Clinical Development

BYM338/bimagrumab

Study CBYM338E2202E1 / NCT02468674

A 24 week off drug extension, parallel group, study assessing durability of effect on skeletal muscle strength and function following a 6-month double-blind, placebo controlled study evaluating bimagrumab in older adults with sarcopenia (InvestiGAIT extension)

RAP Module 3: Detailed Statistical Methodology

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Table of contents

1   Introduction to the RAP document

1.1   Scope

The SAP document contains detailed information to aid the production of Statistics & Programming input for trial **"*CBYM338E2202E1*".**

1.2   Changes to SAP document

Any major changes occurring before database lock to the statistical methodology should be reflected in the SAP documentation via version control.

Major changes include, but are not limited to, changes in protocol that affect study design and statistical methodology. For study BYM338E2202E1, the major changes made to SAP document are reflected in Amendment 1 version and details are below:

Amendment 1 (June 2018)
This amendment was developed to reflect the changes in Protocol Amendment 1. The purpose of the amendment was to revise the extension study design to align it with the changes recently implemented in the core study CBYM338E2202 while maintaining and further focusing the primary purpose of the extension study to evaluate the durability of effect 24 weeks of bimagrumab therapy upon discontinuation.
Changes to the RAP
Statistical and analytical plan: Changed the primary objective of the study.
Statistical methods: Analysis sets: Changed to reflect the analysis sets of the protocol and that we have two Populations.
Patient disposition, background and demographic characteristics: Changed to reflect that we have two Populations. Updated the analysis sets summary table to also be done ▮▮▮▮▮▮
Treatments (study drug, other concomitant therapies, compliance): Changed to reflect that we have two Populations. Updated the duration of exposure summary tables to also be done ▮▮▮▮▮
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Statistical methods for Pharmacodynamic (PD) parameters: Changed to reflect that we have two Populations. The primary objective/endpoint of the study was changed to reflect existing protocol, the secondary endpoints to reflect the current protocol and removed imputation by LOCF and to include CI at selected summary statistics. Change the definition of Sarcopenic to remove SPPB total score<=9. ▮▮▮▮▮▮▮▮▮▮▮▮▮. Added an ANCOVA analysis and a supportive analysis section for selected secondary endpoints.
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Statistical methods for safety and tolerability data : Changed to reflect that we have two Populations and to remove patient diary as per the new protocol. Added summary tables for notable vital signs, newly occuring notable values in clinical laboratory evaluations, and notable echocardiography values along with the definition of notable echocardiography values. Calarified the notable criteria for liver ▮▮▮▮▮ enzyme abnormalities. Changed the adverse events section ▮▮▮▮▮▮▮▮▮ add clarity on the handling of AE's continuing from the core study and how AESI will be analyzed.
Interim analyses : Changed to reflect that an IA is required.

Sample size calculation : Changed to reflect the change in the primary endpoint.
Clinical Study Report – Appendix 16.1.9 Documentation of statistical methods : Changed to reflect the changes in the analysis.

2   Study design and objectives

2.1   Study objectives

Objective	Endpoint	Analysis
Primary		
The primary objective is to assess the durability of effect of bimagrumab (BYM338) on physical function as measured by the SPPB total score at Week 49.	Total SPPB at Week 49	Section 3.5
Secondary		
• To evaluate the long term safety effect of bimagrumab following treatment withdrawal as assessed by measures such as vital signs, clinical laboratory variables, electrocardiogram (ECG), and adverse events (AE)	Safety variables	Section 3.7
• To evaluate the durability of effect of BYM at week 49 as measured by:		Section 3.6
• 6MWT	6MWT at Week 49	
• Usual gait speed over 4 meters (Gait speed)	Gait speed at Week 49	
• Total lean body mass (total LBM) and appendicular skeletal muscle index (ASMI) measured by dual energy X-ray absorptiometry (DXA)	Total LBM and ASMI at Week 49	
•		

2.2   Study design

This Phase IIb extension study is a 24 weeks off drug follow-up observation trial to determine the durability of effect and the safety of bimagrumab in older patients with sarcopenia.

After completing 24 weeks of treatment in the core study (CBYM338E2202), newly consenting patients in the extension study CBYM338E2202E1 will continue with the same uniquely identified patient number and be followed for an additional 24 weeks off drug. They will complete the EOS at week 49.

Figure 2-1   Study design for patients enrolled after the protocol amendment #1
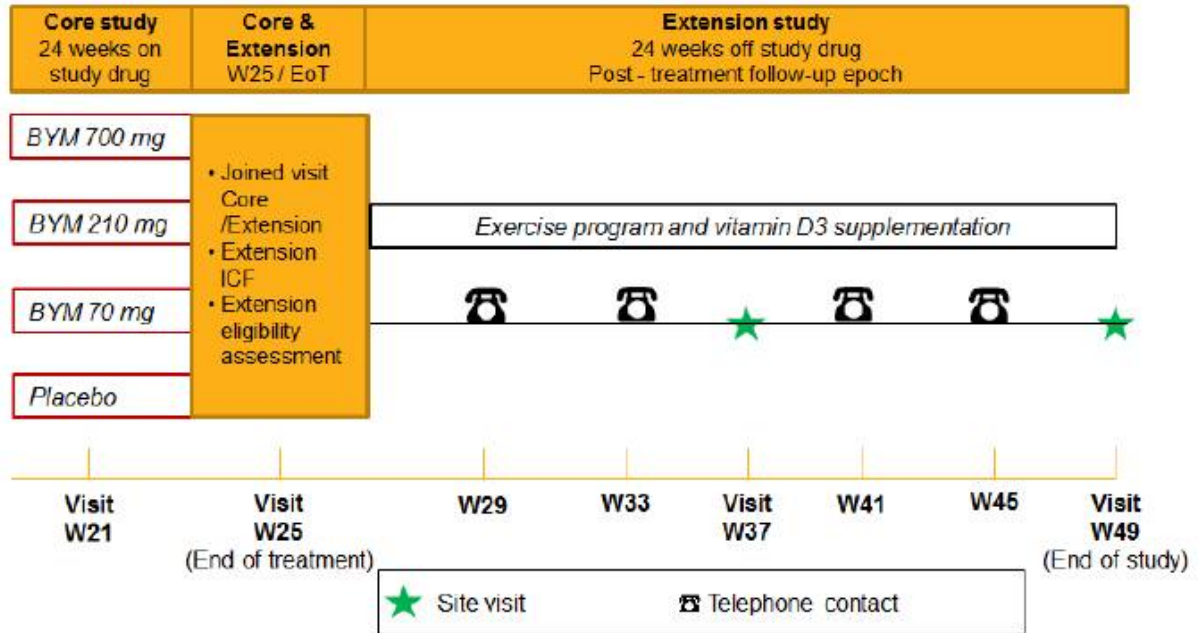
Patients enrolled prior to protocol amendment #1 will follow the original study design and will continue to be treated as per the regimen assigned at the entry of the extension study.

