day 1, Weeks 4, 5, 8, 10, 12 and 16 (follow-up), plus Week 9 and 11 in PK substudy only

PK analyses will be performed using the PK analysis set, as defined in Section 4.

A listing of serum unbound and total concentrations, sorted by treatment group, participant and timepoint, will be produced. The listing will also include the actual times and will include all participants and all timepoints.

Additionally, the following presentations for serum unbound and total concentrations of ponsegromab will be produced, separately for 1) all participants (excluding Week 9 and 11 timepoints) and 2) for only participants in the PK substudy (including all timepoints):

- A summary of concentrations by treatment group and timepoint, where the set of statistics will include n, arithmetic mean, SD, coefficient of variation (CV%), minimum, Q1, median, Q3, maximum, geometric mean, geometric CV%, and the number of concentrations above the LLQ
- Median concentration-time plot (on a semi-log scale, all treatments on the same plot), Q1 and Q3 may be included
- Mean (±SD) concentration-time plot (on a semi-log scale, all treatments on the same plot)
- Median trough concentration-time plot (on a linear scale, all treatments on the same plot), Q1 and Q3 may be included
- Mean (±SD) trough concentration-time plot (on a linear scale, all treatments on the same plot).

Note that the separate presentations for the participants in the PK substudy may be reported in a supplemental CSR rather than the main CSR.

### 6.4.4. Serum unbound and total concentrations of GDF-15 on Day 1, Weeks 4, 5, 8, 10, 12 and 16 (follow-up), plus Week 9 and 11 in PK substudy only

PD analyses will be performed using the PD analysis set, as defined in Section 4.

A listing of unbound and total GDF-15 serum concentration levels, sorted by treatment group, participant and timepoint, will be produced. The listing will also include the fold change from baseline and will include all participants and all timepoints. For unbound GDF-15, the listing will also include a column to indicate whether the absolute GDF-15 concentration is below the healthy volunteer median level or not.

Additionally, the following presentations for unbound and total GDF-15 serum concentration levels will be produced, separately for 1) all participants (excluding Week 9 and 11 timepoints) and 2) for only participants in the PK substudy (including all timepoints):

- A summary of concentrations (absolute values and fold changes from baseline) by treatment group and timepoint, where the set of statistics will include (as data permit) n, arithmetic mean, SD, CV%, minimum, Q1, median, Q3, maximum, geometric mean, geometric CV% and the number of concentrations above the LLQ
- A summary of whether the absolute unbound GDF-15 concentrations are below the healthy volunteer median level or not, by treatment group and timepoint, as described in Section 5.2.2
- Median concentration-time plots (for absolute values only) (on a linear scale, all treatments on the same plot), Q1 and Q3 may be included
- Mean (±SD, if appropriate) concentration-time plots (for absolute values only) (on a linear scale, all treatments on the same plot).

In all presentations, the fold changes will be presented as percent change from baseline ([fold change from baseline -1]*100).

Note that the separate presentations for the participants in the PK substudy may be reported in a supplemental CSR rather than the main CSR.

### 6.4.5. Incidence of ADA and NAb

Immunogenicity analyses will be performed on the immunogenicity analysis set defined in Section 4.

If applicable and data permit, immunogenicity analyses will include:

- A listing of ADA and NAb results for all participants
- A summary (both table and figure, if appropriate) of the overall incidence of ADA and NAb
- The percentage of participants who are ADA and NAb positive at each timepoint and the cumulative percentage of ADA-positive or NAb-positive participants up to each timepoint.

If appropriate (e.g. the number of ADA-positive participants is ≥3 per treatment group), the additional analyses below may be performed:

- A spaghetti plot of individual participant ADA and NAb titer over time
- A summary of ADA and NAb titer by time

- Analysis of unbound and total ponsegromab concentration by ADA and NAb status. This may include summary tables and box and/or spaghetti plots of concentration data by ADA and NAb status
- Analysis of unbound and/or total ponsegromab concentration by maximum ADA and NAb titer tertile, which may include summary tables and box plots of concentration data by titer tertile if a large number of ADA-positive participants is reported (e.g n>10)
- Analysis of unbound and/or total GDF-15 concentration (as data permit) by ADA and NAb status, which may include summary tables and box and/or spaghetti plots of concentration data by ADA and NAb status
- Analysis of unbound and/or total GDF-15 concentration (as data permit) by maximum ADA and NAb titer tertile, which may include summary tables and box plots of concentration data by titer tertile if a large number of ADA-positive participants is reported (e.g n>10)
- An individual plot of unbound and total ponsegromab concentration, unbound and/or total GDF-15 concentration (as data permit), ADA and NAb titer in ADA-positive participants.

#### 6.4.6. Change from baseline score for PROMIS-Fatigue at Week 12

PROMIS Fatigue T-score will be summarized and analyzed in a similar way to the secondary endpoint described in Section 6.2.1.

#### 6.4.7. Change from baseline score for PROMIS-Physical Function at Week 12

PROMIS Physical Function T-score will be summarized and analyzed in a similar way to the secondary endpoint described in Section 6.2.1.

#### 6.4.8. PGI-C at Week 12; Change from baseline in PGI-S at Week 12

Absolute values in PGI-C will be summarized descriptively by treatment group and timepoint as described in Section 5.2.2.

Absolute values and changes from baseline in PGI-S will be summarized descriptively by treatment group and timepoint as described in Section 5.2.2.

#### 6.4.9. Tumor status according to RECIST 1.1 guidelines using CT scan at Week 12

The overall tumor response will be summarized by treatment, as described in Section 5.2.2, using the categories defined in Appendix 11 of the protocol.

#### 6.4.10. 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

Absolute values and changes from baseline in LSMI will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

Change from baseline in LSMI will be analyzed using ANCOVA as described in Section 5.2.5. Additional terms for type of therapy [i.e. platinum or not] and type of cancer will be fitted in the model.

Absolute values and percent changes from baseline in skeletal muscle and adipose tissue measures (listed in Section 3.4.10) will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

### 6.4.11. Change from baseline albumin and pre-albumin levels at Week 12

Absolute values and fold changes from baseline in albumin and pre-albumin will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1.

