Statistical Analysis Plan: J4Z-MC-GIDA

A randomized, double-blind, placebo-controlled multi-center study of intravenous bimagrumab, alone or in addition to open label subcutaneous semaglutide, to investigate the efficacy and safety in overweight or obese men and women

NCT05616013

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STATISTICAL ANALYSIS PLAN

(Part 1)

PROTOCOL NUMBER: VER201-PH2-031 (Lilly Alias: J4Z-MC-GIDA)

TITLE: A randomized, double-blind, placebo-controlled multi-center study of intravenous bimagrumab, alone or in addition to open label subcutaneous semaglutide, to investigate the efficacy and safety in overweight or obese men and women

STUDY DRUG: Bimagrumab (LY3985863)

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LIST OF ABBREVIATIONS

ADA	Anti-Drug-Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphate
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
BIA	Biomolecular Interaction Analysis
BMD	Bone Mineral Density
BMI	Body Mass Index
CBC	Complete Blood Count
CCK18	Caspase-Cleaved K18
CK	Creatine Kinase
CP	Concomitant Procedures
CRF	Case Report Form
DMC	Data Monitoring Committee
DXA	Dual-Energy X-Ray Absorptiometry
ECG	Electrocardiogram
FAS	Full Analysis Set
FLI	Fat Loss Index
FSH	Follicle Stimulating Hormone
GGT	Gamma-Glutamyl Transferase
HbA1c	Hemoglobin A1C
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HOMA2	Homeostasis Model Assessment, version 2
hsCRP	High-sensitivity C-reactive protein
IBW	Ideal Body Weight
ICE	Inter-current Event
IEC	Independent Ethics Committees
IL-6	Interleukin 6
IL-18	Interleukin 18
IgG	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Boards
i.v.	Intravenous

IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite for Clinical Trials
LDL	Low Density Lipoprotein
LLN	Lower Limit of Normal
miR-122	MircoRNA 122
MMRM	Mixed Model for Repeated Measurements
NGAL	Neutrophil gelatinase-associated lipocalin
OLE	Open-label extension
PD	Pharmacodynamic(s)
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic(s)
PT	Prothrombin Time
QOL	Quality of Life
QTc	Corrected QT Interval
QUICKI	Quantitative Insulin-Sensitivity Check Index
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SF-36	Short Form 36 Health Survey Questionnaire
s.c.	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
TEAE	Treatment Emergent Adverse Event
TGF-β	Transforming Growth Factor Beta
ULN	Upper Limit of Normal
VAT	Visceral Adipose Tissue
WD	Withdrawal
WHtR	Waist-to-Height Ratio

CONTENTS

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1. INTRODUCTION

This document describes the planned statistical analyses for the core treatment period (first 48 weeks) of Protocol VER201-PH2-301 (Lilly Alias: J4Z-MC-GIDA), a study conducted by Versanis Bio, Inc, a wholly owned subsidiary of Eli Lilly and Co. The purpose of the study is to evaluate the safety and efficacy of intravenous bimagrumab and subcutaneous semaglutide for weight loss in overweight or obese adults. Analyses for the extension treatment period of the study will be covered by a separate SAP addendum for the Extension Treatment period.

This analysis plan supplements the study protocol (VER201-PH2-301 Protocol Version 5.0 dated 9th April 2024). If the protocol is amended, this statistical analysis plan will be revised as required. The SAP v 1.0 is approved before any sponsor team member were unblinded. The plan will be finalized before the study database is locked for the core treatment period of the study.

2. STUDY OBJECTIVES

The planned study is designed to evaluate the effect of bimagrumab alone or in addition to the approved obesity therapeutic semaglutide in obese or overweight subjects with at least one obesity related co-morbidity, without T2DM.

2.1 Primary Objectives

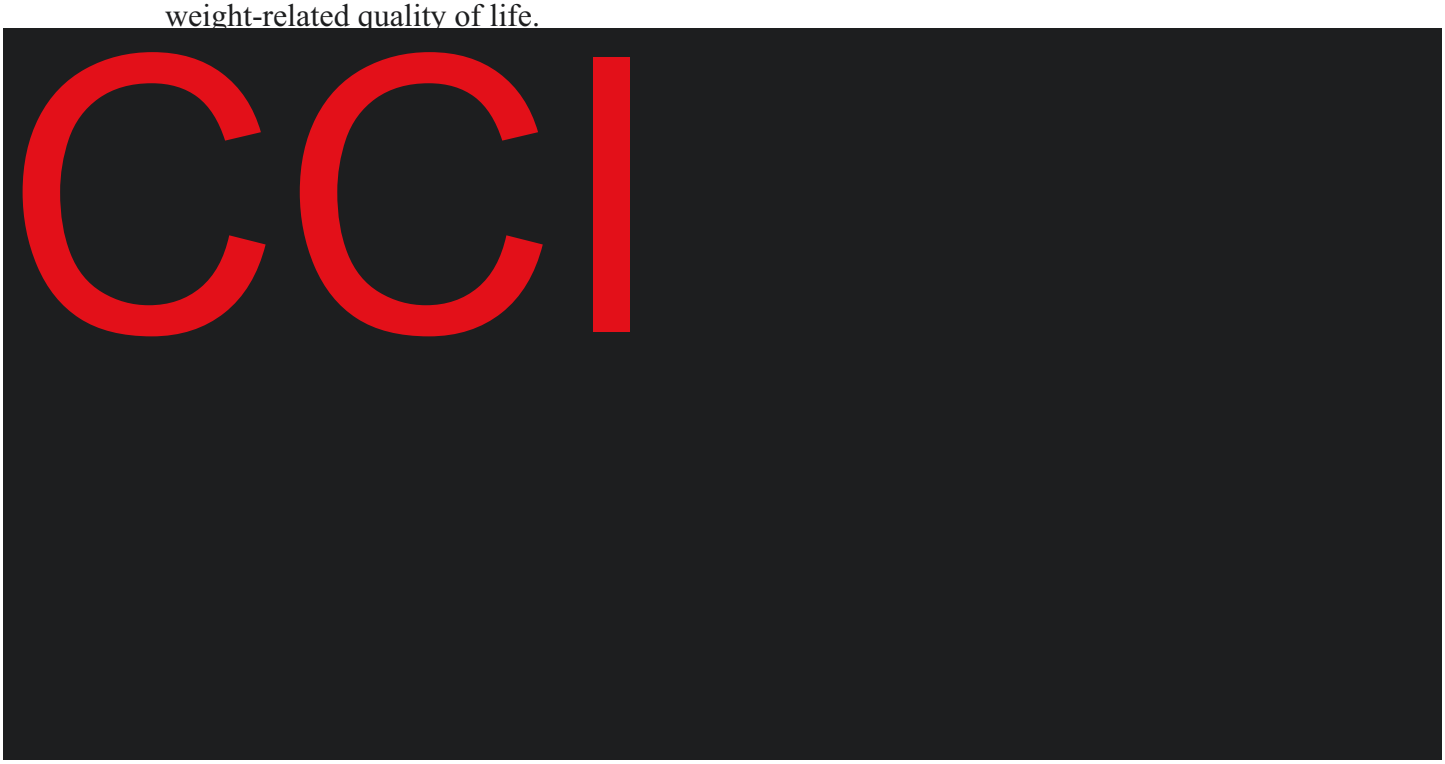
To assess the treatment effect of bimagrumab, semaglutide, and bimagrumab in addition to semaglutide vs placebo on body weight.

2.2 Secondary Objectives

To assess the treatment effect of bimagrumab, semaglutide, and bimagrumab in addition to semaglutide vs placebo on waist circumference (WC, cm).

To assess treatment effects on fat mass, visceral adipose tissue (VAT), trunk fat mass, subcutaneous adipose tissue (SAT), and lean mass.

- To assess the safety and tolerability of bimagrumab, semaglutide and bimagrumab in addition to semaglutide.
- To assess the proportion of subjects in each treatment group experiencing a change in the categorical classification of obesity based on body mass index (BMI) and waist-to-height ratio (WHtR) group.
- To assess treatment effects in each treatment group on glucose metabolism.
- To assess treatment effects in each treatment group on self-reported health status and weight-related quality of life.



3. STUDY DESIGN

3.1 General Description

This is a non-confirmatory, multi-center, randomized, double-blind, placebo-controlled (for bimagrumab) study of intravenous bimagrumab, alone or in addition to open label

subcutaneous semaglutide, to investigate efficacy and safety in adult men and women between the ages of 18 and 80, inclusive, who are obese or who are overweight with at least one obesity related co-morbidity. Women must be post-menopausal, post-surgically sterilized or using an intrauterine device.

For the 48-week core treatment period, subjects will be randomized to one of 9 treatment arms formed by the combinations of dosages of bimagrumab and semaglutide in a 3 x 3 factorial design consisting of 3 dose levels of bimagrumab – placebo, 10 mg/kg, and 30 mg/kg, and 3 dose levels of semaglutide – none, semaglutide 1.0mg, and semaglutide 2.4mg. Stratification across the treatment arms will be based on gender.

The 48-week core treatment period will be followed by a 24-week treatment extension period, during which two of the treatment arms will follow a modified treatment assignment: participants randomized to study treatment arms 1 (bimagrumab placebo) and 4 (bimagrumab 10 mg/kg) will switch treatment to bimagrumab 30 mg/kg at Week 48.

Doses of bimagrumab or placebo will be administered intravenously in Week 1 (Day 1), followed by a loading dose at Weeks 4, then every 12 weeks at Weeks 16, 28, 40. Doses of semaglutide will be administered weekly by self-injection.