Figure 2-2   Study design for patients enrolled prior to protocol amendment #1
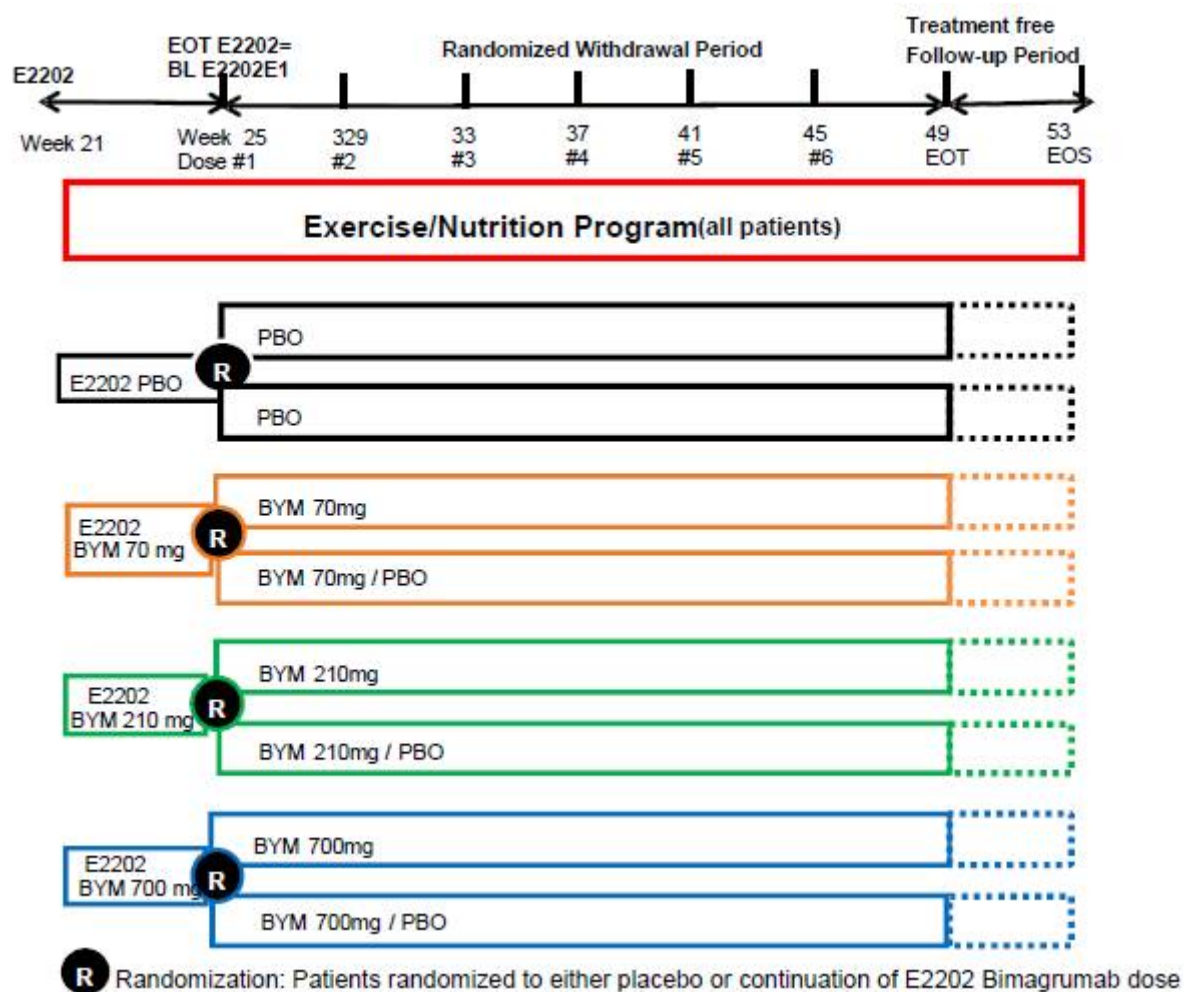
3   Statistical and analytical plans

The planned analysis is described in Section 9 of the protocol (Appendix 16.1.1).

The primary objective of this study is to assess the durability of effect of bimagrumab (BYM338) in older adults with sarcopenia as measured by week 49 SPPB.

Unless otherwise stated, summary tables/figures/listings will be on all subjects included in the population under consideration. Data will be summarized with respect to demographic and baseline disease characteristics, efficacy, and safety assessments.

3.1   Statistical methods: Analysis sets

The following analysis sets are defined:

Full analysis set (FAS): The FAS comprises of all subjects enrolled in the study.

Safety set (SAF): The safety set comprises of all subjects who received at least one dose of study drug from the core or extension study and enrolled in the extension study. Subjects will be analyzed according to the treatment actually taken.

Per-protocol set (PP): The Per-protocol set comprises all subjects in the FAS who do not have major deviations that could confound the interpretation of analyses conducted on the FAS. The following are common examples of such protocol deviations:

- Subject entered the study even though they did not satisfy the entry criteria
- Subject developed study/treatment withdrawal criteria during the study but was not withdrawn
- Subject received the wrong treatment or incorrect dose
- Subject took a prohibited concomitant medication

The PP set will be identified and finalized based on blinded review of the data, prior to the final database lock.

To facilitate different analysis on patients enrolled before and after the protocol amendment #1, two populations are defined as below:

- Population I is defined to include patients enrolled prior to protocol amendment 1, who will be continuing the treatment as originally assigned and follow the original schedule until end of the study.
- Population II is defined to include patients enrolled after protocol amendment 1, who will be followed up per schedule defined in this protocol amendment.

3.2   Patient disposition, background and demographic characteristics

The analysis in this section will be based on FAS. For Population I, all summaries will be presented by treatment group in the extension study and overall. For Population II, all summaries will be presented by treatment assigned in the Core study and overall.

Relevant raw and derived data as described in this section will be presented in by-patient data listings. All by-patient data listings will be sorted by Population, treatment group,　　　 center and patient if not indicated otherwise.

Where relevant, "overall" refers to the addition of a "Total" treatment column within the planned presentation of the data.

3.2.1   Patient disposition

All patients will be summarized using number (n) and percentage (%), overall 　　　　center, by each treatment group and overall, for

Populations I and II separately. Furthermore, for each study epoch (screening, treatment and follow-up as applicable to the populations) the number of patients per treatment group and the overall number of patients who entered the epoch, completed, and discontinued within the epoch will be summarized in a similar manner, including the reasons for discontinuation.

At the final analysis, the number (n) and percentage (%) of patients with protocol deviations will be summarized by category and deviation, for each treatment group and overall, ████ ████████████████████████████. Patients with protocol deviations will be listed.

The number (n) and percentage (%) of patients included in each analysis set will be summarized by treatment group and overall, ██████████████████████████ for Populations I and II separately. At the final analysis, the reasons for exclusions from analysis sets will be tabulated overall for all patients ██████████████████████████████████ for each treatment group and overall. Patient exclusion from analysis sets will be listed for all patients with reason(s) for exclusion, including both major protocol deviations and/or other exclusion criteria.

3.2.2   Patient demographics and other baseline characteristics

Descriptive statistics for demographics and baseline characteristics at Week 25 will be presented to describe the FAS. All summaries will be presented by treatment group and overall ███████████████████████████████████████ for Populations I and II separately.

Descriptive statistics (n, mean, median, standard deviation, minimum and maximum (not for IA), Q1 and Q3) will be presented for continuous variables for each treatment group and overall in the FAS. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and overall. Unless otherwise specified, percentages will be based on the number of patients in the FAS with data available.

3.2.2.1   Demographics

Demographic variables taken at screening, including age, sex, child bearing potential of female subjects, height (cm), weight (kg), body mass index (BMI) (kg/m2), race and ethnicity will be summarized.

3.2.2.2   Other patient characteristics

Patient characteristics at Week 25 will be summarized. Patient characteristics will include: nutritional status, protein intake, total and appendicular lean body mass (LBM and ASMI), 6 minute walk test (6MWT), Gait Speed, Short Physical Performance Battery (SPPB) total score, ███████████████████████████████████████.

3.2.2.2.1 Nutritional status/protein intake

For both populations, nutritional status at Week 25 will be summarized by both descriptive measures for quantitative variables (calculated protein intake) and qualitatively for patient's daily protein intake categories (< 0.8 grams protein/kg and ≥ 0.8 grams protein/kg), nutritional

status (sufficiently nourished/malnourished), and action taken if malnourished if available (dietary counseling with or without intervention/no dietary counseling).

3.2.2.2.2 Efficacy assessments

Total LBM, ASMI

Week 25 data (all relevant pre-treatment assessments, including baseline value, relative to Week 25) of total LBM, ASMI will be summarized using descriptive statistics for both population I and population II, separately.

Six Minute Walk Test (6MWT)

The 6 minute walk test (6MWT) is a simple, economical and reproducible test that measures how many meters a person can walk in 6 minutes. All subjects will be included in the descriptive statistics with the actual distance walked. In circumstances where the test is interrupted for reasons other than patient fatigue the test may be repeated once, preferably on the same day (with a minimum 20 minute rest period). Total distance walked will be summarized by descriptive statistics. Walking aids used for the test will be summarized by category as defined in the CRF page.

Summaries at Week 25 will be provided for both population I and population II, separately.

SPPB

The short physical performance battery (SPPB) evaluates lower extremities in three functional components: Standing balance, gait speed and chair stand. A score will be calculated for each of the three components. In addition a total SPPB score will also be calculated. Total standing balance score is calculated as the sum of the scores of side-by-side stand, semi-tandem stand and tandem stand.

- Side-by-side stand: held for 10 sec = 1 point, not held for 10 sec or not attempted = 0 points.
- Semi-tandem stand: held for 10 sec = 1 point, not held for 10 sec or not attempted = 0 points.
- Tandem stand: held for 10 sec = 2 points, held for 3 to 9.99 sec = 2 points, held for less than 3 sec or not attempted = 0 points.

Gait speed will be assessed as part of the SPPB, over a 4 meter distance of a 6 or 4 meter course. Gait speed assesses a person's usual walking speed. The patient will perform two recorded trials of walking across the defined course. The fastest time in seconds (to the nearest 0.01 sec will be recorded. If only one walk was performed, this time will be used. Any walking aid(s) used during the SPPB gait speed test performance will be captured in the eCRF. The scoring system is as follows:

- Time < 4.82 sec = 4 points.
- Time ≥ 4.82 to ≤ 6.20 sec = 3 points.
- Time ≥ 6.21 to ≤ 8.70 sec = 2 points.
- Time > 8.70 sec = 1 point.