### 6.4.12. Survival status at end of Part A

Survival status at the end of Part A (Week 12) will be summarized descriptively by treatment group and overall, as described in Section 5.2.2.

Time to death will be summarized descriptively by treatment group, as described in Section 5.2.1. A cumulative incidence plot, as described in Section 5.2.6 will also be produced. Time to death will be analyzed using a Cox-proportional hazards model, as described in Section 5.2.7. All deaths will additionally be listed.

### 6.4.13. Response as defined by a ≥3.5% increase from baseline in body weight at Week 12

Response as defined by a ≥3.5% increase from baseline in body weight will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.2, with no imputation for missing data, including all post-baseline timepoints up to Week 12 (ie. Weeks 4, 8 and 12). Barcharts of the percentages over time will also be produced, with all treatments on the same plot.

The percentage of responses (and 90% CIs) at Week 12 will also be reported by treatment after multiple imputation for missing values as per Section 5.3.1. These responses will also be analyzed separately using a logistic regression model (as described in Section 5.2.8), where missing values will be imputed using multiple imputation as per Section 5.3.1. The logistic regression model will be fitted to the data at Week 12 only.

## 6.5. Subset Analyses

Additional analyses will be performed on the primary endpoint (change from baseline body weight) to assess the effect of the following two subgroup factors:

- Type of cancer (i.e. NSCLC, PANC or CRC)
- Type of therapy (ie, platinum or not) at randomization [+/- 28 days]
- Screening Roche GDF-15 (dichotomized using < or ≥ overall study median level (or an alternative cut-point, if appropriate))

These analyses will be performed on the censored analysis set, as defined in Section 4.

For each subgroup factor, absolute values, changes from baseline and percent changes from baseline in body weight will be summarized descriptively by subgroup factor, treatment group and timepoint, as described in Section 5.2.1. Tables will include baseline and all post-baseline timepoints.

For each subgroup factor, change from baseline in body weight will be analyzed using an MMRM model, as described in Section 6.1.1.1. Additional terms for the subgroup factor and its interaction with treatment group, time and the treatment-by-time interaction, will be included in the model. Other terms (eg, type of therapy [i.e. platinum or not] and type of cancer; described in Section 6.1.1.1) will be dropped from the model, as appropriate. LS means (and 90% CIs) and mean differences versus placebo (and 90% CIs) will be provided. The p-values for the subgroup interaction terms will be included in the tables, e.g. as a footnote. No adjustments will be made for multiplicity.

If the MMRM model cannot be fitted to the data, or the model is deemed inappropriate, the model may be simplified, or the analysis may not be performed.

Additionally, screening Roche GDF-15 will be plotted vs Week 12 change from baseline body weight using a scatterplot. The plot will include all participants and may be colored/trellised by different cancer types and/or type of therapy.

## 6.6. Baseline and Other Summaries and Analyses

### 6.6.1. Baseline Summaries

D*emographic data, concomitant medications, GDF-15 concentrations* (at screening, using the Roche Elecsys assay)*, height, weight, BMI, ECOG PS* (at screening). LSMI, sarcopenia status and BMI-adjusted weight loss category will be summarized, as defined in Section 5.2.1 or 5.2.2, as appropriate.

*In addition, a subset of medical history data will be reported; this* will *include type and stage of cancer*, TNM stage, the extent of the cancer (e.g metastatic vs non-metastatic; location of metastatic disease), the time from cancer diagnosis to randomization, and the percent weight loss in the 6 months prior to screening*, where feasible*. Cancer therapy details will also be summarized, as defined in Section 5.2.1 or 5.2.2, as appropriate, including line and type of prior cancer therapy, type and intent of current cancer therapy and whether participants are currently receiving no cancer treatment, or cancer treatment with or without platinum-based chemotherapy (both at randomization [+/- 28 days] and during treatment phase) and whether surgery or radiation was part of this cancer treatment.

Baseline inflammation will also be summarized, as defined in Section 5.2.1 or 5.2.2, as appropriate, including CRP, albumin, CRP-albumin ratio, modified Glasgow Prognostic Score, NLR and PLR.

The above baseline summaries will also be produced separately for the PK substudy only but may be reported in a supplemental CSR rather than the main CSR.

*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.*

### 6.6.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition for each phase of Part A of the study (screening, treatment and follow-up for participants not continuing to Part B of the study). They will additionally show which participants were analyzed for efficacy, PK, PD, immunogenicity as well as for safety. Frequency counts and percentages will be supplied for

participant discontinuation(s) by treatment group and overall. Data will be reported in accordance with the sponsor reporting standards.

### 6.6.3. Concomitant Medications and Nondrug Treatments/Procedures

All prior and concomitant medication(s) as well as non-drug treatment(s)/procedure(s) will be reported according to current sponsor reporting standards.

Additionally, any actions taken with participants' anti-cancer therapy (e.g. discontinuation or dose-reduction) during the study will be summarized descriptively by treatment group, as defined in Section 5.2.2.

### 6.6.4. Treatment Compliance

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

### 6.6.5. Retained Research Samples

*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* (other than CRP, as described in Section 3.5) *are not planned to be included in the CSR.*

### 6.6.6. Population PK

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.

## 7. INTERIM ANALYSES

### 7.1. Introduction

*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* the protocol.

*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, ongoing monitoring of the safety of participants will be performed by an IRC. Further details are provided in Section 10.1.5.1 of the protocol and will be further documented in an IRC charter.

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

## 7.2. Interim Analyses and Summaries

An interim analysis may be conducted after approximately 50% of randomized participants reach the Week 12 visit in Part A or discontinue the study prior to that visit.

The participants to be included in the interim analysis are:

| Interim Population | Description |
|---|---|
| Interim Safety Population | All participants randomized prior to the date of data snapshot. |
| Interim Efficacy Population | Participants who were randomized up to 11SEP2023 |

All interim analyses will be carried out using the relevant Analysis Set (as defined in Section 4) applied to the Interim Populations described above.