The study will consist of a screening period to assess eligibility, a baseline visit, followed by clinic visits/phone contacts every 4 weeks during the core treatment period. Clinic visits are scheduled at:

> Weeks 1 (Day 1), 4, 16, 28, and 40 for blinded study treatment (intravenous bimagrumab or placebo) dosing and additional assessments.
>
> Weeks 12, 24, and 48 for DXA scanning and other assessments.

Site staff will call participants at Weeks 2, 8, 20, 32, 36, and 44 to ensure there are no safety issues and to address any questions the participant may have.

Qualified dieticians will reach out to participants on a monthly basis to provide dietary and exercise counseling, and to calculate participant's dietary intake via 24-hour recall assessment (see study operations manual for detailed description). If desired, these touchpoints may be combined with the in-clinic visits or safety calls.

Should participants report any adverse events over the phone, these will be recorded in the eCRF.

3.2 Length of Study

The total study duration will be approximately 110 weeks and will consist of a screening period of up to 6 weeks, a 72-week treatment period (48 weeks core plus 24 weeks extension), and a 32-week post-treatment follow-up period.

The primary endpoint analysis will take place after 48 weeks of core treatment. The remainder of this SAP will cover the analyses on data collected up to this time point only. A separate SAP addendum will cover the post-Week 48 analyses.

3.3 Schedule of Events

The schedule of assessments can be found in Section 1.3 of the Protocol.

3.4 Determination of Sample Size

CCI participants will be randomized to 1 of 9 treatment groups. The sample size calculation is based on the primary efficacy estimand for weight. Based on the FDA guidance on treatment for weight management, the minimum meaningful treatment effect for weight loss is CCI% of baseline body weight over 1 year of treatment. Assuming the minimum treatment effect of 5% weight loss with a standard deviation (SD) of CCI%, for a minimum effect size of 0.62 (Jastreboff, et al., 2022) (Wildman, 2009), a sample size of CCI participants per treatment arm will have approximately CCI% statistical power to detect a treatment difference between any active group and placebo/no treatment using a 2-sided t-test at alpha=CCI. Assuming a CCI% dropout rate, enrollment will target CCI subjects per treatment arm. Sample size was estimated using a t-test for 2 means in NQuery Advisor V9.1 (www.statsols.com).

4. PLANNED ANALYSES

4.1 Internal safety review committee

There is no internal safety review committee planned for this study. Subject safety will be continuously monitored by the site Investigator and medical monitor, which includes safety signal detection at any time during the study.

4.2 Independent review committee

This study will have a contracted independent Data Monitoring Committee (DMC), consisting of at least 2 independent clinicians, knowledgeable in obesity treatment, and 1 biostatistician. In addition, one non-voting members from Eli Lilly (safety) may be included for their expertise. Prior to initiating enrolment, a DMC charter will be drafted and approved by the committee members. The primary role of the DMC will be to advise on study conduct that will ensure subject safety. This may include recommendations to discontinue a specific treatment arm that appears to be showing characteristics of intolerance, or the entire study. Although the DMC may make recommendations to the Sponsor about changes in the conduct of the study, final decisions will be made by the Sponsor.

Unblinded data may be provided to the DMC in accordance with the DMC charter. MCG may provide descriptive and/or analytical statistical data as requested by the DMC to this end. Examples of such data include:

Summary of demographics and baseline characteristics

Summary of TEAEs, by System Organ Class (SOC) and by Preferred Term (PT)

Summary of AEs, by SOC and severity

Summary of AEs and SAEs deemed to be related to study drug, by SOC and PT

Summary of serious adverse events (SAEs), by SOC and PT

- Summary of adverse events of special interest, by SOC and PT
- Summary and listing of deaths and accompanying Narratives
- Summary and listing of discontinuations from study
- Summary of key laboratory measurements

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4.3 Interim Analysis

An unblinded interim analysis (IA) will be conducted when approximately 80% of the participants have completed the Week 24 visit or discontinued study treatment. The interim analysis will evaluate efficacy as well as the safety profile of both the combination and monotherapy treatment arms. The team conducting the unblinded interim analysis will be independent from the main study team and will use the results for internal decision-making purposes only. The Data Management Committee will have access to the interim analysis results. The detailed plan of unblinding is included in a separate blinding and unblinding plan.

4.4 Final Analysis – Core Study Period

The core study period is the randomized, double-blind, placebo-controlled portion of the study. This phase is the focus of this SAP. The final analysis for the core study period will be performed once all enrolled subjects have completed the end of study/Week 48 visit and a 48-week primary analysis database lock has occurred. The data will be unblinded and the analyses described in this SAP will be conducted.

The 48-week primary analysis database lock will include locking the data for all visits up to week 48.

4.5 Final Analysis – Open-Label Extension Phase

Following the analysis of the core study period, the study will then become open-label. Details of analyses of the open-label extension (OLE) phase, which includes data collected from 48 weeks through 72 weeks, and the withdrawal (WD) phase, which will end after the last participant completed 104 weeks, will be documented in a separate SAP addendum. The final analysis will be conducted once all enrolled subjects have completed the end of study/Week 104 visit and database lock has occurred.

At the time of the open-label analysis, the external data transfers will be programmatically compared to those received at the time of the 48-week primary analysis database lock and any differences will be documented.

5. ANALYSIS POPULATIONS

5.1 Full Analysis Set/Intention-to-Treat Population

The Full Analysis Set (FAS)/Intention-to-Treat (ITT) Population will include all subjects who provided informed consent and were randomised to a treatment group. This population will be used for subject disposition outputs, demographics, baseline characteristics and efficacy outputs unless otherwise specified.

5.2 Safety Analysis Set

The Safety Analysis Set (SAF) will include all subjects who received at least one dose of study medication. Subjects will be analyzed as randomized, regardless of the actual treatment received. This population will be used for all safety, pharmacokinetics, and pharmacodynamics outputs unless otherwise specified.

6. DATA HANDLING CONVENTIONS

6.1 Treatment Groups

Data will be grouped by treatment group, using the following treatment names and order.

a) Placebo

b) Bima 10mg/kg

c) Bima 30mg/kg

d) Sema 1.0mg

e) Sema 2.4mg

f) Bima 10 mg/kg + Sema 1.0 mg

g) Bima 10 mg/kg + Sema 2.4 mg

h) Bima 30 mg/kg + Sema 1.0 mg

i) Bima 30 mg/kg + Sema 2.4 mg

These groupings will apply for all analyses up to Week 48. For listings the extension group arm will also be included as below:

Placebo / Bima 30mg/kg

Bima 10mg/kg / Bima 30mg/kg

Bima 30mg/kg / Bima 30mg/kg

Placebo + Sema 1.0mg / Placebo + Sema 1.0mg

Placebo + Sema 2.4mg / Placebo + Sema 2.4mg

Bima 10 mg/kg + Sema 1.0 mg / Bima 10 mg/kg + Sema 1.0 mg

Bima 10 mg/kg + Sema 2.4 mg / Bima 10 mg/kg + Sema 2.4 mg

Bima 30 mg/kg + Sema 1.0 mg / Bima 30 mg/kg + Sema 1.0 mg

Bima 30 mg/kg + Sema 2.4 mg / Bima 30 mg/kg + Sema 2.4 mg

For summaries that include a total arm, this will use the name 'All Subjects'.

6.2 Data Presentation

Descriptive analyses will be completed for this study. For continuous parameters, these will include the number of observations, mean, median, standard deviation, minimum and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the database. Mean, median and standard deviation will be presented to 1 more decimal place than the raw data. Categorical parameters will be summarized as frequency counts and percentages. Percentages will be rounded to 1 decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated. All confidence intervals reported will be two-sided 95% confidence intervals.

6.3 Premature Withdrawal and Missing Data

For the primary and key secondary efficacy analyses, missing data will be imputed according to the estimand strategy utilized. For analyses using the treatment policy estimand, intercurrent events (ICEs) will not be utilized to exclude data from analyses. Missing data will be assumed to be missing at random (MAR) and will be imputed using multiple imputation (MI) within group defined by randomised treatment group and treatment status at week 48. Details of the multiple imputation approach for the primary estimand are provided in Section 10.1.6. Sensitivity analyses will be conducted to test the degree to which departures from the MAR assumption influence the conclusions for the primary endpoint using the treatment policy estimand only. The sensitivity analyses are described in Section 10.2. For analyses using the trial product/hypothetical estimand,

which will take into consideration impacts of ICEs on interpretability of data, ICEs will be utilized. Missing data or data impacted by ICEs will be assumed to be missing at random (MAR) and will be handled by the Mixed Model with Repeated Measures (MMRM).

All other efficacy analyses, as well as disposition, demographic, and safety analyses will be completed based on available data and no imputation algorithms will be applied for missing data unless otherwise specified. All data for subjects who withdraw early from the study will be used for these analyses up to the point of their discontinuation including data after subjects withdraw from treatment (retrieved drop out data).

6.4 Common Derivations

6.4.1 First Day of Study Drug Administration(TR01SDT)

The start date of semaglutide will be defined as the earliest 'Start date of dose' from the semaglutide dispensing page of the eCRF. This is because:

Although the actual treatment start date of semaglutide is recorded in the participant eDiary, this date is missing for some participants.

As participants take their first dose in the clinic, the planned start dose date of semaglutide from the dispensing page should be correct and complete for all participants.

The start date of bimagrumab/placebo will be defined as the earliest date of study drug administration from the study drug administration page of the eCRF.

The start date of first study drug will be defined as the start date of bimagrumab/placebo. It is expected that the start date of semaglutide and start date of bimagrumab/placebo will be the same since they are given on the same day in the clinic. The start date of first study drug is saved in variable TR01SDT in the ADAM datasets.