- Patient is unable to do the walk = 0 points.

At first the chair stand test will be done one time (singular chair stand test). If the patient used arms to stand or the test could not be completed then the test procedure will be stopped and the score for the test is 0 points. If the patient stood up without using arms the aim of the second part of the test is to stand up five times (repeated chair stand test). The scoring system is as follows:

- Time to complete 5 stands ≤ 11.19 sec = 4 points.
- Time to complete 5 stands ≥ 11.20 to ≤ 13.69 sec = 3 points.
- Time to complete 5 stands ≥ 13.70 to ≤ 16.69 sec = 2 points.
- Time to complete 5 stands ≥ 16.70 to ≤ 60 sec = 1 point.
- Patient is unable to complete 5 chair stands or has completed stands in > 60 sec = 0 points.

The total SPPB score will be calculated as the sum of the total standing balance score, gait speed test score and chair stand test score.

Handling of missing data: If a test is not done (i.e. test not done is ticked in the eCRF) there will be no imputation of data. Since the standing balance tests become progressively more difficult with each test, if the result for the tandem stand or semi-tandem stand is missing the result will be imputed by 0 points, provided that the previous test(s) had been performed. In all other cases there will be no imputation.

Week 25 data (all relevant pre-treatment assessments, including baseline value, relative to Week 25) of the total SPPB score with the corresponding scores of the three individual component tests: Standing balance, gait speed, and chair stand will be tabulated in a frequency table. Categories for each of the individual component tests will be:

- 0 points.
- 1 point.
- 2 points.
- 3 points.
- 4 points.

Categories for the total SPPB score will be:

- 0 to 6 points.
- 7 to 9 points.
- 10 to 12 points.

In addition to the scores, the actual time of the timed function tests will be summarized for the individual components using descriptive statistics (see Section 5.22.1 [Precision and summary statistics]). For balance tests, if the patient attempted the test and is indicated as "Held for 10 seconds" then a value of 10 seconds will be used.

If a patient did not attempt a test or failed, the patient will have a missing time for that test.

3.2.2.2.3 Diaries

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Exercise adherence diary

Site staff should query the patient on adherence to the exercise program, ███████████████ ██████ recorded in the exercise diary during the monthly telephone call. Exercise adherence diary at Week 25 will be summarized for both population I and population II, separately.
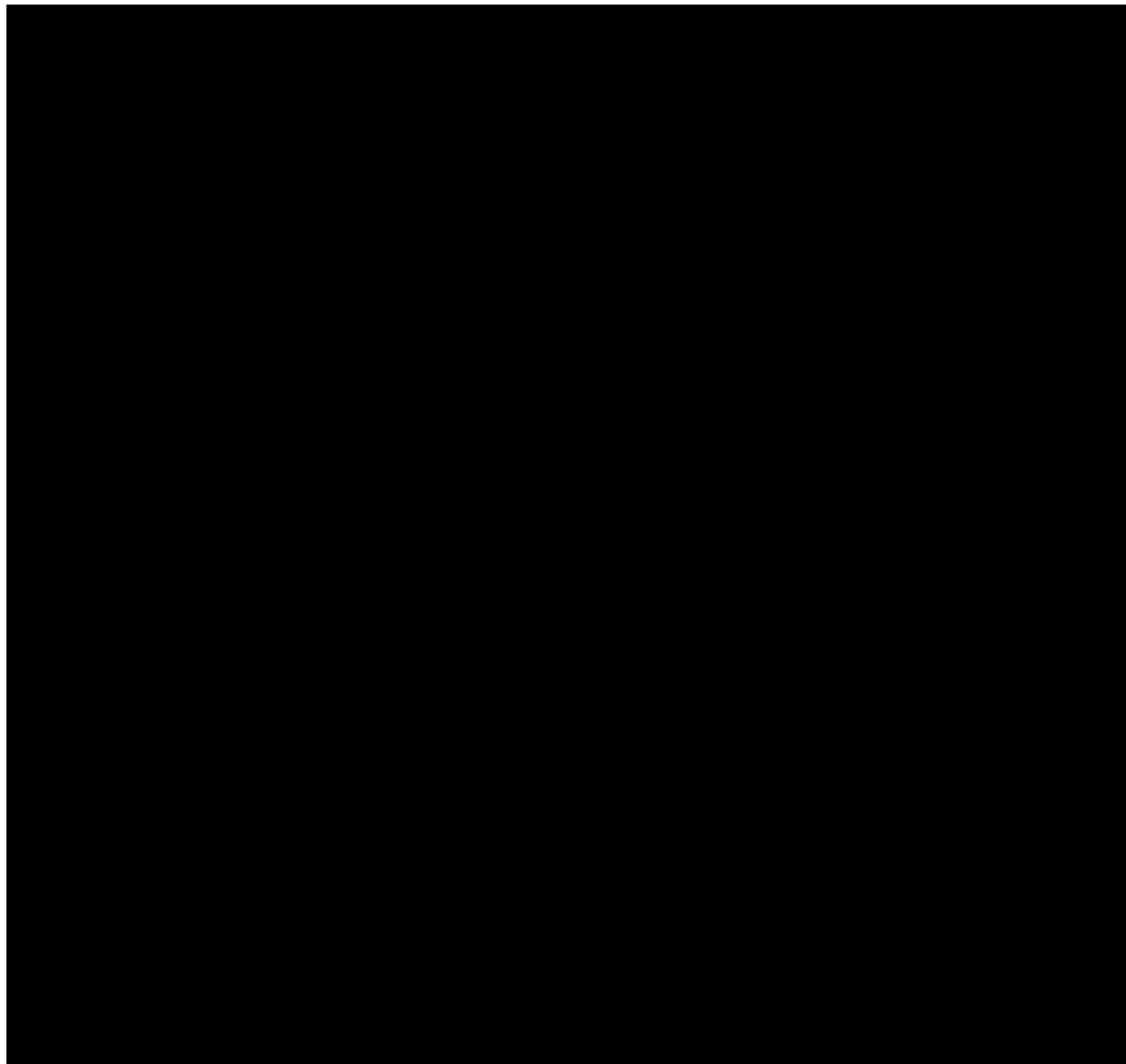
3.3 Treatments (study drug, other concomitant therapies, compliance)

The analysis in this section will be based on SAF set.

For Population I, all summaries will be presented by treatment group in the extension study and overall. For Population II, all summaries will be presented by treatment assigned in the Core study and overall.

Relevant raw and derived data as described in this section will also be presented in by-patient data listings. All by-patient data listings will be sorted by Population, treatment group, ███ center and patient if not indicated otherwise.

Where relevant, "overall" refers to the addition of a "Total" treatment column within the planned presentation of the data.

3.3.1 Study drug administration

For Population 1, the analysis of study treatment data will be based on the safety analysis set. For each subject, cumulative exposure to study treatment will be calculated as the number of days of drug exposure=last infusion date - first infusion date + 56 days. The first infusion date refers to the first dose date following the last dose in the core study. The duration of exposure

to study drug will be summarized by treatment group, ███████████████████████ as a continuous variable. The volume administered will also be summarized by visit and by treatment group as a continuous variable.

For Population 2, no exposure data will be presented.

3.3.2 Prior and concomitant medications

Prior medications, concomitant medications ongoing at the entry of the extension study and concomitant medications initiated in the extension study will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Within ATC Level 1, the PTs will be sorted by descending frequency of the total number of patients with at least one medication in each PT. In the event of ATC categories and/or PTs with equal total frequencies, the relevant ATC categories and/or PTs will be sorted alphabetically. Tables will also show the overall number (n) and percentage (%) of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Summary by treatment group in this study will be provided for Populations I and II separately.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment for population I, or prior to the first visit (Week 25) in the extension study for population II. Any medication given at least once between the day of first dose of study treatment and the date of the last study visit for population I, or between the first visit (Week 25) in the extension study and the end of the study visit for population II, will be a concomitant medication, including those which were ongoing at the entry of the extension study and continued into the study. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taking. If it cannot be established that the use of a prior medication has ended prior to the first dose of study treatment due to a missing end date, then it will be considered concomitant. Algorithms for date imputations will be provided in RAP Module 8 (Programming Specifications).

3.4 Analysis of the primary variable(s)

The primary analysis population for efficacy will be the Full Analysis Set.