### 7.2.1. Efficacy Endpoints

For **body weight**, the descriptive summaries and main statistical analyses, described in Section 6.1.1.1, will be performed. Additionally, Bayesian predictive probabilities will be calculated, separately for each dose versus placebo, for end of study success based on both the MMRM results at Week 12 and the primary Bayesian $E_{max}$ model results. The predictive probabilities will be calculated using the method described by Grieve (1991)[3], incorporating vague priors. Additionally, the subset summary tables by tumor type, as described in Section 6.5, will be produced.

For digital endpoints **(gait speed, 95$^{th}$ percentile gait speed, MVPA and sedentary activity time)**, PROs **(FAACT-ACS, FAACT-5IASS, CRCSD-appetite, CRCSD-fatigue, PROMIS-fatigue and PROMIS-physical function)** and **LSMI**, the descriptive summaries and statistical analyses, described in Sections 6.2.1, 6.2.2, 6.2.3, 6.4.6, 6.4.7 and 6.4.10, will be performed. Additionally, Bayesian predictive probabilities will be calculated , separately for each dose versus placebo, using the method described by Grieve (1991)[3], incorporating vague priors, for end of study statistical significance based on the MMRM/ANCOVA results at Week 12.

Additionally, the overall tumor response according to RECIST guidelines will be summarized as described in Section 6.4.9.

### 7.2.2. Safety Endpoints

Adverse events, laboratory abnormalities, vital signs and ECG abnormalities will be summarized and analyzed as described in Section 6.2.4. A subset of these outputs, previously agreed with the C3651003 IRC, will be produced.

### 7.2.3. Other Summaries

Baseline summaries will be produced, as described in Section 6.6.1, for both the interim Safety and Efficacy populations.

## 8. REFERENCES

1. Martin L (2015): Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015 Jan 1;33(1):90-9.

2. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987; Wiley, New York.

3. Grieve AP (1991): Predictive probability in clinical trials: Biometrics, 47(1) 323-9.

## APPENDICES

### Appendix 1. FAACT Scoring Guidelines

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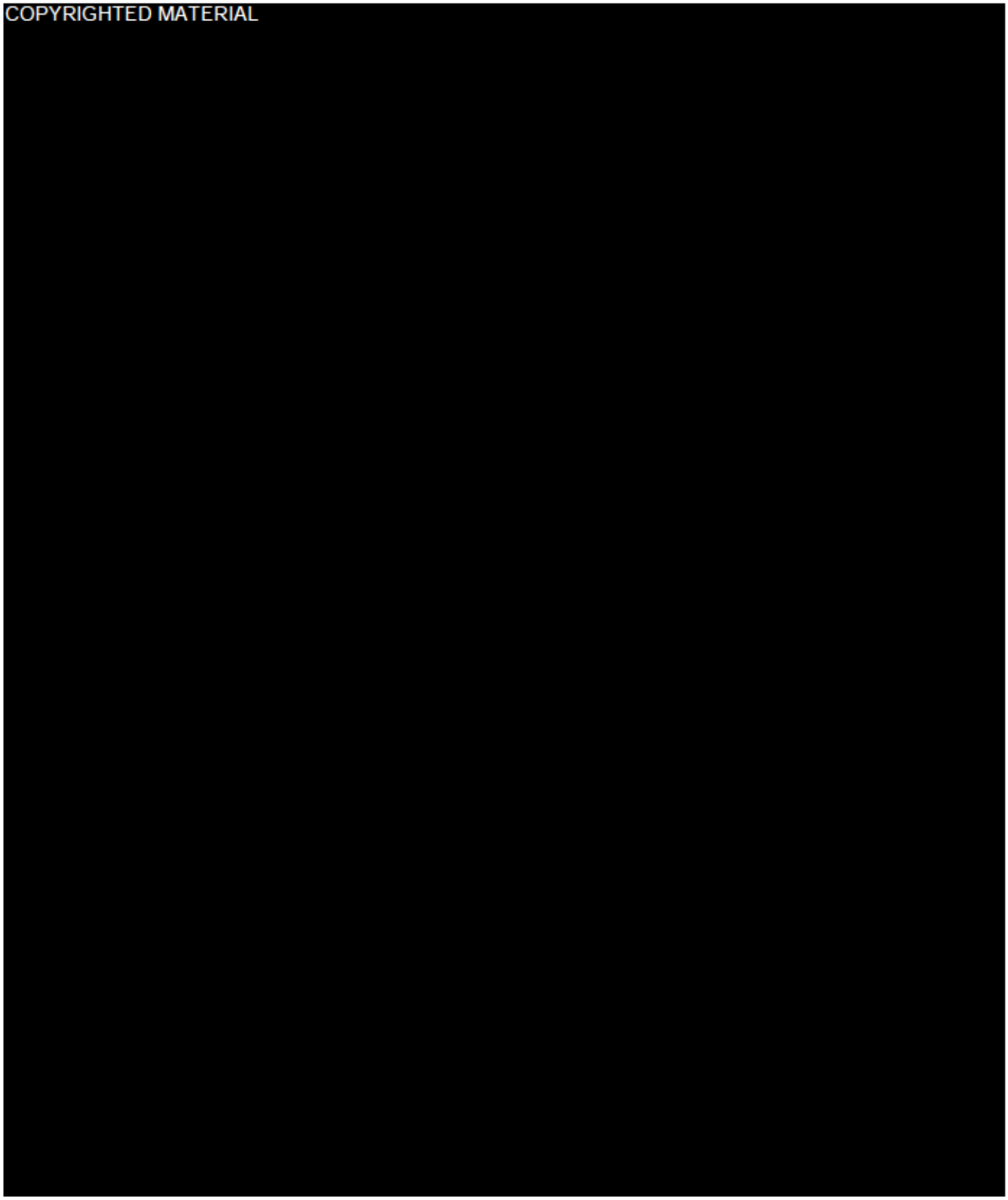