6.4.2 Last Day of Study Drug Administrationduring Core Study Period (TR01EDT)

The date of last study drug during the core study period will be equal to the first dose of study drug during the extension period i.e. the first administration or dispensing record on or after the date of CCI (Week 52). If the participant has not taken a dose during the extension study period, the date of last study drug is defined as the latest of CCI (Week 1) - CCI (Week 48), the end of treatment visit, and the date of discontinuation of treatment from the completion page.

The end date of study drug during the core study period is saved in variable TR01EDT in the ADAM datasets.

6.4.3 First Day of Study Drug Administration during Extension Treatment Period (TR02SDT)

For participants who took extension study treatment, the start date of study drug during the extension study period (TR02SDT) is the same as the end date of study drug during the core study period (defined in Section 6.4.2).

6.4.4 Last Day of Study Drug Administrationduring Extension Treatment Period (TR02EDT)

For participants who took extension study treatment and completed CCI (Week 72), the end date of study drug during the extension study period (TR02EDT) is the date of the CCI (Week 72) visit.

For participants who took extension study treatment but did not complete CCI (Week 72), the end date of study drug during the extension study period is the latest of CCI (Week 52) - CCI (Week 72), the end of treatment visit, and the date of discontinuation of treatment from the completion page.

6.4.5 Baseline

For all parameters presented by time point in the summary tables, baseline will be defined as the last, valid, non-missing assessment prior to study drug administration. This includes assessments that were recorded as unscheduled visits.

For DXA scans, baseline will be defined as last, evaluable assessment prior to the first study drug administration. This includes assessments that were recorded as unscheduled visits. Missing baseline will be imputed using the first post-baseline assessment if evaluable assessment available within [redacted] days after the first study drug administration. The number of patients with missing baseline due to unevaluable DXA scan who repeat scan after first dosing is expected to be low.

Study Days will be defined relative to the date of first study drug administration and will be used to calculate visit windows. Study Day 1 will be defined as the day of first study drug administration. The day before Study Day 1 is Study Day -1. Study Day 0 is not defined.

For assessments occurring on or after the date of first study drug administration:

Study Day = date of assessment - date of first study drug administration +1

For assessments occurring prior to the date of first study drug administration:

Study Day = date of assessment – date of first study drug administration

6.4.6 Core Study Completion

A subject is considered to have completed the core study period if the subject completes all 5 doses of bimagrumab/placebo per protocol.

6.5 Visit Window Conventions

Visit windows will be applied to all efficacy and safety assessments which will be summarised over time using the rules defined below. Unless otherwise specified, if there is more than one assessment within a visit window then the observation closest to the target day will be selected, or, if equidistant then the latter will be selected. All observations, including those excluded from the summary table as a result of this algorithm, will be included in the listings. Different windows are applied to the measures depending on the scheduled assessments for the measures.

6.5.1 Visit Windows for Body Weight including BIA, Wait Circumference, and Vital Signs

The visit windows applied to body weight including BIA, waist circumference, and vital signs are defined in Table 6.1.

Table 6.1. Visit Windows for Body Weight including BIA, Waist Circumference, and Vital Signs

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.2 Visit Windows for DXA Scans

The visit windows applied to DXA scans are defined in Table 6.2.

As described in Section 6.4.1 as a few baseline DXA scans were unevaluable and had to be repeated, the visit window for Baseline DXA scans is up to [redacted] days after the date of first study drug administration. Conceptually, this is the same as choosing the closest DXA scan within [redacted] days of treatment start date if there is an unevaluable/missing baseline assessment.

Table 6.2 Visit Windows for DXA Scans

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.3 Visit Windows for Grip Strength, QoL Questionnaires, PD Biomarkers, and Dietary Intake

The visit windows applied to grip strength, QoL questionnaire, PD biomarker, and Dietary Intake assessments are defined in Table 6.3.

Table 6.3. Visit Windows for Grip Strength, QoL Questionnaires, PD Biomarkers, and Dietary Intake

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

*Up to CCI allowed for grip strength and up to CCI allowed for dietary intake.

6.5.4 Visit Windows for ECG

The visit windows applied to ECG assessments are defined in Table 6.4.

Table 6.4. Visit Windows for ECG

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.5 Visit Windows for Hematology (CBC), Clinical Chemistry, Coagulation, and Safety Biomarkers

The visit windows applied to hematology, clinical chemistry, coagulation, and safety biomarker assessments are defined in Table 6.5.

Table 6.5. Visit Windows for Hematology (CBC), Clinical Chemistry, Coagulation, and Safety Biomarkers

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.6 Visit Windows for Urine Chemistry and Urinalysis

The visit windows applied to urine chemistry and urinalysis assessments are defined in Table 6.6.

Table 6.6. Visit Windows for Urine Chemistry and Urinalysis

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.7 Visit Windows for Anti-drug Antibodies

The visit windows applied to anti-drug antibodies assessments are defined in Table 6.7.

Table 6.7. Visit Windows for Anti-drug Antibodies

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.8 Visit Windows for Pharmacokinetics

The visit windows applied to pharmacokinetic assessments are defined in Table 6.8.

Table 6.8. Visit Windows for Pharmacokinetics

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		

6.5.9 Visit Windows for eDiary Assessments

The visit windows applied to eDiary assessments are defined in Table 6.9.

Table 6.9. Visit Windows for eDiary

Analysis Visit	Target Study Day	Visit Window (Study Days)
CCI		
CCI		

6.6 Software

All analyses will be performed using SAS version 9.4 or later.

7. STATISTICAL CONSIDERATIONS

7.1 Statistical Tests

Unless otherwise specified, all statistical tests will be conducted at the two-sided 5% significance level.

7.2 Multiplicity Adjustments

No multiplicity adjustment will be performed for this study. All statistical tests will be performed at the two-sided 5% significance level.

7.3 Multi-center Studies

Since this is a multi-centre study, all statistical models will include country as a fixed effect.

7.4 Other Strata and Covariates

To decrease the chance of an imbalance in gender across treatment arms, randomization was stratified by gender. All statistical models will include gender as a stratification factor.

For all change from baseline analyses, the baseline values will be used as a covariate.

As mentioned in Section 7.3 country will be included in all statistical models as a fixed effect.

7.5 Subgroup Analyses

There are no planned subgroup analyses.

8. OUTPUT SHELLS

Template shells for the tables, listings, and figures are presented in a separate document. All outputs will be presented in landscape format.

9. STUDY POPULATION

9.1 Subject Disposition

The number and percentage of subjects who were included in each analysis population, who completed the core treatment period, who completed the core study period, and who completed each visit in the core period will be presented by treatment group. The reason

for early withdrawal from treatment and early withdrawal from study will be summarized by treatment group.

Data listings will be provided for screen failures, subject disposition, subjects prematurely discontinued from the study, and subjects excluded from analysis (with reasons for exclusion) by treatment group. Protocol deviations will be listed.

9.2 Protocol Deviations

The Protocol Deviation Management Plan (PDMP) details the process for capturing and reporting protocol deviations in this study.

A Protocol Deviation is defined as any nonconformance, divergence, or departure (whether planned or unplanned), irrespective of the degree of seriousness or potentially resulting consequences from the study design or procedures defined in the protocol.

Important Protocol Deviations are a subset of PDs that may significantly impact the completeness, accuracy and/or reliability of study data or that may significantly affect a participant's rights, safety or well-being. Further details are provided in the PDMP.

A final list of important protocol deviations will be approved by the Sponsor, the Medical Monitor, and others as appropriate, and provided to McCloud Consulting Group after database lock. The final list will include date of deviation, date of identification, date resolved, category, deviation description, and mitigation/ comments. Important protocol deviations will be presented in the study listings for inclusion in the CSR. Important subject-level protocol deviations will also be summarized by treatment group and category using the ITT population.

9.3 Demographics and Baseline Characteristics

All demographic and baseline characteristic data recorded prior to study treatment will be listed by subject and treatment group.

The following demographics will be summarized by treatment group.

Sex, age at informed consent, race, ethnicity

Height, weight, BMI, waist circumference, fat mass (kg) from BIA, lean mass (kg) from BIA, percent body fat (%) from BIA, percent lean body mass (%) from BIA, fat mass (kg) from DXA, lean mass (kg) from DXA, percent body fat (%) from DXA, percent lean body mass (%) from DXA at baseline

Duration of obesity/overweight in years

Age will be derived as Year of initial informed consent – Year of birth.

9.4 Medical History and Pre-existing Conditions

Medical history will be coded using the latest version of the MedDRA dictionary (refer to the Data Management Plan for the version number).

The number and percentage of subjects with past and current medical conditions will be summarized by treatment group. The summary will be presented separately for obesity related conditions and other conditions. Medical history will also be listed by subject and treatment group.

9.5 Prior and Concomitant Medications, and Procedures

Prior and concomitant medications will by coded using the latest WHO dictionary (refer to the Data Management Plan for the version number). Prior and concomitant surgeries and medical procedures will be coded using the latest version of the MedDRA dictionary (refer to the Data Management Plan for the version number).

The start and stop dates will be used to identify when a concomitant medication was taken during the study. The date of procedure will be used to identify whether a surgery/procedure was conducted during the study.

Prior and concomitant medications will be grouped by classification and preferred term (PT), and summarised by treatment group. Prior and concomitant medications will be

summarised separately. Prior and concomitant medications will be listed separately by treatment group and subject.

The same approach will be taken for procedures, including surgeries. Prior and concomitant procedures will be grouped by classification and preferred term (PT), and summarised by treatment group. Prior and concomitant surgeries/procedures will be summarised separately. Prior and concomitant procedures will be listed separately by treatment group and subject.