The primary objective of this study is to assess the durability of effect of bimagrumab (BYM338) in older adults with sarcopenia as measured by the SPPB total score.

The primary endpoint is SPPB at week 49.

3.4.1 Descriptive statistics

Descriptive statistics (i.e. N, mean, SD, median, 25th percentile, 75th percentile, minimum, maximum (not included for Interim Analysis), the number of non-missing observations, and 95% confidence intervals), per treatment, for each population separately, will be provided for the primary endpoint.

Longitudinal plots (Mean +/- SE), by treatment of observed values vs time profile will be produced, for each population separately.

3.4.2 Statistical model, hypothesis and method of analysis

For Population I, a 95% confidence interval for the difference in the primary endpoint between each continued BYM338 dose arm vs. corresponding placebo switched from the same BYM dose will be calculated at Week 49. The CI of the difference will be calculated using a t-test comparing the values at Week 49 between BYM338 dose arms vs. corresponding placebo. Summary statistics will also be presented by treatment arm.

For Population II, the summary statistics will be presented by treatment assigned in the core study.

3.4.3 Handling of missing values/censoring/discontinuations

Summary statistics will be provided for observed data (no imputation in general, except special cases of the balance test described in section 1.3.2.2.2).

3.4.4 Supportive analysis

The same analysis will be performed on the PP analysis set ▮▮▮▮▮▮ in two ways:

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Proportions of patients being sarcopenic at Week 25 and Week 49 will be summarized by treatment, for population I and II separately. The criteria of being sarcopenic are from core study protocol inclusion criteria:

- Gait speed < 0.8 m/sec
- ASMI <= 7.26 kg/m^2 for men and <= 5.5 kg/m^2 for women, or for Asian countries <= 7.0 kg/m^2 for men and <= 5.4 kg/m^2 for women

3.5 Analysis of secondary ▮▮▮▮▮▮▮▮▮

The analyses described in this section will be based on FAS.

3.5.1 Variables

Secondary efficacy variables include:

- 6MWT at Week 49
- Gait speed at Week 49
- Total LBM and ASMI as measured by DXA at Week 49
- ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

[REDACTED]
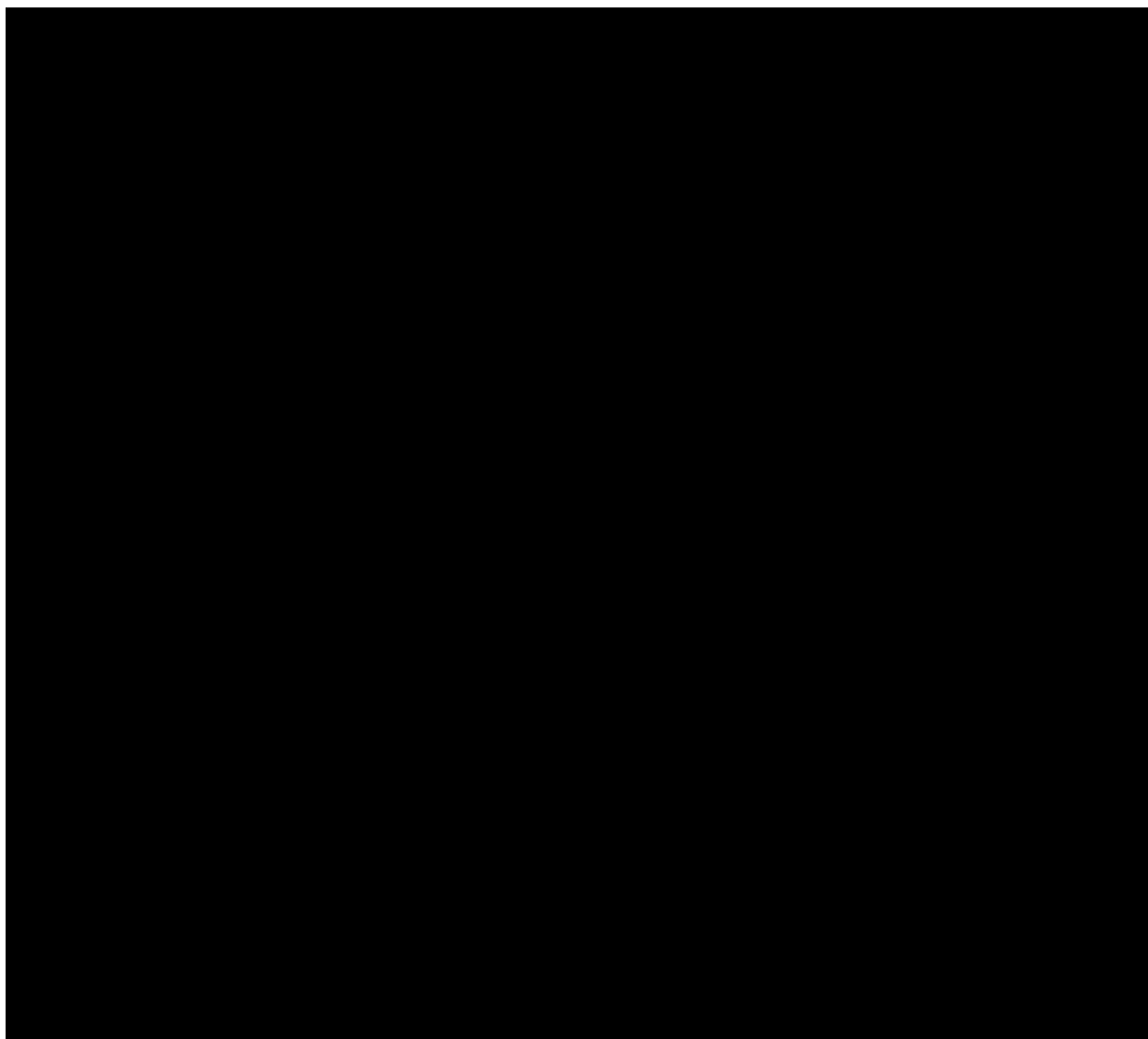
3.5.2   Descriptive statistics

Descriptive statistics (i.e. N, mean, SD, median, 25th percentile, 75th percentile, minimum and maximum (min/max not included for Interim Analysis), the number of non-missing observations, and 95% confidence interval), per treatment group and visit, will be provided for each continuous variable and each population separately.

Longitudinal plots (Mean +/- SE), by treatment of observed values vs time profile will be produced for each continuous variable and each population separately.

For Population II, [REDACTED] Lean body mass (LBM and ASMI) will be logarithmically

transformed before the analysis. The results of the analysis will be back-transformed from the log-scale before reporting.

3.5.3 Statistical model, hypothesis and method of analysis

3.5.3.1 6MWT, Gait speed, SPPB total score, total LBM and ASMI

For population I, the 95% confidence interval will be provided for the difference between each continued BYM dose arm and corresponding placebo (switched from the same BYM dose arm) at each visit. 95% confidence interval will also be provided for the difference between each continued BYM dose arm and the placebo arm continued from the core study at each visit.

The confidence interval at Week 49 for SPPB total score between each continued BYM dose arm and corresponding placebo (switched from the same BYM dose arm) for population I is provided as the primary analysis. For population II, the summary statistics at Week 49 are provided as the primary analysis.

For population II, SPPB total score, 6MWT, Gait speed, total LBM and ASMI at Week 49 will be explored at final analysis using an analysis of variance model (ANCOVA) with treatment assigned in the core study ▮▮▮▮▮▮▮ as fixed effects and Week 25 SPPB total score as covariate.