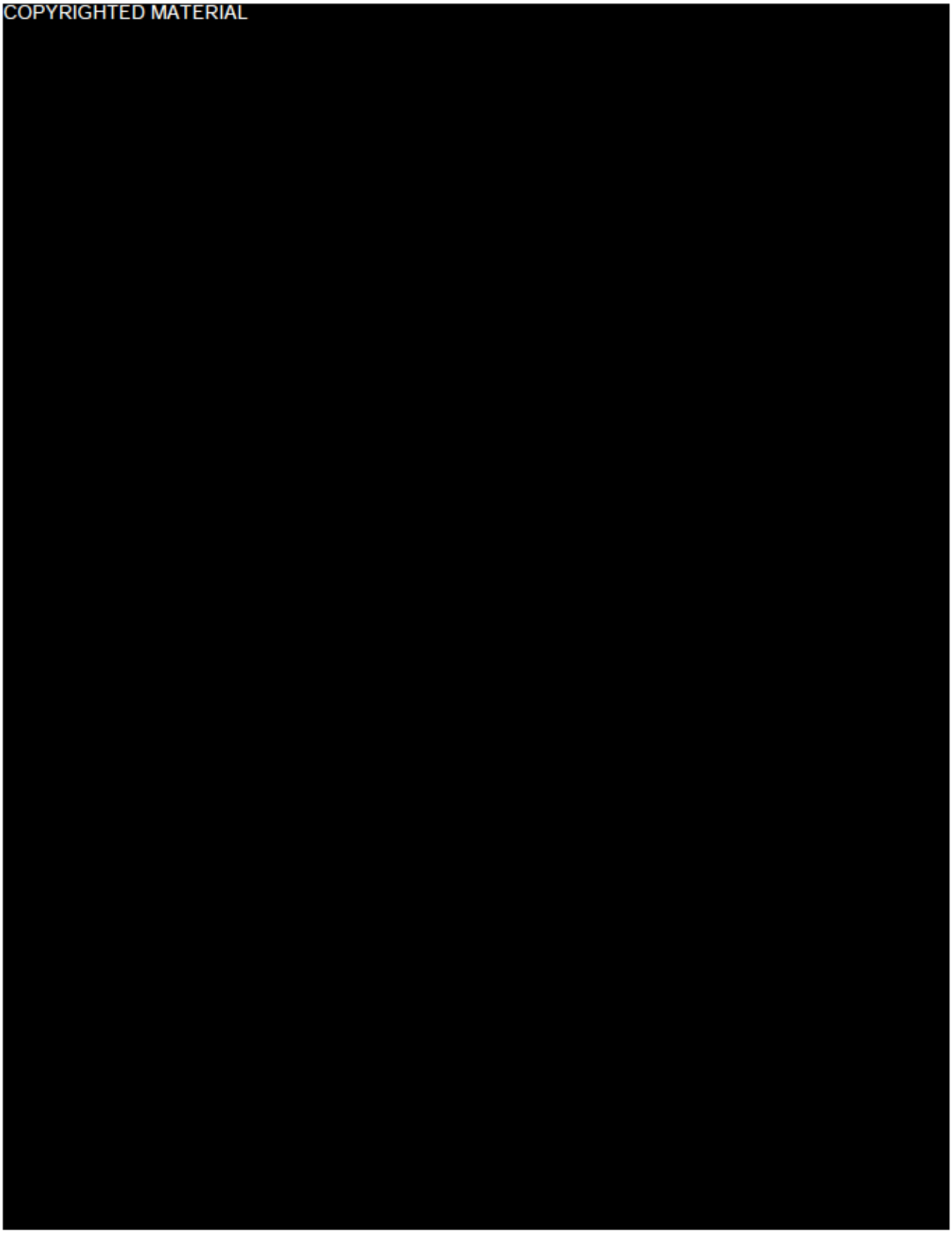

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

## Appendix 2. Sampson Criteria

### Clinical Criteria for Diagnosing Anaphylaxis

**Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   *AND AT LEAST ONE OF THE FOLLOWING*
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*PEF*, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

### Programmatically Identifying Potential Cases of Anaphylaxis

A participant is said to have an episode fulfilling the Sampson Criteria if at least one of the following criteria is met:

**Criterion 1:** The participant experienced an onset of both Condition 1 and Condition 2 below, on the day of, or on the day after, study drug administration.

a) Condition 1: a skin or mucosal membrane adverse event (AE) (using MedDRA PTs under Skin or Mucosal Membrane grouping),

b) Condition 2: a respiratory compromise AE (using MedDRA PTs under the Respiratory grouping), or an end-organ dysfunction/reduced blood pressure AE (using MedDRA PTs under End-organ dysfunction or Reduced Blood Pressure grouping), or reduced systolic blood pressure (characterized by a PT of hypotension, blood pressure decreased or blood pressure systolic decreased).

**Criterion 2:** The participant experienced an onset of any 2 or more conditions below, on the day of, or on the day after, study drug administration.

a) Condition 1: a skin or mucous membrane involvement AE (using MedDRA PTs under Skin or Mucosal Membrane grouping)

b) Condition 2: a respiratory compromise AE (using MedDRA PTs under the Respiratory grouping);

c) Condition 3: an end-organ dysfunction/reduced blood pressure AE ( using MedDRA PTs under 'End-Organ Dysfunction or Reduced Blood Pressure grouping), or reduced systolic blood pressure (characterized by a PT of hypotension, blood pressure decreased or blood pressure systolic decreased);

d) Condition 4: a gastrointestinal AE (using MedDRA PTs under the gastrointestinal grouping).

If the same specific AE belongs to more than one Condition/AE grouping above (i.e., 'Skin or Mucosal Membrane' grouping, 'Respiratory Compromise' grouping, 'End-Organ Dysfunction/ Reduced Blood Pressure' grouping, 'Gastrointestinal' grouping), the event should be assigned to not more than one of the above Conditions and in such a way as to maximize the number of Conditions fulfilled to support Criterion 2. For example, if the AE of Dyspnea (which belongs to the 'Respiratory Compromise' grouping) and the AE of Chest Pain (which may belong either to the 'Respiratory Compromise' grouping or to the 'End-Organ Dysfunction/ Reduced Blood Pressure' grouping) occurred, then the AE of Chest Pain will be assigned to the 'End-Organ Dysfunction/ Reduced Blood Pressure' grouping, so that Criterion 2 is fulfilled (if the AE of Chest Pain were assigned to the 'Respiratory Compromise' grouping, then Criterion 2 would not be fulfilled because the AE of Dyspnea also belongs to the 'Respiratory Compromise' grouping).