Prior medications are those medications that were stopped prior to first investigational product administration. Concomitant medications are medications that are taken at least once after investigational product administration. Medications stopping on the same day as investigational product administration will be considered as concomitant medications.

For partially missing dates, the following conventions will be used in order to classify the medications as prior or concomitant:

If start date is completely missing, start date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.

If year and month are present and day is missing, set day to first day of the specified month.

If end date is completely missing, end date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.

If year and month are present and day is missing, set day to last day of the specified month.

10. EFFICACY

All efficacy data will be listed by treatment group and participant using the ITT population.

10.1 Primary Efficacy

10.1.1 Primary Estimand – Treatment Policy Strategy

The treatment policy strategy will be used to quantify the average treatment effect of bimagrumab, semaglutide or a combination of bimagrumab with semaglutide relative to placebo after 48 weeks, in all randomized participants, regardless of adherence to treatment and regardless of intercurrent events. This strategy closely adheres to full analysis set (FAS) with an intention-to-treat (ITT) population.

The following expansion of this estimand strategy will quantify the average treatment effect of combination treatment of semaglutide with bimagrumab relative to each monotherapy of the same dosage strength after 48 weeks, in all randomized participants regardless of adherence to treatment and regardless of intercurrent events (ICE).

10.1.2 Primary Endpoint

The primary endpoint is mean absolute change from baseline in total body weight (kg) at Week 48.

10.1.3 Analysis of Primary Endpoint using Treatment Policy Strategy

The primary analysis will utilize an Analysis of Covariance (ANCOVA) model with total body weight change from baseline to week 48 as the dependent variable, country and gender as stratification factors, baseline total body weight as the baseline covariate, and treatment group as a predictor variable.

In accordance with the “treatment policy” approach for the primary endpoint, missing data in the primary analysis will be assumed to be missing at random (MAR) and will be imputed with multiple imputation using 100 imputed datasets separately within groups defined by randomised treatment and treatment status at Week 48. Details of the multiple imputation approach for the treatment policy estimand are provided in Section 10.1.6.

The primary comparisons of interest will be the difference in Least Squares means (LSMeans, means adjusted for the covariates in the model) at Week 48. The results will be presented as LSMeans and standard errors (SEs) for each of the treatment groups, as well as the LSMeans of treatment differences for all 36 possible pairwise treatment comparisons and their associated 95% confidence intervals.

In addition to the analysis results, the summary statistics for the actual total body weight values at Week 48 and change from baseline will be presented for each of the treatment groups.

10.1.4 Secondary Estimand – Trial Product (Hypothetical) Strategy

The "trial product policy (hypothetical)" strategy will be utilized to quantify the average treatment effect of bimagrumab, semaglutide or a combination of bimagrumab with semaglutide relative to placebo after 48 weeks, in all randomized participants who received at least one dose of study treatment, adhered to treatment and did not experience the ICEs defined below.

The following expansion of the trial product/hypothetical estimand will quantify the average treatment effect of combination treatment of semaglutide with bimagrumab relative to each monotherapy of the same dosage strength after 48 weeks, in all randomized participants who received at least one dose of study treatment, adhered to treatment and did not experience the ICE defined below.

The ICE for the trial product/hypothetical estimand is:

1. Permanent discontinuation of study drug

Primary efficacy endpoint data occurring after the date of an ICE will be excluded from the analysis using the trial product/hypothetical estimand.

Any time a participant permanently discontinues treatment, this will be considered an ICE and the date of the onset of the ICE will be the treatment discontinuation date. This is the

end date of study treatment during core treatment period (TR01EDT) defined in Section 6.4.2

10.1.5 Analysis of the Primary Endpoint Using the Trial Product/Hypothetical Strategy

The analysis of this estimand will use a Mixed Model with Repeated Measures (MMRM), with change from baseline to weeks 4, 12, 16, 24, 28, 40 and 48 in total body weight as the dependent variable, country and gender as stratification factors, baseline weight as a baseline covariate, week and treatment group as factors, and week by treatment group as an interaction variable. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on LS means and robust "Huber White" standard errors. If this analysis fails to converge, the following covariance structures will be tested in order: autoregressive, and compound symmetry. The first covariance structure that converges will be used.

In accordance with the "trial product (hypothetical)" approach for the primary endpoint, missing data in this estimand analysis will be assumed to be missing at random (MAR) and will be handled implicitly by the MMRM.

The primary comparisons of interest will be the difference in Least Squares means (LSMeans, means adjusted for the covariates in the model) at Week 48. The results will be presented as LSMeans and SEs) for each of the treatment groups, as well as the LSMeans of treatment differences for all 36 possible pairwise treatment comparisons and their associated 95% confidence intervals.

In addition to the analysis results, the summary statistics for the actual total body weight values at each of the visits up to Week 48 and change from baseline will be presented for each of the treatment groups. Plots of the modelled (MMRM) treatment group means and 95% Confidence Intervals over time will be produced.

10.1.6 Multiple Imputation of Missing Data for the Treatment Policy Estimand

For the treatment policy estimand, missing values will be assumed to be missing at random (MAR). Sensitivity analyses will be conducted to test the degree to which missing data and departure from the MAR assumption influence the conclusions. The sensitivity analyses are described in Section 10.2.

Missing values for the treatment policy estimand will be imputed using multiple imputation with 100 samples drawn. The MI will be performed separately within groups defined by randomised treatment and treatment status at Week 48, in total up to 18 groups (9 treatment groups for patients on-treatment at week 48, and 9 treatment groups for patients off-treatment at week 48). If there is insufficient retrieved drop out data to conduct the planned multiple imputation, then missing data will be imputed from the control group, as planned for the sensitivity analysis described in Section 10.2.

The analysis will be conducted using all subjects in the ITT population.

There are 3 stages to the multiple imputation process, as described below.

1. Imputation Phase

During this phase, 100 datasets will be created where missing values in any of the variables in the planned ANCOVA model (described in Section 10.1.3 will be imputed by randomly selecting data from an appropriate distribution.

All variables in the imputation model will be assumed to have a multivariate joint normal distribution and will be modelled as continuous variables. This includes categorical variables, which will be recoded from categorical variables with k levels to k-1 indicator variables.

A Markov Chain Monte Carlo (MCMC) procedure will be used, where missing data will be selected from a multivariate joint normal distribution conditional on the observed data. The imputation model will include the stratification factors of country and gender, baseline weight and week 48 total body weight.

The multiple imputation procedures will be implemented using PROC MI in SAS with a random seed of 4895420.

Imputed data will be used in the analysis as imputed, even if it seems to fall outside the plausible range. This is because post-imputation truncation of data can lead to biased estimates (Rodwell, Lee, Romaniuk, & Carlin, 2014).

2. Analysis Phase

The 100 imputed datasets will be analysed 100 times using the planned ANCOVA model described in Section 10.1.3.

3. Pooling Phase

The parameter estimates from the 100 analyses conducted in step 2 will be combined into a single set of statistics that reflect the uncertainty associated with the imputed values using PROC MIANALYZE in SAS. Using the parameter estimates and standard errors from the 100 imputed datasets, this procedure applies Rubin's (1987) rules to make valid univariate statistical inferences.

10.2 Sensitivity Analyses

Sensitivity analyses will be conducted to test the degree to which missing data and departure from the MAR assumption influence the conclusions for the analysis of the primary endpoint using treatment policy estimand.

One violation of the MAR assumption would be if the statistical behaviour of participants with missing data transitions to that of participants in the Placebo group. This scenario will be modelled using control based imputation approach. A similar multiple imputation approach for missing data will be applied as described in Section 10.1.6. However, under the control based approach, missing data for the treatment groups will be imputed based on the imputation model derived from the Placebo arm only. This approach will be a possible worst case of departure from the MAR assumption, and the study conclusions will

be examined under this scenario. The SAS code for the sensitivity analysis will be as follows:

```
proc mi data= <DATASET> nimpute=100 seed=4895420;
    class country sex trt01p;
    var sex country baseline week_48;
    monotone method=reg;
    mnar model (week_48 / modelobs=(trt01p='Placebo+No
Sema'));
run;
```

10.3 Secondary Efficacy

10.3.1 Secondary Efficacy Endpoints

The following sections set out the definitions and analyses for the secondary efficacy endpoints. The secondary efficacy endpoints are described in Table 10.1. These follow the order of secondary endpoints set out in the Protocol.

All secondary efficacy analyses will be conducted using the treatment policy estimand strategy. In addition the continuous secondary variables will also be analysed using the trial product/hypothetical estimand strategy.