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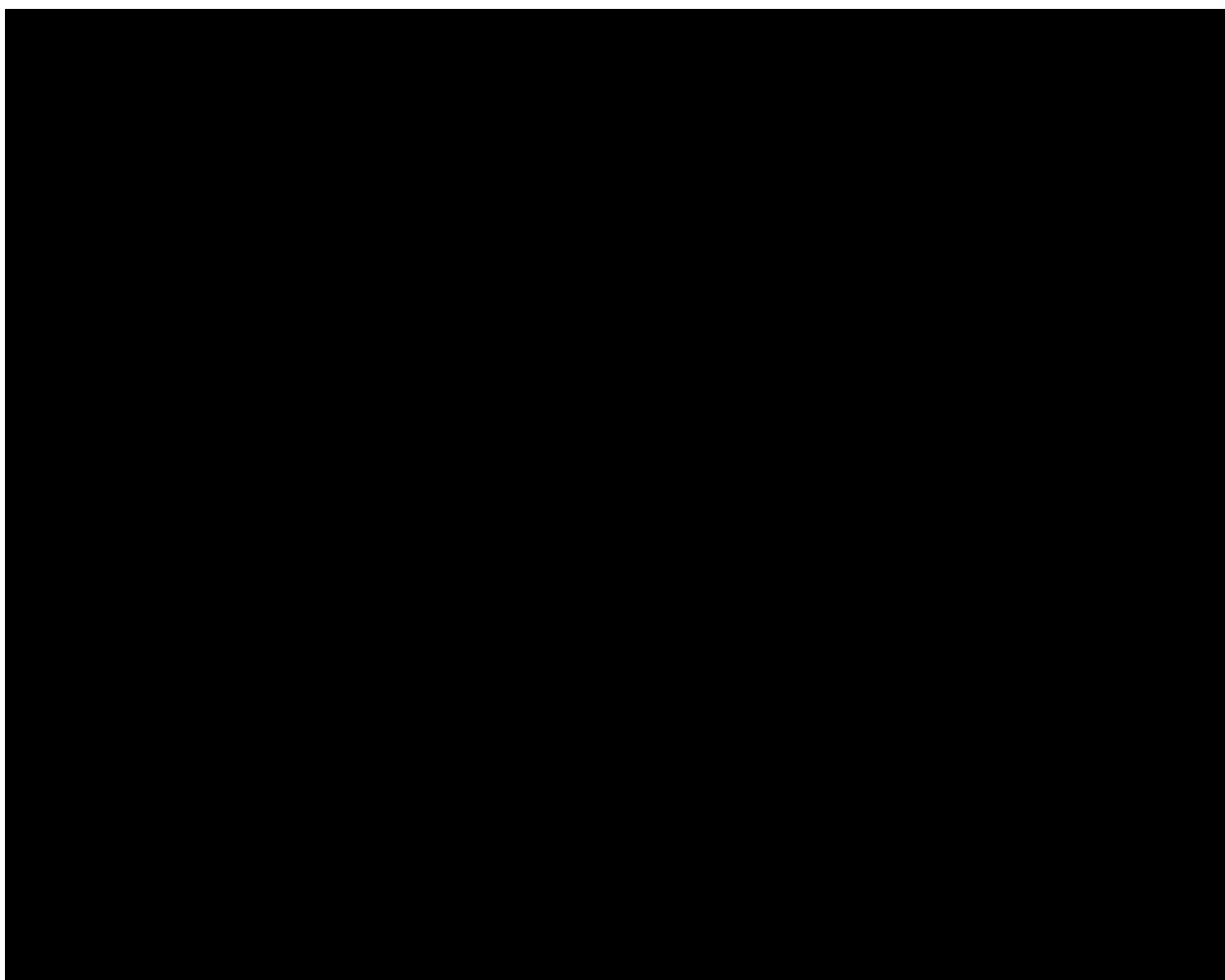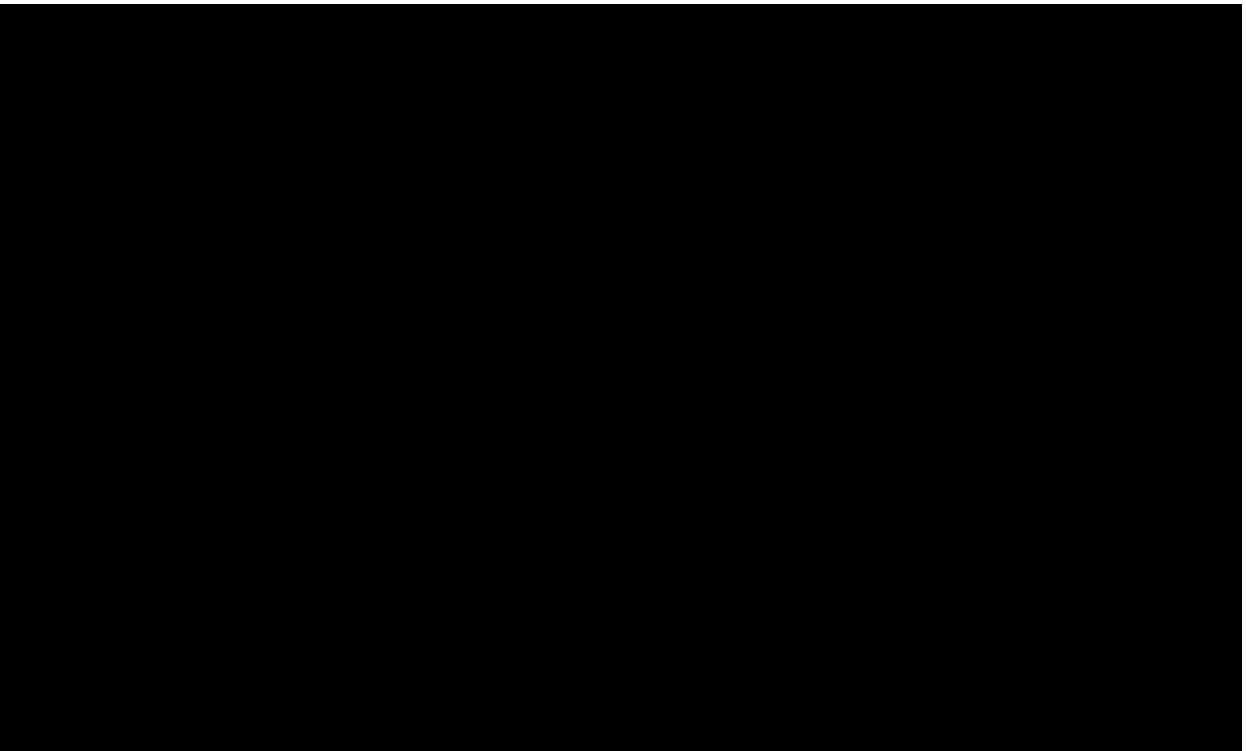
3.5.3.8   Exercise adherence

Below analysis applies to both population I and population II.

During the study, patients will be instructed to complete an Exercise Adherence e-diary. The diary will capture physical activity per defined categories in the diary. ████████████
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For each exercise category, summary statistics for the total time spent will be provided by treatment group (for population I, and treatment assigned in the core study for population II) and visit.

3.5.3.9   Other assessments

400 Meter Walk Test

400 meter walk test was removed upon protocol amendment 1. If any data captured prior to protocol amendment 1 are available in the database, those will be listed only, by treatment arm at the final analysis.

3.5.4 Supportive analysis

The same analysis defined above for the Gait speed, 6MWD, ██████████████, and total LBM will also be performed ███████ :

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3.6 Statistical methods for safety and tolerability data

Analyses in this section will be based on SAF.

For Population I, all summaries will be presented by treatment group in the extension study and overall. For Population II, all summaries will be presented by treatment assigned in the Core study and overall. ██████████████████████████████████████

Relevant raw and derived data as described in this section will also be presented in by-patient data listings. All by-patient data listings will be sorted by treatment group, ██████ center and patient if not indicated otherwise.

Descriptive statistics (mean, median, standard deviation, minimum and maximum) for safety variables will be presented for the SAF analysis set.

Where relevant, "overall" refers to the addition of a "Total" treatment column within the planned presentation of the data.

3.6.1.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, echocardiography, ██████████████, nutrition status and protein intake, as well as subject demographics, baseline characteristics, and treatment information.

3.6.1.2 Descriptive analyses

Vital signs

Vital signs include height (cm), weight (kg), BMI (kg/m2), temperature (oC), pulse (beats/min), mean systolic blood pressure (SBP) (mmHg) and mean diastolic blood pressure (DBP) (mmHg). Height will be measured only once at Screening, hence BMI will be calculated for each visit using the Screening value of height and with the actual body weight value measured at the scheduled visit. Mean sitting SPB/DBP will be calculated from the three assessments taken per visit and will be used for tabulation (as recorded in the Vital Signs eCRF).

Summary statistics (including mean, SD, median, minimum and maximum) will be provided by treatment and visit/time, for each population separately.

For population I, notable vital signs values will be considered "newly occurring" if they had not been present at Week 25 but present during the treatment epoch. If assessments cannot be made at Week 25 due to missing value(s), post-Week 25 values meeting the notable criterion will be considered as newly occurring. Similar definition applies for population II, post-treatment follow-up epoch. Notable vital signs are considered to be the following:

- Systolic blood pressure:
  - >150mmHG or increase from Week 25 of >=20 mmHg
  - <90mmHG or decrease from Week 25 of >=20 mmHg
- Diastolic blood pressure:
  - >90mmHG or increase from Week 25 of >=15 mmHg
  - <50mmHG or decrease from Week 25 of >=15 mmHg
- Pulse rate:
  - >100bpm or increase from Week 25 of >=15 bpm
  - <60bpm or decrease from Week 25 of >=15 bmp

Summaries of newly occurring notable values will be summarized by population and by epoch.