**Criterion 3:** The participant experienced reduced systolic blood pressure (characterized by a PT of hypotension, blood pressure decreased or blood pressure systolic decreased) on the day of, or on the day after, study drug administration, and at least 1 qualifying event. A qualifying event is defined as <u>any</u> of the following occurring during the current study or, if applicable, in the parent study from which the participant rolled over into the current study, after the first administration of the study drug (in the current or the parent study, as applicable) and before the administration of the same study drug associated with the current reduced systolic blood pressure event:

a) An event meeting Criterion 1 or Criterion 2;

b) An Injection Site reaction (ISR), as reported by the investigator;

c) An AE under the Anaphylactic Reaction Standardised MedDRA Query (SMQ), or the Angioedema SMQ, or the Hypersensitivity SMQ, considered to be related to the study drug, as reported by the investigator.

For episodes with multiple AEs fulfilling more than one Sampson Criteria at the same visit, the following hierarchy is used: Criterion 1, Criterion 2, Criterion 3. For example, when Criterion 1 is fulfilled, Criterion 2 and Criterion 3 are not evaluated.

## Appendix 3. PROMIS Score Conversion Tables

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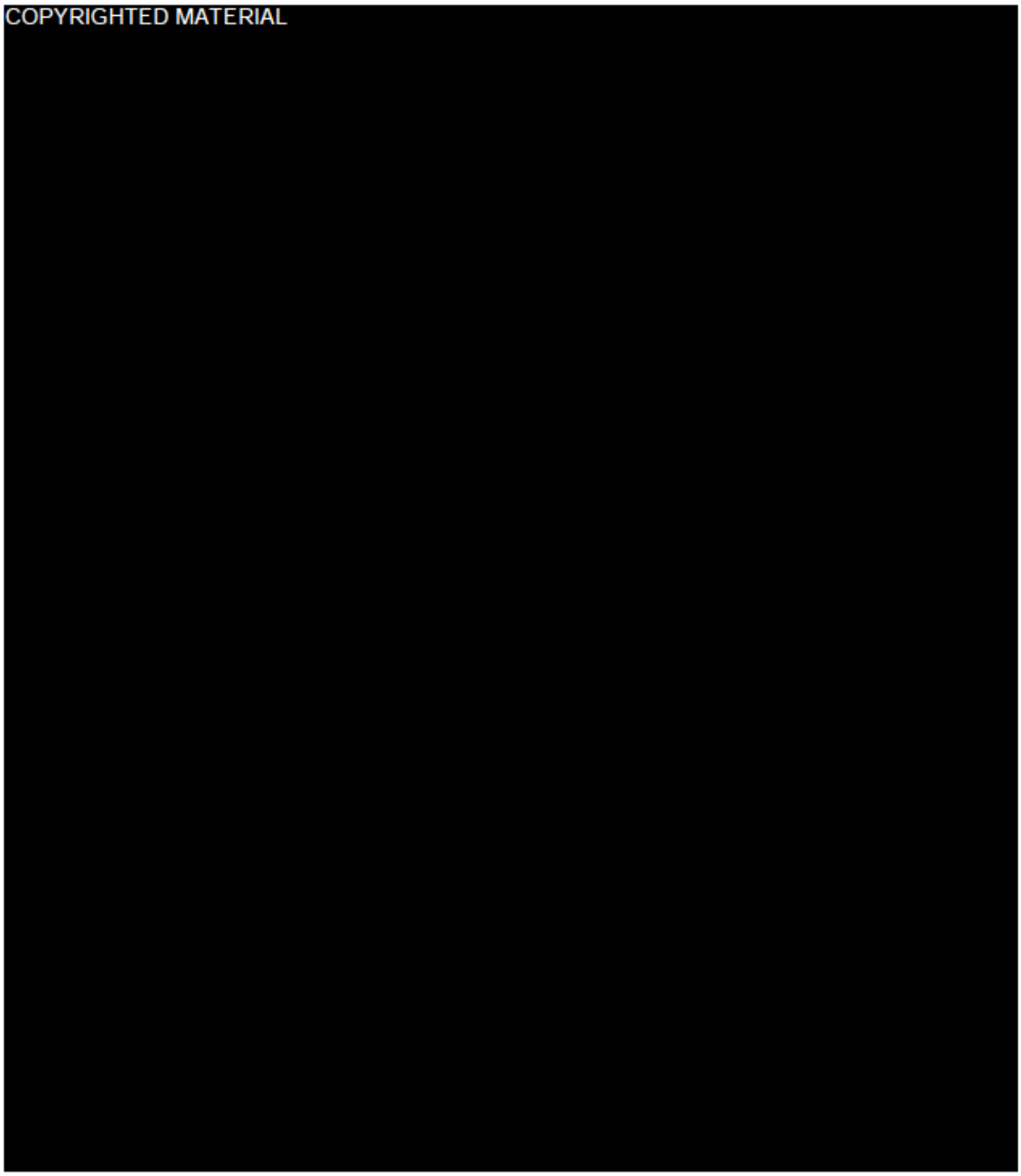

## Appendix 4. Example SAS Code

Example SAS code for MMRM Model

```
proc mixed data = dataset method=reml;
      class subject treatment time therapy cancer;
      model cfb = treatment base time base*time time*treatment therapy
                  cancer / ddfm=kr residual outp=resid_out;
      repeated time /subject=subjid type = un;
      lsmeans treatment*time/diff cl alpha=0.1;
      ods output lsmeans=lsmeans_out;
      ods output diffs=diffs_out;
run;
```

Example SAS code for ANCOVA Model

```
proc mixed data = dataset;
      class treatment therapy cancer;
      model cfb = treatment base therapy cancer / residual outp=resid_out;
      lsmeans treatment / diff cl alpha=0.1;
      ods output lsmeans=lsmeans_out;
      ods output diffs=diffs_out;
run;
```