Table 10.1. Secondary Efficacy Endpoints

Objective	Endpoints	Type
To assess treatment effect of bimagrumab, semaglutide, and bimagrumab in addition to semaglutide vs placebo on body weight	1. Percent change from baseline in body weight at 48 weeks	Continuous

To assess treatment effects on waist circumference	2. Mean absolute change from baseline in waist circumference (cm) at 48 weeks	Continuous
To assess treatment effects on fat mass, visceral adipose tissue (VAT), trunk fat mass, subcutaneous adipose tissue (SAT), and lean mass	3. Mean absolute change from baseline and percent change from baseline at 48 weeks in total body fat mass (kg and % body fat) by dual-energy x-ray absorptiometry (DXA). The percent change from baseline for fat mass at each nominal visit is defined as: (post baseline fat mass [kg] – baseline fat mass [kg]) / baseline fat mass [kg] * 100%.	Continuous
	4. Mean absolute change from baseline and percent change from baseline at 48 weeks in VAT (kg), SAT (kg) and trunk fat mass (kg) by DXA	Continuous
	5. Proportion of subjects at 48 weeks with the following reductions from baseline: i. Waist circumference ≥ 5 cm, ≥ 10 cm, and ≥ 15 cm ii. Body weight ≥ 5%, ≥ 10%, and ≥ 15% iii. Fat mass ≥ 5%, ≥ 10%, ≥ 15%, ≥ 20%, ≥ 25% by DXA iv. Fat mass ≥ 10% with < 5% decrease (or increase) in lean mass by DXA	Response rate

	6. Ratio of VAT/SAT ratio, and ratio of android/gynoid fat mass ratio at 48 weeks versus baseline by DXA	Ratio
	7. Percentage of weight loss due to fat mass or lean mass at 48 weeks by DXA	Continuous
	8. Mean absolute change from baseline and percent change from baseline at 48 weeks in fat mass (kg and % body fat) by bioelectrical impedance analysis (BIA)	Continuous
	9. Mean absolute change from baseline and percent change from baseline at 48 weeks in total body lean mass (kg and % body lean) by DXA and BIA, as well as appendicular lean mass, android fat mass, and gynoid fat mass by DXA	Continuous
To assess treatment effects on categorical classification of obesity	10. Proportion of subjects in each BMI or WHtR category at any visit up to 48 weeks. The BMI categories are: Healthy weight: 18.5 kg/m^2 to 24.9 kg/m^2 Overweight: 25 kg/m^2 to 29.9 kg/m^2 Obesity class I: 30 kg/m^2 to 34.9 kg/m^2 Obesity class II: 35 kg/m^2 to 39.9 kg/m^2 Obesity class III: ≥ 40 kg/m^2 The WHtR categories are: < 0.5 0.5 – 0.59 ≥ 0.6	Categorical

To assess treatment effects on glucose metabolishm	11. Mean change and percent change from baseline in HbA1c at 48 weeks	Continuous
To assess treatment effects on self-reported health status and weight-related quality of life	Change from baseline at 24 weeks and 48 weeks in: 12. Quality of Life Short Form 36 survey (SF-36) total score and physical functioning score 13. Impact of Weight on Quality of Life-Lite for Clinical Trials survey (IWQoL-Lite for CT) total score and physical function	Continuous

10.3.2 Analysis of Continuous Secondary Efficacy Endpoints

Most of the secondary endpoints are continuous.

Each continuous secondary efficacy endpoint will be analysed using a similar ANCOVA model and MI approach as was used for the analysis of the primary endpoint using the treatment policy estimand. The exception is the analysis of percentage of weight loss due to fat mass or lean mass at 48 weeks by DXA, which will be described in Section 10.3.3.

The ANCOVA will include change from baseline (or percent change from baseline) to week 48 as the dependent variable, country and gender as stratification factors, baseline value as the baseline covariate, and treatment group as a predictor variable.

The results will be presented as LSMeans and standard errors (SEs) for each of thetreatment groups, as well as the LSMeans of treatment differences for all 36 possible pairwise treatment comparisons, their associated 95% confidence intervals and p-values.

In addition to the analysis results, the summary statistics for absolute values at Week 48 and change from baseline will be presented for each of the treatment groups.

Each continuous secondary efficacy endpoint will also be analysed using a similar MMRM model as was used for the analysis of the primary endpoint using the trial product/hypothetical estimand.

The MMRM will include with change from baseline (or percent change from baseline) to weeks 4, 12, 16, 24, 28, 40 and 48 as the dependent variable, country and gender as stratification factors, baseline value as a baseline covariate, week and treatment group as factors, and week by treatment group as an interaction variable. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on LS means and robust "Huber White" standard errors. If this analysis fails to converge, the following covariance structures will be tested in order: autoregressive, and compound symmetry. The first covariance structure that converges will be used.

The primary comparisons of interest will be the difference in Least Squares means (LSMeans, means adjusted for the covariates in the model) at Week 48. The results will be presented as LSMeans and SEs) for each of the treatment groups, as well as the LSMeans of treatment differences for all 36 possible pairwise treatment comparisons and their associated 95% confidence intervals.

In addition to the analysis results, the summary statistics for the actual values at each of the visits up to Week 48 and change from baseline will be presented for each of the treatment groups. Plots of the modelled (MMRM) treatment group means and 95% Confidence Intervals over time will be produced.

10.3.3 Analysis of Percentage of Weight Loss due to Fat Mass or Lean Mass at 48 weeks by DXA

Percentage of weight loss due to fat mass or lean mass will be analysed using the Fat Loss Index (FLI). The FLI at Week *x* will be calculated as:

FLI at Week *x* =Fat Loss at Week *x*/(Fat Loss + Lean Loss at Week *x*) * 100%

Composite endpoints of >5kg Weight loss and FLI>70%, >80%, and >90% will be analysed.

No hypothesis testing or multiple imputation will be performed for these composite endpoints. The endpoints will be summarised using as observed data and the treatment policy estimand at each timepoint by treatment group. The number and frequency of participants meeting the composite endpoint at each timepoint will be presented. Missing data will be considered as not meeting the endpoint.

10.3.4 Analysis of Ratio Secondary Efficacy Endpoints

There are two ratio secondary endpoints - the ratio of VAT/SAT ratio at Week 48 versus Baseline, and the ratio of android/gynoid fat mass ratio at Week 48 versus Baseline.

The first endpoint can described by formula as below.

Let VSR_{48} denote the VAT/SAT ratio at Week 48

Let VSR_{BL} denote the VAT/SAT ratio at Baseline.

The endpoint is $VSR_{48}/VSR_{BL.}$

VAT/SAT ratio will be summarised descriptively by treatment group over time. The number of observations, arithmetic mean, standard deviation (SD), minimum, median, and maximum will be summarised, as well as the geometric mean, geometric SD and geometric coefficient of variation. The ratio of VAT/SAT ratio (Week 48 versus Baseline) will also be summarised descriptively in the same manner.

To assess the treatment effect, the log-transformed ratio of VAT/SAT ratio (Week 48 versus Baseline) will be analysed using an ANCOVA model. The ANCOVA will include log-transformed ratio of VAT/SAT ratio (Week 48 versus Baseline) as the dependent variable, centre and gender as stratification factors, log-transformed Baseline VAT/SAT ratio as a baseline covariate, and treatment group as a predictor variable.

The geometric means of the ratio of VAT/SAT (Week 48 versus Baseline) and 95% CIs will be estimated for each of the nine treatment groups based on the ANCOVA model described above, by exponentiating the estimated LSMeans and their CIs. The treatment effects and their 95% CIs will also be estimated from the same model as the ratio of geometric means, for all 36 possible pairwise treatment comparisons, by exponentiating the difference of estimated LSMeans and their associated 95% CIs and p-values.

The second ratio endpoint, the ratio of android/gynoid fat mass ratio at Week 48 versus Baseline, will be analysed in the same manner.

10.3.5 Analysis of Response Rate Secondary Efficacy Endpoints

The secondary efficacy response rate endpoints will be analysed using a logistic regression model with response as the dependent variable, country and gender as a stratification factors, and treatment group as a predictor variable. Odds ratios and 95% confidence intervals for the treatment effect will be presented.

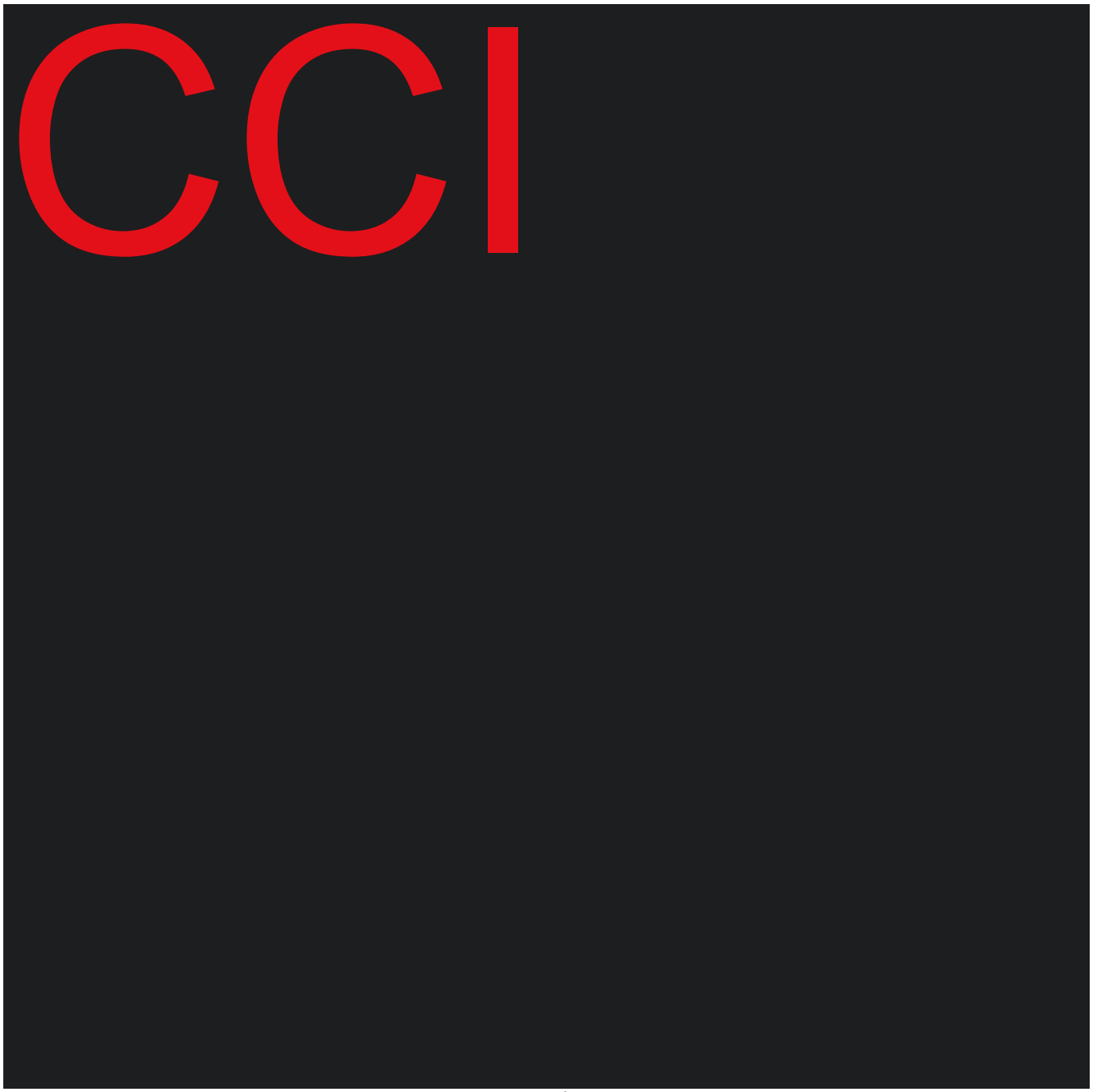
The treatment effect will be tested for statistical significance using the logistic regression model. For each response rate endpoint, the null hypothesis ‘that there no difference between treatment groups in the odds of response’ will be tested against the alternative hypothesis ‘that the odds of response is different between treatment groups’. A two-sided Wald Type 3 Chi-squared test at the 5% significance level will be used.