All vital signs data will be listed by population, treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged.

ECG evaluations

Summary statistics (including mean, SD, median, minimum and maximum) will be presented for ECG variables by visit and treatment group, for each population separately.

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Both Bazett (QTcB) and Fridericia (QTcF) corrections will be presented for QTc.

QTc will also be summarized by computing the number and percentage of subjects with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- PR > 250 msec
- QTc change from Week 25 > 30 msec
- QTc change from Week 25 > 60 msec

A listing of all newly occurring or worsening abnormalities by epoch will be provided for both populations, as well as a by-subject listing of all quantitative ECG parameters.

Clinical laboratory evaluations

All laboratory data will be listed by Population, treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics (including mean, SD, median, minimum and maximum) will be provided by treatment and visit/time for Hematology, Clinical chemistry and Coagulation testing, for each population separately. For urinalysis, frequency tables will be presented.

Summaries of newly occurring notable values will be similar to those of vital signs.

Notable values are values which are considered as:

- Low: Value below the lower limit of the normal range (LLN).
- High: Value above the upper limit of the normal range (ULN).

Liver ███████████ enzyme abnormalities

Newly occurring or worsening liver enzyme abnormalities will be summarized, for each population separately, using:

- Number of subjects with newly occurring notable liver ███████ enzyme abnormalities will be summarized similarly to those of vital signs. Notable criteria for the table:

    o ALT or AST > 3 x ULN

    o ALT or AST > 5 x ULN

    o ALT or AST > 8 x ULN

    o TBL > 1.5 x ULN

    o TBL > 3 x ULN

    o ALP > 2 x ULN

    o ALP > 5 x ULN

    o ALT or AST > 5 x ULN & TBL > 2 x ULN

    o ALP > 5 x ULN & TBL >2 x ULN

    o Hy's law

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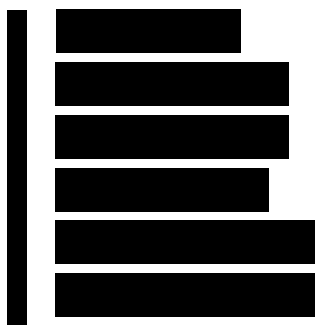
- Shift tables of LFTs/███████ enzymes presenting a cross-tabulation of Week 25 and worst post Week 25 values

- Change from Week 25 summary tables of LFTs/███████ enzymes by visit.

Adverse events

Summaries will be provided for:
- Adverse events by SOC and PT

- Adverse events by severity
- Treatment emergent adverse events (Population I only)
- Post-treatment adverse events (Population II only)
- Death
- ████████████████████████████████████
- Adverse events of special interest (AESI)

Summary by treatment group in this study will be provided for Populations I and II separately.

All by-patient data listings will be sorted by Population, treatment group, center and patient if not indicated otherwise.

Adverse events continuing from the core study but not worsening in severity during the extension, will also be entered in the extension study database. These adverse events, will be presented in the listings but not in the tables. Adverse events continuing from the core study, but worsening in severity during the extension, will be entered as new events in the database and will be included in both tables and figures.

In addition to summary tables, safety topics of interest such as: cardiovascular events spontaneous muscle contractions; diarrhea and diarrhea-like events defined in the Safety Profiling Plan (SPP) will be listed separately.

Adverse events by SOC and PT

The number (n) and percentage (%) of patients with adverse events will be summarized by primary SOC, PT and treatment group. Unless otherwise specified, primary system organ classes will be sorted by descending order of total frequency and within each primary system organ class, the preferred terms will be sorted by descending order of total frequency as well. In the event of SOCs and/or PTs with equal total frequencies, the relevant SOCs and/or PTs will be sorted alphabetically. A subject with multiple adverse events within a SOC or PT is only counted once towards the total of this SOC or PT.

Separate summaries will be provided by SOC and PT for:
- Adverse events
- Treatment emergent adverse events (Population I only)
- Post-treatment adverse events (Population II only)
- Serious adverse events
- Treatment emergent serious adverse events (Population I only)
- Post-treatment serious adverse events (Population II only)
- Other significant adverse events leading to discontinuation of study treatment
- And adverse events leading to dose interruption (including study treatment discontinuation) (Population I).

Adverse events by severity

The number (n) and percentage (%) of patients with adverse events will be summarized by severity, primary system organ class, PT and treatment group. If a patient reported more than

one adverse event with the same PT, the adverse event with the greatest (maximum) severity will be presented. If a patient reports more than one adverse event within the same primary system organ class, only one adverse event will be counted for that patient at the highest severity level in the total row for each primary system organ class. If adverse event "severity" is missing, this variable will be listed as missing and treated as missing in summaries.

Separate summaries will be provided for:
- Adverse events
- Treatment emergent adverse events (Population I only)
- Post-treatment adverse events (Population II only)

Treatment emergent adverse events
Adverse events will be deemed treatment-emergent if events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity, until 56 days after the last dose of study treatment. For Population II, the dose received at Core Week 21 visit is the scheduled last dose. For patient entering the extension study, their last visit in the core study is Week 25, which is the first visit in the extension study. Therefore, treatment emergent adverse events after Week 25 (Core EOT) are collected in the extension study. Such treatment emergent adverse events cannot be identified completely based on extension study database alone, therefore cannot be summarized with accuracy. .

Treatment emergent adverse events will be summarized for population I. Only primary paths within MedDRA (SOC) will be considered for adverse event reporting.

Post-treatment adverse events
Adverse events with date of onset or worsening after the date of last infusion of study drug + 56 days are considered as post-treatment adverse events.

Based on the extension study database alone, the post-treatment adverse events will not be identified accurately according to above definition. Also, to take into consideration that adverse events starting between Week 25 and Week 29 could potentially fall into the definition of treatment emergent adverse events, adverse events of population II will be summarized by time interval, with adverse events starting date in the interval of:

- Week 25 to Week 25 + 35 days
- Week 25 + 36 days onward

The summary will be done for Population II only.

Deaths

All the deaths in the clinical database will be listed.

Deaths may be summarized by primary reason for death (specification) and will be presented by primary system organ class, PT and treatment group, for each population separately. Contributing reason for deaths will be listed only.

Adverse events of special interest (AESI)

The number (n) and percentage (%) of patients with adverse events of special interest will be summarized by risk level PT (levels 1-7) and treatment group. For each risk level PT, exposure-adjusted incidence rate (IR), will be calculated as the number of patients experiencing at least one AE in each category relative to the total patient years of the "at risk"*100. The total patients years of the "at risk" is defined, as the the sum of time in years to first occurence of a particuliar AE or time in years to EOS visit for subject who did not encounter a particuliar AE. For Population I, for each treatment group, total exposure will be calculated as the sum of exposure (days) of all patients per treatment group, divided by 365.25 (years). The calculation formula, for the number of days of drug exposure can be found in Section 3.3.1.

Other safety evaluations

Echocardiography

Summary statistics will be presented by visit and treatment group for the following measurements:

- Left ventricular wall (posterior) and septal thickness
- Left ventricular mass and mass index
- End-diastolic volume
- End systolic volume
- Left ventricular ejection fraction
- Left ventricular diastolic diameter
- Left atrial size and volume
- Right ventricular wall thickness and function
- Interrogation of all valves for function, stenosis, regurgitation and morphology.

Summary statistics for echocardiography measurements at each scheduled visit as relevant, will be presented for each treatment group (see Section 2.1 [Precision and summary statistics]), for each population separately.

Notable echocardiography values are considered to be the following:
- LV posterior wall thickness:
    - change from baseline >50% (increase)
    - wall thickness at the end >15 mm
- Septal thickness:
    - change from baseline >50% (increase)
    - wall thickness at the end >15 mm
- Left ventricular ejection fraction:
    - relative decrease of >15% from baseline
    - absolute value of LVEF <45

For notable echocardiography values, baseline is defined as Week 25.

Summaries of newly occurring notable values will be summarized by population and by epoch, and notable values will be flagged.

All echocardiography results will be listed by Population, treatment, subject and visit/time.

Nutrition status/protein intake

Nutrition status/protein intake during the study will be similarly as described in 3.2.2.2.1.

3.6.1.3 Graphical presentation of results

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

3.8 Interim analyses

An interim analysis will be triggered by the analysis of the core study Part A. Data from primary and key secondary efficacy parameters will be summarized. The interim analysis will provide a preliminary evaluation of endpoints over approximately 12 months; and together with core study Part A data will support next step decision making. Analyses based on PP set will not be included for IA.