Example SAS code for Cox Proportional Hazards Model:

```
proc phreg data=dataset;
      class treatment(ref='Placebo') / param=ref order=internal;
      class therapy cancer;
      model time*censor(1)= therapy cancer treatment / ties=Breslow
            risklimits alpha=0.1;
      hazardratio 'Comparisons vs Placebo' treatment / diff=ref alpha=0.1;
run;
```

Example SAS code for Cumulative Incidence Plots:

```
proc lifetest data = dataset method=km plots=cif outcif=cifatrisk
intervals=0 to 12 by 4;
      strata treatment;
      time day*censor(1) / eventcode=0;
run;
```

NOTE: the censor variable has a value = 1 when the related time is censored and has a value = 0 when the event of interest occurs. There should be no other values available for this censored variable in this dataset (including missing values). If required, missing observations should be removed prior to analysis.

Example SAS code for Proportion of Responses (with multiple imputation):

Assume the SAS dataset is in a long format. The variable 'treatment' should be coded similar to 'Placebo', 'Ponsegromab 100mg', 'Ponsegromab 200mg', 'Ponsegromab 400mg', so that 'Placebo' comes first.

NOTE: If a participant discontinues due to death, they should be included in the imputation, but once their value has been imputed then they should be classified as a non responder.

```
proc sort data=analysis out=analysis_long;
   by subjid time treatment therapy cancer base;
run;

* Create wide dataset for multiple imputation;
proc transpose data= analysis_long out=analysis_wide prefix=wk;
   by subjid treatment therapy cancer base;
   id time;
   var pcfb;
run;

* Perform multiple imputation;
proc mi data=analysis_wide seed=169 nimpute=20 out=analysis_mi;
   class treatment;
   fcs nbiter=10 reg(/details);
   var base treatment therapy cancer wk4 wk8 wk12;
run;


* Need to add in here code to classify any participants that discontinue
due to death as non responders;


* Determine responders and non-responders at Week 12 for all imputed
  datasets;
data analysis_mi_12;
   set analysis_mi;
   if wk12 >= 3.5 and wk12 ne . then resp = 1;
   if wk12 < 3.5 and wk12 ne . then resp = 0;
run;

* Create datasets and combine proportions;
proc freq data=analysis_mi_12;
   tables _imputation_* treatment *resp / out=prop_mi outpct;
run;

data prop_mi_0;
   set prop_mi;
   if resp=0;
   keep _imputation_ treatment count;
   rename count=count_0;
run;
```

```
data prop_mi_1;
   set prop_mi;
   if resp=1;
   keep _imputation_ treatment count;
   rename count=count_1;
run;

data prop_mi_combined;
   merge prop_mi_0 prop_mi_1;
   by _imputation_ treatment;
   total = count_0 + count_1;
   p = count_1 / total;
   q = count_0 / total;
   se_p = sqrt((p*q)/total);
run;

proc sort data=prop_mi_combined;  by treatment _imputation_;  run;

proc mianalyze data=prop_mi_combined alpha=0.1;
   by treatment;
   modeleffects p;
   stderr se_p;
   ods output parameterestimates=prop_mi_out;
run;
```

Example SAS code for Logistic Regression Model (with multiple imputation):

The same imputed datasets as produced above for the 'Proportion of Responses' will be utilized. Note: the imputed dataset should be ordered with 'Resp'=1 first to ensure that the odds ratios are for a response = 1 and the reference group is Placebo.

```
* Fit logistic regressions to each imputed dataset and combine results;
proc sort data=analysis_mi_12; by _imputation_ treatment descending resp;
run;

proc genmod data=analysis_mi_12 order=internal  descending;
   by _imputation_;
   class resp treatment;
   model resp = treatment therapy cancer base
                / dist=bin link=logit alpha=0.1;
   lsmeans treatment / cl diff alpha=0.1 exp;
   ods output lsmeans=odds_mi diffs=oddsrat_mi;
run;

*Odds ratios;
data oddsrat_mi;
   set oddsrat_mi(where=(_TREATTXT="Placebo"));
   if TREATTXT = ' Ponsegromab 100mg ' then treatment = 100;
   if TREATTXT = ' Ponsegromab 200mg ' then treatment = 200;
   if TREATTXT = ' Ponsegromab 400mg ' then treatment = 400;
   if treatment = . then delete;
   SE = StdErr;
run;

proc sort data=oddsrat_mi; by treatment _imputation_;  run;
```

```
proc mianalyze data=oddsrat_mi  alpha=0.1;
   by treatment;
   modeleffects estimate;
   stderr SE;
   ods output parameterestimates=OddsRatios_mi_out;
run;

data OddsRatios_mi_out;
   set OddsRatios_mi_out;
   oddsratio = exp(estimate);
   LCLoddsratio = exp(LCLMean);
   UCLoddsratio = exp(UCLMean);
run;

* Odds;
data odds_mi;
set odds_mi;
   if TREATTXT = 'Placebo' then treatment = 0;
   if TREATTXT = 'Ponsegromab 100mg ' then treatment = 100;
   if TREATTXT = 'Ponsegromab 200mg ' then treatment = 200;
   if TREATTXT = 'Ponsegromab 400mg ' then treatment = 400;
   if treatment = . then delete;
   SE = StdErr;
run;
proc sort data=odds_mi; by treatment _imputation_;  run;

proc mianalyze data=odds_mi  alpha=0.1;
   by treatment;
   modeleffects estimate;
   stderr SE;
   ods output parameterestimates=Odds_mi_out;
run;

data Odds_mi_out;
   set Odds_mi_out;
   odds = exp(estimate);
   LCLodds = exp(LCLMean);
   UCLodds = exp(UCLMean);
run;
```

## Appendix 5. Bayesian Emax Model Methodology Details

Data Provided by Programmer

A .csv dataset of LS means from the MMRM analysis should be produced by programming for use in R by the reporting statistician and QC statistician. The file should be in the following format (Note that column headers should be labelled as specified below (including capitalization), as R is case sensitive): -

| Dose | Mean | SE |
|---|---|---|
| 0 | 0 | 0.3 |
| 2.5 | 0.2 | 0.4 |
| 10 | 0.4 | 0.5 |
| 40 | 0.3 | 0.3 |
| 80 | 1.6 | 0.4 |
| 120 | 1.8 | 0.5 |

The residual standard deviation (Residual_SD) on Week 12 from the unstructured covariance matrix from the MMRM will also be provided by programming in a separate .csv file.