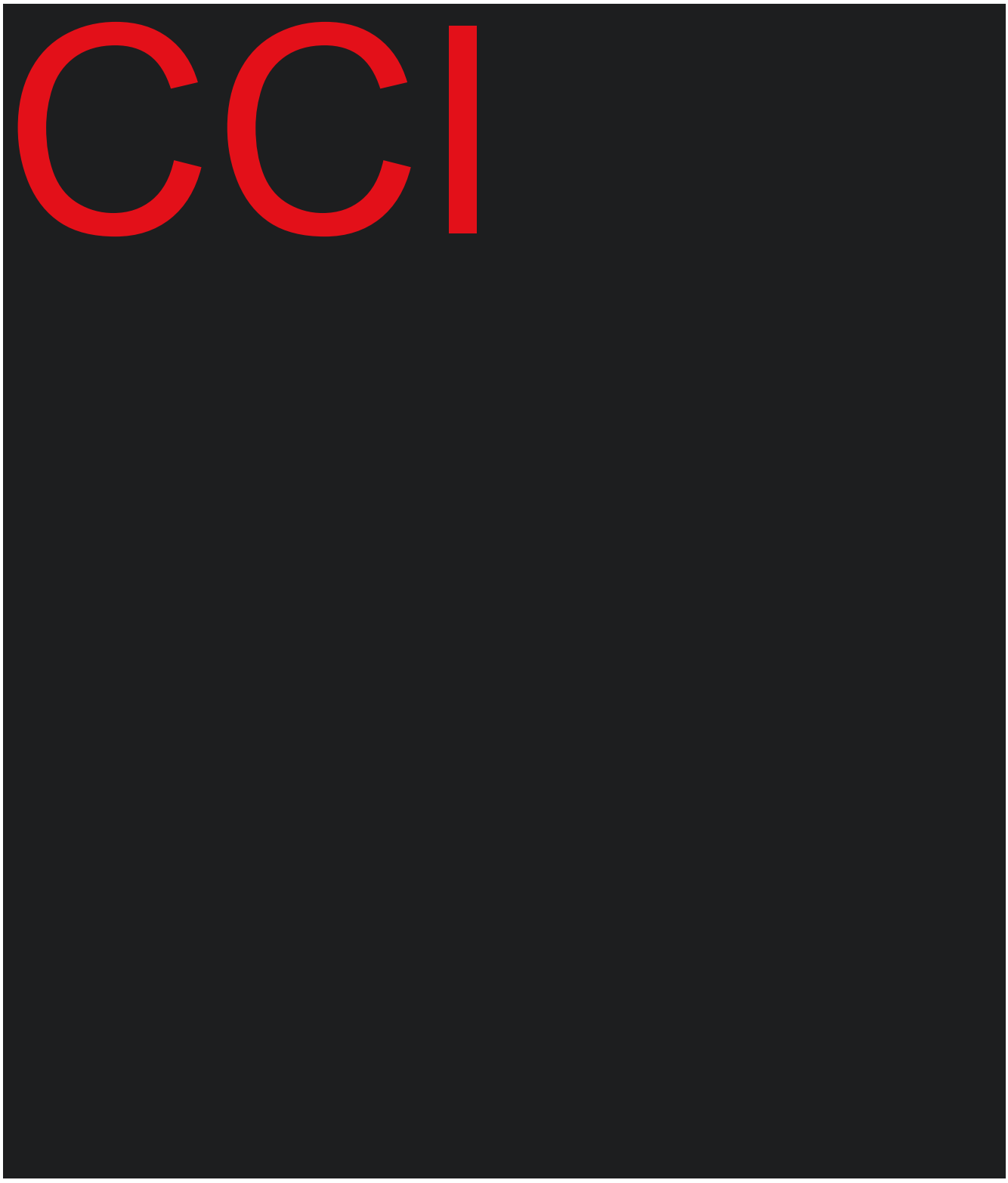
For each response rate secondary efficacy variable, the number and percentage of responders at Week 48, will be presented by treatment group.

10.3.6 Analysis of Categorical Secondary Efficacy Endpoints

The categorical endpoints will be summarized at each time point by treatment group. The summary will show the number and percentage of subjects in each category, including missing category. Shift tables from baseline to Week 24, and to Week 48 will also be presented.

The treatment effect on distribution of category at week 48 will be analysed using the Chi-square test. The Chi-square test will be applied separately for each pairwise treatment comparison. In addition, a stacked bar chart will be presented, displaying the proportion of participants in each category at baseline, week 24 and week 48 for each treatment group.

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11. SAFETY

11.1 Exposure

11.1.1 Bimagrumab/Placebo Exposure

The total duration of exposure during the Core Study Period (weeks) and number of infusions during the Core Study Period will be summarized with descriptive statistics (n, mean, SD, median, minimum and maximum) by treatment group. A list of study drug treatment assignment will be provided.

Total duration of exposure during the core study period in weeks is defined as (TR01EDT-TR01SDT+1)/7, where TR01SDT and TR01EDT are defined in Sections 6.4.1 and 6.4.2.

The overall treatment compliance rate for bimagrumab/placebo infusions will be summarized by treatment group. A patient is considered compliant if at least 80% of the time prior to the permanent treatment discontinuation, the patient received planned dose per administration (i.e., a partial infusion does not count). The algorithm is described in further detail below.

Compliant during core study period = Yes if (number of times 'Did participant receive the correct dose' = 'Y' at Visits 2 to 15)/(planned number of doses during Visits 2 to 15) >= 80%.

Planned number of doses during the period TR01SDT to TR01EDT = 5 for core treatment period completers

Planned number of doses during the period TR01SDT to TR01EDT is based on last visit attended for core period discontinuers as described in Table 11.1:

Table 11.1 Planned Number of Bimagrumab/Placebo Doses for Participants who Discontinued Core Study Treatment

Last Visit Attended	Planned Bimagrumab/Placebo doses
VISIT 2 (Week 1)	1
VISIT 3 (Week 2)	1
VISIT 4 (Week 4)	2
VISIT 5 (Week 8)	2
VISIT 6 (Week 12)	2
VISIT 7 (Week 16)	3
VISIT 8 (Week 20)	3
VISIT 9 (Week 24)	3
VISIT 10 (Week 28)	4
VISIT 11 (Week 32)	4
VISIT 12 (Week 36)	4
VISIT 13 (Week 40)	5
VISIT 14 (Week 44)	5
VISIT 15 (Week 48)	5

11.1.2 Semaglutide Exposure

Semaglutide will be administered weekly by self-injection. Semaglutide dispensing is recorded in the eCRF whilst administration is self-reported in the participant eDiary.

The total duration of exposure during the Core Study Period (weeks) and number of injections during the Core Study Period will be summarized with descriptive statistics (n, mean, SD, median, minimum and maximum) by treatment group. A list of study drug treatment assignment will be provided.

Total duration of exposure is defined in Table 11.2 below. TR01SDT, TR01EDT, TR02SDT and TR02EDT are defined in Sections 6.4.1, 6.4.2, 6.4.3, and 6.4.4 respectively.

Table 11.2 Total Duration of Semaglutide Exposure (weeks)

Treatment Arm	**Exposure during Core Study Period (weeks)**	**Exposure by time of Core Study Database Lock (weeks)**
Placebo + No Sema/Bima 30mg/kg + No Sema	0	0
Bima 10mg/kg + No Sema/Bima 30mg/kg + No Sema	0	0
Bima 30mg/kg + No Sema/Bima 30mg/kg + No Sema	0	0

All other treatment arms	(TR01EDT-TR01SDT+1)/7	(TR01EDT-TR01SDT+1)/7 or (TR02EDT-TR01SDT+1)/7 if participant has entered the Extension Treatment Period

The overall treatment compliance rate for semaglutide injection will be summarized by treatment group. A patient is considered compliant if at least 80% of the time prior to the permanent treatment discontinuation, the patient reported receiving planned number of injections. The algorithm is described in further detail below.

Compliant during core study period for core period completers = Yes if (number of injections recorded in diary during the period TR01SDT to CCI (Week 48 date)/48 >= 80%.

Compliant during core study period for core period discontinuers = Yes if (number of injections recorded in diary during the period TR01SDT to TR01EDT)/(planned number of doses during the period TR01SDT to TR01EDT) >= 80%.