The interim analysis will cover following analyses:

- Patient disposition

- Analysis sets

- Demographics and patient characteristics at Week 25 (nutritional status, protein intake, 6MWT, SPPB total score, Gait Speed, ███, and ASMI)

- Treatments (Study drug for population I, prior and concomitant medication for both populations)

- Primary analysis: SPPB at Week 49, summaries of population I and II separately

- Secondary analyses: 6MWT, Gait speed, LBM and ASMI, summaries for population I and II separately

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- Safety analyses:

  o Nutrition status/protein intake

  o Population I: TEAE, ECG, Vital sign, and notable Lab

  o Population II: notable Lab.

- Supportive analysis:

  o Proportion of sarcopenic patients at Week 25 vs Week 49.

██
██ Such analysis
will be detailed in a separate document when it becomes necessary and/or be generated for the
final analysis.

3.8.1   Interim Analysis FIR

Among the outputs planned to be released for the IA, key statistical outputs listed below will
be released in priority:

- Summary of patients disposition by treatment

- Summary of patients under each analysis set by treatment

- Summary of demographic characteristics by treatment

- Summary of patient characteristics at Week 25 (6MWT, SPPB total score, Gait Speed, ████, and ASMI) by treatment.

- Analysis of primary endpoint: SPPB at Week 49 for both populations.

- In addition to primary endpoint, statistical summary from Week 25 to Week 49 performance along with figures of time course and/or change from Week 25 will be provided for following endpoints (secondary endpoints) for both populations:

  o 6 minute walk test (6MWT)

  o SPPB total score

  o Gait Speed (GS)

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3.9   Sample size calculation

All the subjects from the core (E2202), if eligible, can enter this extension study after they
complete informed consent. The study is not powered for hypothesis testing.

With 40 to 50 patients per each bimagrumab dose arm, assuming a standard deviation of SPPB of 1.5, 2.0, 2.5, and 3.0, the half-width of 95% confidence interval for SPPB is presented below in **Error! Reference source not found.**.

Table 3-1: Half-width of 95% confidence interval of SPPB

	SD=1.5	SD=2.0	SD=2.5	SD=3.0
50 patients per arm	0.42	0.55	0.69	0.83
40 patients per arm	0.46	0.62	0.77	0.93

4   Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Clinbay according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

5   Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

5.1   Introduction

This appendix details the statistical methods in addition to the report text. All analyses will be performed by using SAS® Version 9.3 or higher.

5.2   Precision and summary statistics

If not otherwise specified, default summary statistics for quantitative variables for all analyses ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ will include:

- The number of patients in each category (n).
- Mean
- Standard deviation (SD)
- Minimum
- Median
- Maximum

For the Interim Analysis, to avoid patient level unblinding, minimum and maximum will not be included in the summary statistics for all except Safety summaries.

Summary statistics for all qualitative variables will be presented in contingency tables and will include number (n) and percentage (%) of patients. Percentages will be presented to one decimal place. The number of missing assessments will be displayed as part of a "missing" category, where appropriate.

Where Confidence Intervals will be presented alongside the summary statistics, these will originate from a one-sample t-test.

Data will be aligned within tables by the decimal point.

All values will be rounded using the SAS® function ROUND. If the original data has N decimal places (as derived from the raw data) (i.e. decimal precision [N]), then the summary statistics will contain the following decimal places (with a maximum of 3 decimals):

- The minimum, maximum: N.
- The mean and median: N + 1.
- The SD and standard error (SE): N + 2.

For application of inferential statistics, the least squares (LS) means and corresponding confidence intervals (CIs) will be reported with one extra decimal relative to the individual raw data. The odds ratios and corresponding CIs will be reported with two decimal places where relevant.

The p-values will be reported as follows:

- < 0.0001 will be presented as "<0.0001" (i.e. 0.00009 will be presented as "<0.0001").
- ≥ 0.0001 will be rounded to four decimal places.

Note: Rounding will be applied after the "<0.0001" rule.

All significant p-values (i.e. < 0.05) will be flagged by means of an "*" for ease of review.

5.3   Study Day 1 and other study days

The date of first infusion of study drug at the extension study for population I, and the date of the first follow-up visit for population II is defined as Study Day 1. All other study days will be labeled relative to Day 1.

For event dates on or after Day 1, study day for an event date is calculated as: (event date – first infusion/follow-up visit date at extension study) +1, which could be Day 1, Day 2, Day 3, etc.

For event dates before Day 1, study day for an event date is calculated as: (event date – first infusion/follow-up visit date at extension study), which could be Day -1, Day -2, etc., referring to 1 day, 2 days, etc., before Day 1, respectively, subsequently Day 0 is not defined.

5.4 Definition of Baseline and post-baseline measurements

Baseline is defined as the core study baseline, for both populations. In the planned analyses, Week 25 has been referred to majority of the time, and it is referring to a relative baseline to the extension study, which is defined as the Visit 1 pre-dose assessments of the extension study (Week 25, EOT visit of the core study) for population I and for population II defined as the Visit 1 assessments of the extension study (Week 25, EOT visit of the core). This visit will be labeled as Week 25 in the reports.

5.5 Analysis visits

5.5.1 Visit naming

Table 1   Visit schedule for both populations

Visit No.	Visit	Target Visit Day	Start day of visit window	Mid-point	End day of visit window
1	Week 25	1	-	1	15
2	Week 29	29	16	29	43
3	Week 33	57	44	57	71
4	Week 37	85	72	85	99
5	Week 41	113	100	113	127
6	Week 45	141	128	141	155
7	Week 49 (EOT)*	169	156	169	183
8	Week 53 (EOS)*	197	184	197	End of study

For population II, Week 49 (EOS) and no Week 53.

Multiple assessments within visits

For visit multiple records may exist in one particular visit for a particular assessment (e.g. laboratory assessments). The following rules (unless otherwise specified) will be applied to obtain one value per patient per assessment per visit which will be used in the assessment by-visit summaries.

- the closest to the actual target visit day is chosen for both continuous variables and categorical variables based on continuous variables (if two assessments have the same distance, then the earlier one by assessment date or visit date will be chosen);
- For qualitative variables (i.e., laboratory abnormalities or most extreme values analysis), the worst/most extreme (high & low) record will be used.

5.6   Handling of missing values/censoring/discontinuations

In general, unless otherwise indicated, no data imputation will be done for the missing values.

5.7   Imputation of missing and incomplete dates

Adverse event and concomitant medication dates will be imputed per the Novartis standard tables, listings and figures (TLFs) conventions as detailed in the RAP Module 8 (Programming Specifications). All missing or incomplete dates shall however be listed in by patient data listings as recorded in the eCRF.

5.8   Statistical methodology and assumptions

5.8.1   Two sample t-test

For Population I, the two-sample t-test will be used in order to obtain 95% confidence intervals for the difference between:

- each continued BYM338 dose arm vs. corresponding placebo, and
- Each continued BYM338 dose arm vs. continued placebo arm,

for the following endpoints:

- Week 25 to 49 on the 6MWT
- Week 25 to 49 on the SPPB
- Week 25 to 49 on the Gait speed
- Week 25 to 49 in log transformed values on LBM and ASMI

The t-test will assume Equal variances when the null hypothesis of variance equality cannot be rejected, and Unequal variances when the variance equality hypothesis is rejected.

5.8.2   ANCOVA

For Population II, ANCOVA model is used to explore the durability of BYM338 on the following endpoints:

- Week 49 on the SPPB
- Week 49 on the 6MWT
- Week 49 on the Gait speed
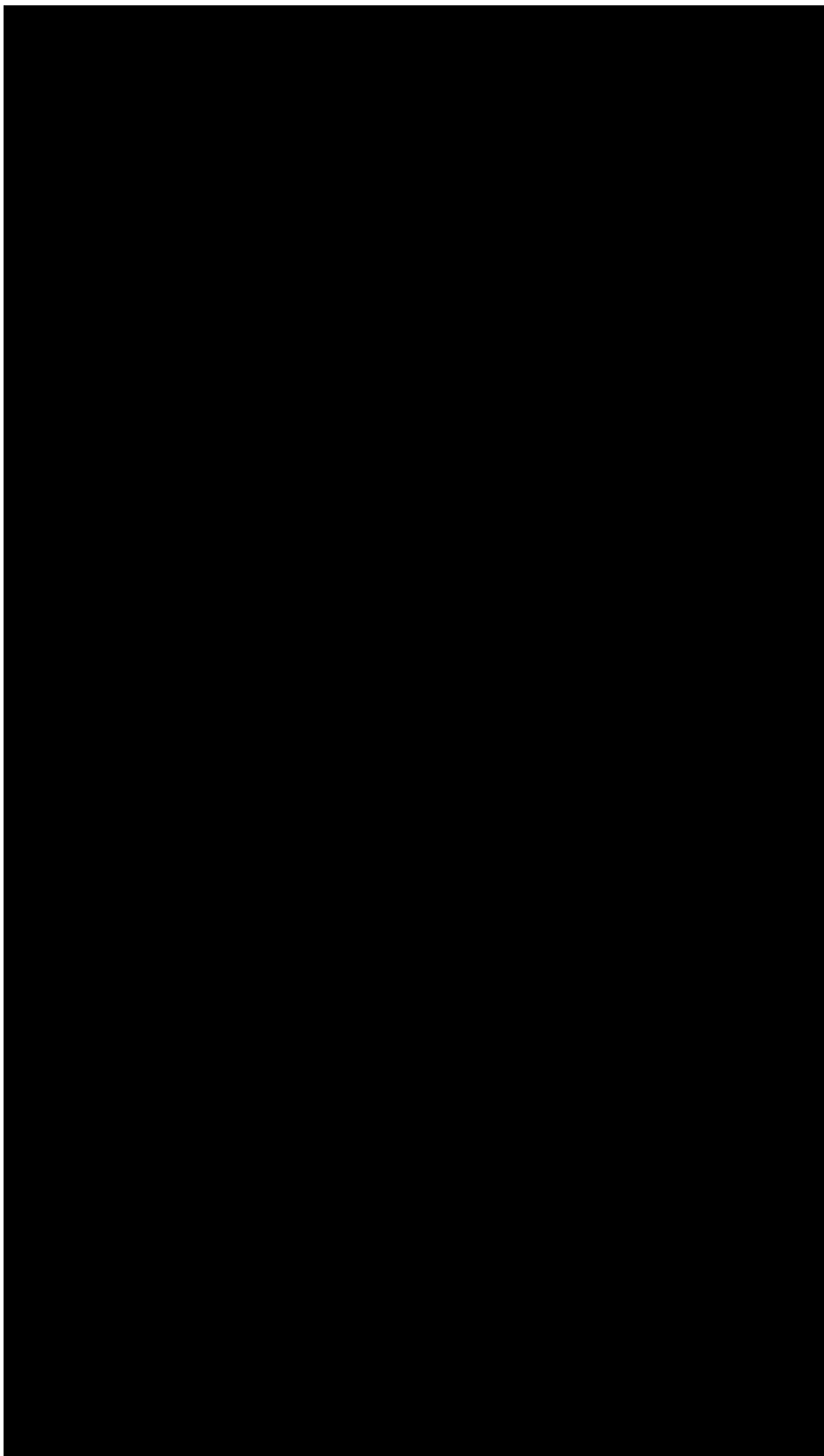- Week 49 in log transformed values on LBM and ASMI

The endpoint value at extension baseline as a covariate, treatment arm (as assigned in the core study for population II)   will be included as fixed effects. The 95% confidence intervals for the difference between arms receiving BYM338 and Placebo during the core study will be estimated.
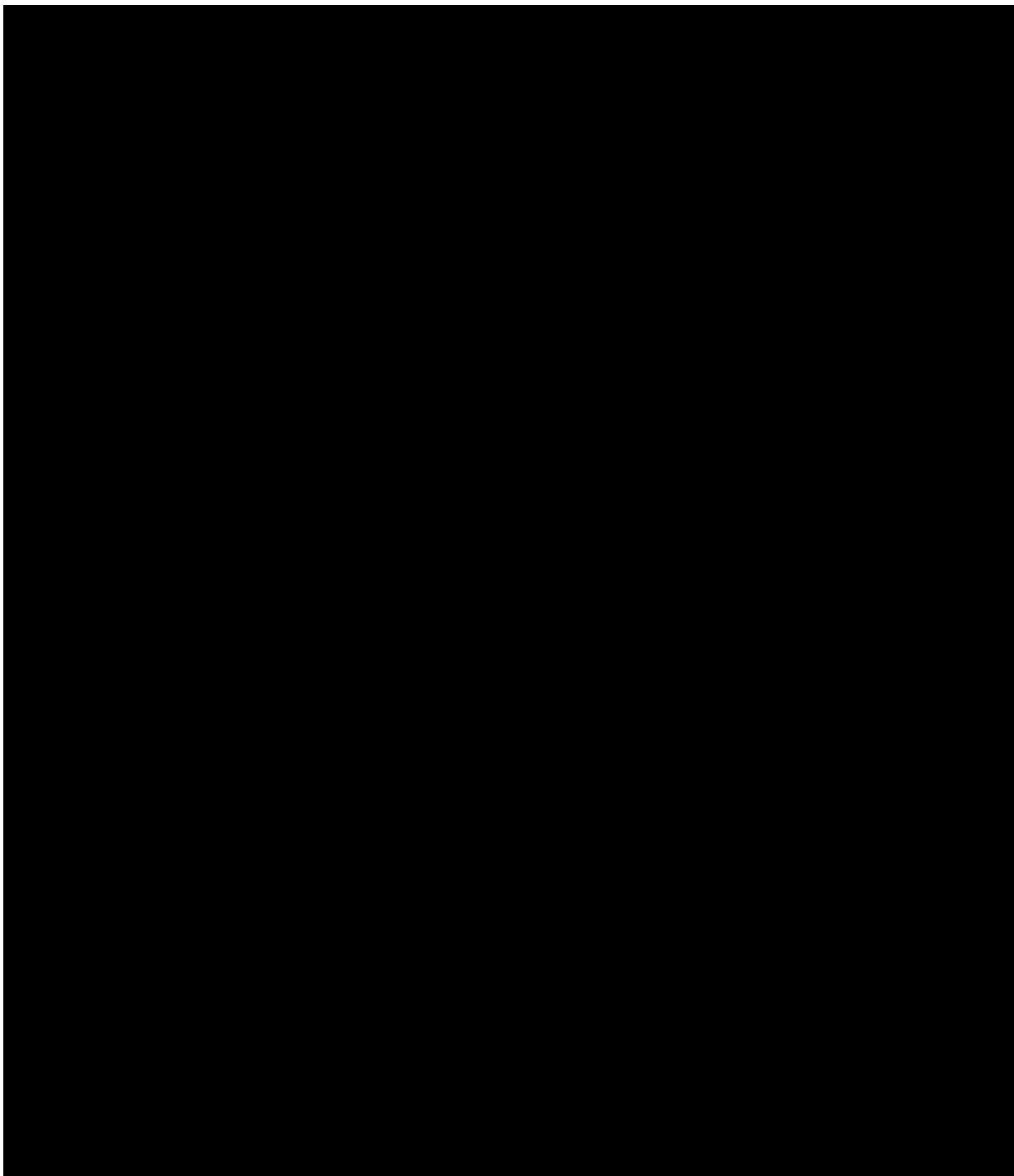
6   Appendix

6.1   Protocol deviations

Exceptions to the following inclusion/exclusion are considered as major protocol deviations. The list with corresponding actions to remove subjects from certain analysis set will be defined prior to unblinding.

Inclusion/Exclusion Criteria Number Inclusion	**Exclusion Criteria Text**
Inclusion 1	Men and postmenopausal women aged 70 years or older that have participated in, and have completed the full study treatment period per protocol (24 weeks/EOT visit) in the preceding core study (CBYM338E2202);
Inclusion 2	Written informed consent must be obtained before any assessment of the extension study is performed (can be obtained at the EOT visit of the core study).
Exclusion 1	Use of prohibited treatments as per recommendations in Protocol Table 5-1;
Exclusion 2	History of severe hypersensitivity reaction in the core study;
Exclusion 3	History of breaking the blind (inadvertently or for emergency reasons) in the core study;
Exclusion 4	History of adverse event(s) in the core study that in the judgement of the investigator, taking into account the subject's overall status, prevent the subject from entering the extension study);
Exclusion 5	Clinically significant abnormal liver function tests that would have resulted in discontinuation of study drug while participating in the core study as per protocol (as outlined in Protocol Appendix 1) such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin (except Gilbert's Disease);
Exclusion 6	Patient has any medical condition or laboratory finding (e.g., an unexplained or clinically significant lab result), which, in the opinion of the investigator taking into consideration the subject's overall status, prevents the subject from continuing participation in the study, may interfere with participation in the study, might confound the results of the study, or pose an additional safety risk to the subject in administering bimagrumab;
Exclusion 7	Concurrent enrollment in a clinical trial involving an investigational drug or off-label use of a drug, or any other type of medical research judged to be scientifically or medically incompatible with this study (not including enrollment in BUM338E2202 core study).

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients, within and across study sites.

7   References

References are available upon request.