Fitting the Emax Model

The 4-parameter Emax model will be fitted using the latest version (currently 2.3.5) of the clinDR package. This analysis will be conducted by the reporting statistician. A different statistician will conduct QC of the analysis. The outputs of the analysis will be provided as .csv files to the programming team for creation of programming tables and figures.

The default burn-in and number of samples will be utilized along with thinning of 20, which will include 3 chains to assess convergence.

Model diagnostics will be examined, including trace and auto-correlations plots. If these raise concerns over model convergence, additional burn-ins, samples and thinning will be investigated to improve convergence. Changes to the priors below may also be considered (e.g. increase precision of hill) to improve convergence, if deemed necessary, and would be documented in final tables as appropriate. The final diagnostic plots will not be included in the clinical study report.

Priors

Prior distributions will be specified for the placebo response ($E_0$), the difference in response (difTarget) between the highest dose (dTarget = 400mg) and placebo, and the residual standard deviation (sigma). Note that Emax is derived from other parameters and is thus not explicitly supplied.

| Parameter | Prior |
|---|---|
| $E_0$ | t(Mean = -0.58, SD = 1.84, df=3) |
| difTarget | t(Mean = 0, SD = 49, df=5) |
| sigma | Uniform(lb=0.49, ub=49) |

*$E_0$: 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 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.*

*difTarget: A vague t-distribution will be used for the 400 mg placebocorrected 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.*

ClinDR default settings will be used to specify prior distributions for the Hill parameter and the $ED_{50}$. The default distributions in the current version of clinDR (version 2.3.5) are based on a meta-analysis of clinical dose response data 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 ($P_{50}$) is currently ~150 mg Q4W dose, based on latest data for the compound (this may be updated as new data become available).

## R Code

The following R code is included as an example that will be used as a basis for the analysis:

```
library(clinDR)
mmrmRes <- read.csv("LSmeans.csv", header=T, stringsAsFactors=F)


# Determine 'effective' subject numbers based on MMRM SD at Week 12:
mmrm_sd <- 0.825                                  # Provided by programming
mmrmRes$n <- trunc((mmrm_sd/mmrmRes$se)^2,0)
```

```
# Set-up priors and MCMC options:
prior_mmrm <- emaxPrior.control(epmu=-0.58, epsca=1.84,
                                difTargetmu=0, difTargetsca=49,
                                dTarget=400, effdf=5,
                                p50=150,
                                sigmalow=0.49, sigmaup=49)
mcmc_mmrm <- mcmc.control(chains=3, thin=20, seed=169)

# Run Emax model: #
emaxMMRM <- fitEmaxB(mmrmRes$mean, mmrmRes$dose, prior_mmrm, modType=4,
                     count=mmrmRes$n, msSat=mmrm_s d^2, mcmc=mcmc_mmrm)

# Diagnostics and output:
stan_trace(emaxMMRM$estanfit)                    # Look at trace
stan_dens(emaxMMRM$estanfit)                     # Look at densities
stan_ac(emaxMMRM$estanfit)                  # Look at autocorrelation
summary(emaxMMRM)                           # Summary of model parameters
plot(emaxMMRM)                              # Look at fitted vs. observed data to check model fit
emaxMMRMout <- predict(emaxMMRM, dosevec=mmrmRes$dose, clev=0.90)   # Get dose
predictions

# Posterior predictive check for non-monotone dose response
postCheck<-checkMonoEmax(y=mmrmRes$mean,dose=mmrmRes$dose,
        parm=coef(emaxMMRM),sigma2=(sigma(emaxMMRM))^2,nvec=mmrmRes$n)
```

Data Provided by Statistician

Model parameters, posterior medians and credible intervals, and posterior differences and credible intervals, as specified in Section 5.2.4, will be output and provided back to programming in .csv files after QC is complete.

Additionally, at interim, posterior mean differences (versus placebo) and standard errors for each randomized dose will be output and provided back to programming in a .csv file for the calculation of predictive probabilities.

## Appendix 6. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

### Categories for QTcF

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

### Categories for PR and QRS

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

### Categories for Vital Signs

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

Measurements that fulfill these criteria are to be listed.