Planned number of injections during the period TR01SDT to TR01EDT for core period discontinuers = [(TR01EDT - TR01SDT+1)/7]+1 rounded down to the nearest integer

11.2 Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and Preferred Term (PT) for each adverse event (AE).

Treatment emergent AEs will be defined as AEs with an onset date on or after the date of administration of study drug. If the onset date is missing, the AE is regarded as treatment emergent. Only treatment-emergent AEs that onset during the core study period will be summarized. All reported AEs will be listed.

The number of AEs, and the number and percentage of subjects reporting at least one AE will be summarized by PT nested within SOC for each of the following AE types:

1. Any AE
2. Any adverse events of special interest (AESI) (defined in Section 11.2.1)
3. Any AE related to bimagrumab only
4. Any AE related to semaglutide only
5. Any AE related to both bimagrumab and semaglutide
6. Any severe AE
7. Any serious AE (SAE)
8. Any serious AE related to bimagrumab only
9. Any serious AE related to semaglutide only
10. Any serious AE related to both bimagrumab and semaglutide

In addition, TEAEs and AESIs will be summarized by severity (mild, moderate, severe). Summary tables by severity will be split into two tables. The first displaying number and percentage of subjects, and the second displaying the number of events. For the first table of subjects, each subject will only count once in the maximum severity of the same PT. Similarly, each subject will only count once in the maximum severity of the same SOC,

and for the count of subjects with 'at least one AE', each subject will only count once in the maximum severity of any AE they experienced.

For the second table displaying number of events, all events will be included. This includes subjects with multiple occurrences of the same adverse event at different severities.

The following listings will be presented by treatment group and subject:

1. Any AEs
2. Any SAEs
3. Any related AEs

11.2.1 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) for bimagrumab are defined on the basis of an ongoing review of all safety data and include (using CTCAE intensity grading).

AESI will be identified programmatically using MedDRA terms rather than using the AESI flag from the eCRF. TEAEs which meet the criteria in Appendix 2 (Table 16.2) will be selected as AESI. The skin and subcutaneous tissue disorders identified in Appendix 2 (Table 16.3) will be excluded and will not be classified as AESI.

11.2.2 Adjudicated Adverse Events

An adjudication committee called the Clinical Event Committee (CEC) was formed to adjudicate potential events that occur during the course of a trial. Members of the CEC will adjudicate each potential event per study specific protocol, based on the pre-specified definitions, and render an assessment as to whether the case represents a confirmed event (meeting the event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or non-event diagnosis), or lacks sufficient documentation for confirmation of an event. Events are reviewed on an on-going process as cases become available. Events reported in the AE CRF will not be changed. However, adjudication may conclude that an event is not consistent with the AE

CRF. Adjudicated AEs will be listed only. For purposes of summarizing AEs, only AE CRF data will be included in the summary tables. AE CRF data will also be listed.

11.3 Laboratory Evaluations

The following clinical laboratory tests will be analysed at the local laboratory at times stipulated in the Protocol Schedule of Assessments:

Biochemistry (blood sample): Sodium, potassium, chloride, bicarbonate (CO2), phosphate, magnesium, calcium, albumin, total protein, uric acid, urea/blood urea nitrogen (BUN), creatinine, glucose, creatine kinase (CK), lipase, amylase, liver function tests (AST / SGOT, ALT/ SGPT, LDH, GGT, alkaline phosphatase), total and direct bilirubin.

Hematology (blood sample): Hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocytes (% and absolute)), white blood cell (WBC) count with differential (% and absolute) (neutrophils, lymphocytes, monocytes, eosinophils, basophils), erythrocyte sedimentation rate, platelet count.

Coagulation (blood sample): aPTT, PT, INR.

Urinalysis: pH, specific gravity, glucose, protein, bilirubin, nitrite, leukocytes, blood, ketones. Microscopy will be carried out if blood or protein is abnormal.

Urine Chemistry: Microalbumin, urine creatinine, ACR.

Lipid profile (blood sample): Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol. Samples will be collected under fasting conditions unless specified otherwise.

Glucose metabolism parameters (blood sample): HbA1C, insulin, glucose. Samples will be collected under fasting parameters except for the screening visit.

Pregnancy Screen: All women will be screened for pregnancy. The screening pregnancy test will be by blood sample to detect the presence of β-human chorionic gonadotropin (β-HCG). Subsequent visits will utilize rapid urine hCG tests for pregnancy.

Urine drug screen: to include at minimum amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines.

Hepatitis B and HIV screening: HIV antibody, HBsAg, HBsAb, HBcAb, HCVAb.

Clinical safety laboratory data (hematology, biochemistry, and urine chemistry) will be standardised to SI units. The normal range for the standardised data will be data dependent as follows:

Standardized Lower Limit of Normal (LLN) for a parameter = minimum LLN for that parameter in the standardized dataset

Standardized Upper Limit of Normal (ULN) for a parameter = maximum ULN for that parameter in the standardized dataset

Clinical safety laboratory data (hematology, biochemistry, and urine chemistry) will be summarised at each protocol scheduled time point, by treatment group. Actual values and actual changes from baseline will be presented. Continuous urinalysis parameters will be similarly summarized. Categorical urinalysis parameters will be summarized using frequencies and percentages at each protocol scheduled time point by treatment group. For the summary of categorical urinalysis results, the results will be consolidated to the categories displayed in Appendix 16.3 Table 16.4.

The following plots will also be presented for all biochemistry and urine chemistry parameters:

For selected laboratory parameters, scatterplots of shift from baseline to “worst post baseline” value with reference lines for normal ranges will be presented. The

"worst" value will be defined as either the lowest or highest post-baseline value. For some parameters, both the highest and lowest values will be considered the "worst" and the scatterplot will be presented twice. The selected parameters and definition of worst are detailed in Section 16 Appendix 1 (Table 16.1). For these scatterplots, the most frequent normal range will be used as the standard normal range, and all results will be linearly transformed from their original units and original normal range so they fall in a similar relative position within the standard normal range, compared to their original position within their original normal range. Further details of the transformation algorithm are described in Section 16 Appendix 1.

Graphs of mean change from baseline values by treatment group over time.

Urinalysis results evaluation (normal, abnormal not clinically significant or abnormal clinically significant) will be summarised at each protocol scheduled time point, by treatment group, using frequency tabulations.

Abnormal laboratory values will be flagged and will be identified in the listings. Microscopy data, if available, will be listed.

All laboratory results except drug screening will be listed. Drug screening results are kept as source data only.

11.4 Vital Signs

Vital signs measurements will include body temperature, pulse rate and systolic and diastolic blood pressure. Vital signs will be collected at the times stipulated in the Protocol Schedule of Assessments.

Vital sign results will be summarised at each protocol scheduled time point, by treatment group. Actual values and actual changes from baseline will be presented. Vital sign results will be listed by treatment group and subject.

Height will be presented as part of the demographic and baseline assessments.

Weight and body mass index (BMI) will be presented as part of efficacy assessments.

11.5 12-lead ECG

Standard 12-lead ECG (PR, RR, QRS, QT and QTcF) will be performed at times stipulated in the Protocol Schedule of Assessments.

Electrocardiogram evaluation (normal, abnormal not clinically significant or abnormal clinically significant) will be summarised at each protocol scheduled time point, by treatment group at each protocol scheduled time point, using frequency tabulations. Actual values and actual changes from baseline will be presented.

ECG results will also be listed by treatment group and subject.

11.6 Physical Examination

A physical examination will be performed at times stipulated in the Protocol Schedule of Assessments.

Physical examination findings will be listed by subject and visit.

11.7 Dietary Intake

Participants' dietary intake will be recorded via 24-hour recall assessment at Baseline, Week 12, 24, and 48. Dietary intake will include Total Calories (kcal/day), Carbohydrate (g/day), Carbohydrate Percentage by Total Calories (% total calories), Fat (g/day), Fat Percentage by Total Calories (% total calories), Protein (g/kg body weight/day), and Protein Percentage by Total Calories (% total calories).

The dietary intake parameters will be summarised at time point, by treatment group. Actual values and actual changes from baseline will be presented. Dietary intake will be listed by treatment group and participant.

Protein intake is collected in units of g/day and will be converted to g/kg body weight/day using the following algorithm (MacCarron & Devine, 1974):

1. Calculate ideal body weight (IBW) using the following formula:
    - Male: IBW = 50 kg + 2.3*(Actual height in cm/2.54 – 60 inches)
    - Female: IBW = 45.5 kg + 2.3 kg*(Actual height in cm/2.54 – 60 inches)
2. Compare actual weight to IBW
    - Actual weight = X% of IBW
3. If actual weight is >30% above IBW, then calculate adjusted body weight (1-3) for use in converting g/day to g/kg body weight/day
    - Adjusted body weight = IBW + 0.4* (Actual weight – IBW)
4. Convert protein intake (g/day) to protein intake (g/kg body weight/day)
    - If actual weight > 1.3*IBW, protein intake (g/kg body weight/day) = protein intake (g/day) / adjusted body weight
    - If actual weight ≤1.3*IBW, protein intake (g/kg body weight/day) = protein intake (g/day) / actual body weight

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14. IMMUNOGENICITY

Serum samples from all subjects collected according to the SoA will be screened for antibodies binding to bimagrumab (anti-drug antibodies, ADA) and the titer of confirmed positive samples will be reported. Other analyses may be performed to evaluate the neutralizing activity or verify the stability of antibodies to bimagrumab and/or further characterize the immunogenicity of bimagrumab.

ADA results will be summarised at each protocol scheduled time point, by treatment group. Actual values and actual changes from baseline will be presented. ADA results will be listed by treatment group and subject.