## Appendix 7. Immunogenicity Terms and Definitions

| Term | Definition |
|---|---|
| Treatment-induced ADA | Baseline ADA titer is missing or negative and subject has ≥ 1 post-treatment positive ADA titer. |
| Treatment-boosted ADA | Baseline ADA titer is positive and subject has a ≥ 4-fold dilution increase (or other threshold value as defined in the SAP) in ADA titer from baseline in ≥ 1 post-treatment sample. If ADA titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline. If ADA titer is log2 transformed, a 4-fold dilution increase is equivalent to 2 unit increase in titer (log2) from baseline. |
| ADA-positive subject | A subject with ≥ 1 treatment-induced or treatment-boosted ADA response. |
| ADA-negative subject | An ADA evaluable subject without treatment-induced or treatment-boosted ADA response. Subject either has (1) all ADA-negative results throughout the study or (2) is ADA positive at baseline but did not become treatment-boosted post-dose. |
| ADA incidence | The percent of ADA-positive subjects in a treatment group/cohort or study. |
| Treatment-induced NAb | Baseline NAb titer is missing or negative or ADA-negative and subject has ≥ 1 post-treatment positive NAb titer. |
| Treatment-boosted NAb | Baseline NAb titer is positive and subject has a ≥ 4-fold dilution increase (or other threshold as defined in the SAP) in NAb titer from baseline in ≥ 1 post-treatment sample. If NAb titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline. If NAb titer is log2 transformed, a 4-fold dilution increase is equivalent to 2 unit increase in titer (log2) from baseline. |
| NAb-positive subject | An ADA-positive subject with ≥ 1 treatment-induced or treatment-boosted NAb response. For ADA-positive (treatment-boosted) subjects, subject is NAb positive only if the subject has ≥1 treatment-induced or treatment-boosted NAb response at the visit where the subject has a treatment-boosted ADA response. For visits where the subject did not show a boosted ADA response, the subject is classified as NAb-negative for the visit even if the subject has post-treatment positive NAb titer for that visit. |
| NAb-negative subject | NAb evaluable participant who is either (1) an ADA-negative subject or (2) an ADA-positive subject without treatment-induced or treatment-boosted NAb response (i.e. subject has all NAb-negative results throughout the study or subject is NAb positive at baseline but did not become treatment-boosted post-dose).<br>Note: in the event a subject is ADA-positive at baseline but did not show a boosted response post-treatment, subject is classified as ADA-negative and NAb-negative at the subject level even if the subject has post-treatment positive NAb titer. As such all ADA-negative subjects are NAb-negative regardless of NAb titer data." |
| NAb incidence | The percent of NAb-positive subjects in a treatment group/cohort or study. |
| **Duration of ADA and NAb response (subject-level definitions): recommended for studies with ≥ 16 weeks of ADA measurements** | |
| Transient ADA | An ADA-positive subject with (1) a treatment-induced or treatment-boosted ADA sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted ADA samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is ADA negative. |
| Persistent ADA | An ADA-positive subject with first and last positive ADA samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between. |
| Indeterminate ADA | An ADA-positive subject who is not persistent or transient. |
| Transient NAb | A NAb-positive subject with (1) a treatment-induced or treatment-boosted NAb sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted NAb samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is NAb negative or ADA negative. |
| Persistent NAb | A NAb-positive subject with first and last positive NAb samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between. |
| Indeterminate NAb | A NAb-positive subject who is not persistent or transient. |

Note: Duration of response (persistent, transient or indeterminate), on-treatment and off-treatment definitions are only applicable to ADA (or NAb)-positive subjects.

## Appendix 8. List of Abbreviations

| Abbreviation | Term |
|---|---|
| ACS | anorexia and cachexia subscale |
| ADA | anti-drug antibodies |
| AE | adverse event |
| ANCOVA | analysis of covariance |
| au | arbitrary units |
| BDR | blinded data review |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| BP | blood pressure |
| bpm | beats per minute |
| cal | calories |
| CFB | change from baseline |
| CI | confidence interval |
| cm | centimetres |
| CRC | colorectal cancer |
| CRCSD | cancer related cachexia symptom diary |
| CRP | C-reactive protein |
| CSR | clinical study report |
| CT | computed tomography |
| $C_{trough}$ | trough concentration |
| CV | coefficient of variation |
| df | degrees of freedom |
| difTarget | the difference in response between the highest dose and placebo |
| dL | decilitres |
| dTarget | the highest dose |
| $E_0$ | placebo effect |
| ECG | electrocardiogram |
| $ED_{50}$ | dose producing 50% of the maximal effect |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| $E_{max}$ | maximal effect |
| EWB | emotional well-being |
| 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 |
| FACT-G | Functional Assessment of Cancer Therapy - General |
| FDA | Food and Drug Administration |
| FWB | functional well-being |
| GDF-15 | growth differentiation factor 15 |
| HR | heart rate |
| HRQoL | health-related quality of life |
| CRP | C-reactive protein |
| HU | Hounsfield units |
| I-AE | immunogenic adverse event |
| IRC | independent review committee |
| IP | investigational product |
| ISR | injection site reaction |
| IV | intravenous |
| kg | kilogram |

| Abbreviation | Term |
|---|---|
| L5hr | average activity counts for the least active 5 hours of the day |
| lb | lower bound |
| LLQ | lower limit of quantitation |
| LS | least-squares |
| LSMI | lumbar skeletal muscle index |
| m | metres |
| M10hr | average activity counts for the most active 10 hours of the day |
| M15mins | maximum 15 minutes of activity level |
| M6min | maximum daily 6 minutes of activity |
| M60mins | maximum 60 minutes of activity level |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligrams |
| min(s) | minute(s) |
| mL | millilitres |
| mmHg | millimetres of mercury |
| MMRM | mixed model with repeated measures |
| msec/ms | milliseconds |
| MVPA | moderate to vigorous physical activity time |
| n | number |
| N/A | not applicable |
| NAb | neutralizing antibodies |
| ND | not done |
| ng | nanograms |
| NLR | neutrophil-lymphocyte ratio |
| NRS | numerical rating scale |
| NS | no sample |
| NSCLC | non-small-cell lung cancer |
| OLT | open-label treatment |
| P50 | the predicted ED50 for the compound |
| PANC | pancreatic cancer |
| PCD | primary completion date |
| PD | pharmacodynamic(s) |
| PGI-C | Patient Global Impression of Change |
| PGI-S | Patient Global Impression of Severity |
| PK | pharmacokinetic(s) |
| PLR | platelet-lymphocyte ratio |
| PR | interval in ms of the PR portion of the ECG |
| PROACC-1 | Patient Reported Outcomes and Activity in CanCer |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | preferred term |
| PWB | physical well-being |
| Q1 | first quartile |
| Q3 | third quartile |
| Q4W | every four weeks |
| QC | quality control |
| QOL | quality of life |
| QQ | quantile-quantile |
| QRS | interval in ms of the QRS portion of the ECG |
| QT | interval in ms of the QT portion of the ECG |
| QTcF | corrected QT (Fridericia method) |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| s | seconds |

| Abbreviation | Term |
|---|---|
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SD | standard deviation |
| SE | standard error |
| SMQ | standardised MedDRA query |
| SOP | standard operating procedure |
| SV | screening visit |
| SWB | social/family well-being |
| TNM | Tumor (T), node (N), and metastasis (M) cancer staging |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| ub | upper bound |