15. CHANGES FROM PROTOCOL

Not applicable.

16. APPENDICES

16.1 Appendix 1: Details of Laboratory scatterplots

As described in Section 11.3, for selected laboratory parameters, scatterplots of shift from baseline to "worst post baseline" value with reference lines for normal ranges will be presented. Table 16.1 lists the parameters to be plotted along with the definition of the "worst" value as either the lowest or highest post-baseline value, or both. The scatterplot will be presented twice if both lowest and highest are considered "worst".

Table 16.1 Details of Laboratory Scatterplots for Selected Parameters

Type of Laboratory Test	Parameter	Definition of "Worst"	
		Lowest Post-Baseline Value	Highest Post-Baseline Value
Chem	Calcium	x	X
Chem	Glucose	x	X

Chem	BUN/urea		x
Chem	Uric Acid	x	x
Chem	Protein	x	
Chem	Albumin	x	
Chem	Potassium	x	x
Chem	Sodium	x	x
Chem	Total Bilirubin		x
Chem	Direct Bilirubin		x
Chem	Alk.phos.	x	x
Chem	LDH		x
Chem	AST		x
Chem	ALT		x
Chem	GGT		x
Chem	Creatinine Kinase	x	x
Chem	Creatinine	x	x
Chem	Magnesium	x	x
Chem	Amylase	x	x
Chem	Lipase	x	x
Chem	WBC	x	x
Chem	RBC	x	x
Hem	Hemoglobin	x	x
Hem	Abs.reticulocyte count		x
Hem	Abs. Neutrophils	x	x
Hem	Abs. Lymphocytes.	x	x
Hem	Abs. Eosinoph.		x
Hem	Platelets	x	x
Hem	Sedimentation rate		x
Hem	aPTT	x	x
Hem	Prothrombin time	x	x
Hem	INR		x
Total Figures		**21**	**30**

For parameters with multiple normal ranges, the different units and normal ranges were transformed to the same standard units and standard normal range using the linear transformation described below. This transformation was applied to the values in the

laboratory scatterplots only. It preserves the relationship between the original laboratory values and their original normal ranges and the relationship between the standardized values and the standardized reference range. If the original value lies within the original normal range then the standardized value will also lie within the standardized normal range. For original values that fall outside the original normal range the standardized value will also fall outside the standardized normal range, and will approximately maintain the relationship between values and xULN.

Let L_v denote the original value, and (L_{LLN}, L_{ULN}) denote the original normal range.

Let S_v denote the standardized value, and (S_{LLN}, S_{ULN}) denote the standardized normal range. The linear transformation is

$$S_v = S_{LLN} + \frac{(L_v - L_{LLN})}{(L_{ULN} - L_{LLN})} \times (S_{ULN} - S_{LLN})$$

Examples:

Suppose the original ranges for a parameter are (32, 182), (41, 331), and (49, 439). Suppose the standardized normal range is (45, 300).

Suppose the first original result is L_v=32 which is the LLN for the first original normal range, then

$$S_v = 45 + \frac{(32 - 32)}{(182 - 32)} \times (300 - 45)$$

$$= 45 = S_{LLN}$$

which maintains the result's relative position at the lower limit of the normal range.

Suppose the second original result is L_v=107 which is the mid-point of the first original normal range, then

$$S_v = 45 + \frac{(107 - 32)}{(182 - 32)} \times (300 - 45)$$

$$= 45 + \frac{75}{150} \times (300 - 45)$$

$$= 45 + 127.5 = 172.5$$

which is the mid-point of the standardised normal range.

Suppose the third original result is L_v=182 which is the ULN for the first original normal range, then

$$S_v = 45 + \frac{(182 - 32)}{(182 - 32)} \times (300 - 45)$$

$$= 45 + (300 - 45) = 300 = S_{ULN}$$

which maintains the result's relative position at the upper limit of the normal range.

Suppose as fourth original result is L_v=2×182 which is 2xULN for the first original normal range, then

$$S_v = 45 + \frac{(364 - 32)}{(182 - 32)} \times (300 - 45)$$

$$= 45 + 2.213 \times (300 - 45) = 609.4 \sim 2 \times S_{ULN}$$

which maintains the result's relative position at approximately twice the upper limit of the normal range.

16.2 Appendix 2: Details Of MedDRA Terms Used to Define AESI

Table 16.2 MedDRA Terms Used to Define AESI

AESI Category	MedDRA Level	Term	Term Code	Minimum Grade
Muscle related events	HLGT	Muscle disorders	10028302	3
	HLT	Musculoskeletal and connective tissue pain and discomfort	10068757	3
	PT	Musculoskeletal stiffness	10052904	3
Skin-related lesions excluding rashes defined in Table 6	BODSYS	Skin and subcutaneous tissue disorders	10040785	3
Gastrointestinal events	HLGT	Gastrointestinal conditions NEC	10017943	3
	HLT	Gastrointestinal inflammatory disorders NEC	10017921	3
	HLGT	Gastrointestinal motility and defaecation conditions	10017977	3
	HLGT	Gastrointestinal signs and symptoms	10018012	3
Pancreatitis	HLGT	Exocrine pancreas conditions	10015674	Any grade
Malignancy	HLGT	Breast neoplasms malignant and unspecified (incl nipple)	10006291	Any grade
	HLGT	Endocrine neoplasms malignant and unspecified	10014713	Any grade
	HLGT	Gastrointestinal neoplasms malignant and unspecified	10017991	Any grade
	HLGT	Haematopoietic neoplasms (excl leukaemias and lymphomas)	10018865	Any grade
	HLGT	Hepatobiliary neoplasms malignant and unspecified	10019815	Any grade
	HLGT	Leukaemias	10024324	Any grade
	HLGT	Lymphomas Hodgkin's disease	10025319	Any grade
	HLGT	Lymphomas NEC	10025323	Any grade
	HLGT	Lymphomas non-Hodgkin's B-cell	10025320	Any grade
	HLGT	Lymphomas non-Hodgkin's T-cell	10025321	Any grade
	HLGT	Lymphomas non-Hodgkin's unspecified histology	10025322	Any grade

	HLGT	Mesotheliomas	10027412	Any grade
	HLGT	Metastases	10027476	Any grade
	HLGT	Miscellaneous and site unspecified neoplasms malignant and unspecified	10027655	Any grade
	HLGT	Nervous system neoplasms malignant and unspecified NEC	10029211	Any grade
	HLGT	Plasma cell neoplasms	10035227	Any grade
	HLGT	Renal and urinary tract neoplasms malignant and unspecified	10038364	Any grade
	HLGT	Reproductive and genitourinary neoplasms gender unspecified NEC	10038588	Any grade
	HLGT	Reproductive neoplasms female malignant and unspecified	10038594	Any grade
	HLGT	Reproductive neoplasms male malignant and unspecified	10038597	Any grade
	HLGT	Respiratory and Mediastinal neoplasms malignant and unspecified	10038666	Any grade
	HLGT	Skeletal neoplasms malignant and unspecified	10040778	Any grade
	HLGT	Skin neoplasms malignant and unspecified	10040900	Any grade
	HLGT	Soft tissue neoplasms malignant and unspecified	10072990	Any grade
	HLT	Ocular melanomas	10030052	Any grade
	HLT	Ocular neoplasms malignancy unspecified	10030053	Any grade
	HLT	Ocular neoplasms malignant (excl melanomas)	10030057	Any grade

Table 16.3 MedDRA Terms within the SOC, 'Skin and Subcutaneous Tissue Disorders' Which Will Not Be Identified as AESI

Code	Preferred Term	HLT	HLGT
10037844	Rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10067982	Butterfly rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions

10064579	Exfoliative rash	Exfoliative conditions	Epidermal and dermal conditions
10081454	Heliotrope rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10056671	Mucocutaneous rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10075807	Nodular rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10074687	Paraneoplastic rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037855	Rash erythematous	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037857	Rash follicular	Pustular conditions	Epidermal and dermal conditions
10037867	Rash macular	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037868	Rash maculo-papular	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10050004	Rash maculovesicular	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037870	Rash morbilliform	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037871	Rash neonatal	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037876	Rash papular	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037879	Rash papulosquamous	Papulosquamous conditions	Epidermal and dermal conditions
10037884	Rash pruritic	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10057984	Rash rubelliform	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037890	Rash scarlatiniform	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10037898	Rash vesicular	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10042946	Systemic lupus erythematosus rash	Rashes, eruptions and exanthems NEC	Epidermal and dermal conditions
10047111	Vasculitic rash	Skin vasculitides	Skin vascular abnormalities

16.3 Appendix 3: Consolidation of Urinalysis Results Categories

For the summary of categorical urinalysis results, the results will be consolidated in the categories displayed in Table 16.4.

Table 16.4 Consolidation of Urinalysis Results Categories

Parameter Short Code (ADLB.PARAMCD)	Parameter Result (ADLB.AVALC)	Consolidate to	Order
BILU	1+	1+	1
BILU	SMALL (1+)		
BILU	MODERATE (2+)	2+	2
BLD	NEGATIVE	Negative	-1
BLD	HAEMOLYSED-TRACE	Trace - hemolyzed	0.5
BLD	NON-HAEMOLYSED-TRACE	Trace - non-hemolyzed	
BLD	TRACE	Trace	
BLD	1+	1+	1
BLD	SMALL (1+)		
BLD	2+	2+	2
BLD	MODERATE (2+)		
BLD	NON-HAEMOLYSED-MODERATE	Moderate - non-hemolyzed	
BLD	3+	3+	3
BLD	LARGE (3+)		

KETONES	1+	1+	1
KETONES	SMALL		
KETONES	2+	2+	2
KETONES	MODERATE		
KETONES	LARGE	3+	3

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