

Clinical Development

BYM338/Bimagrumab

CBYM338E2202 / NCT02333331

A 28 week, randomized, double-blind, placebo-controlled, two-part, multi-center, parallel group dose range finding study to assess the effect of monthly doses of bimagrumab 70, 210, and 700 mg on skeletal muscle strength and function in older adults with sarcopenia (InvestiGAIT)

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1 Introduction to SAP documentation

1.1 Scope

The SAP document contains detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “**CBYM338E2202**”.

SAP provides the description of the statistical methodology used to analyze the data, **TFL (Table figure and listing)** details the presentation of the data, including shells of summary tables, figures and listings, and **PDS (Programming data specification)** contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Changes to SAP documentation

Refer to corresponding guidance and Early Development Biostatistics (EDB) SAP Addendum template for detailed information on the requirements of documenting changes to SAP documentation.

For the statistical methodology (SAP), any major changes occurring before database lock to the statistical methodology should be reflected in the SAP documentation via version control (new document version to be approved by the trial team as the original module).

Major changes include, but are not limited to, changes in protocol that affect study design and statistical methodology.

Minor changes to the SAP documentation can be captured e.g. by a study note to file / note in SAP Addendum or within the CSR itself. Minor changes include, but are not limited to, change in statistical model. Corrections of typographical errors or modification of spelling (from English to American, for example) do not need to be incorporated into the SAP documentation.

Amendment 2 (October 2017)

Amendment rationale

The purpose of this amendment is to align with study design and endpoints as indicated in protocol V02 (September 2016) and protocol V03 (October 2017).

Key changes in protocol V02:

Two key changes in this amendment:

- a. The short physical performance battery (SPPB) replaced 6 minute walk test (6MWT) as primary outcome; 6MWT became secondary endpoint. This change was based on a combination of factors identified in medical literature and discussions with health authorities.
- b. The original plan was a four arm parallel design. This was modified to a two part design to reduce the exposure to experimental therapy until data are obtained to demonstrate sufficient risk benefit information. Part A was updated to a parallel two arm design with placebo and bimagrumab (BYM338) 700 mg; recruitment to intermediate bimagrumab doses of 70 mg and 210 mg were stopped. Based on Part A data, a decision will be taken

whether to continue to Part B, which will be a parallel four arm design with three active doses (70, 210, 700 mg) and placebo.

Intensive safety monitoring was reduced based on published data from other BYM338 studies and a decision by the independent data monitoring committee (DMC) to a frequency aligned standard medical care.

Key changes to protocol V03:

The primary purpose of this amendment was to present a new safety observation and the resultant modification to the protocol. Also, sample size for Part A was readjusted to ensure sufficient information for decision making.

A new set of assessments has been added around 2 weeks post first study drug administration, and at the second and third dose to generate more data

Table 1-1 Key changes in assessment schedule in protocol amendments (V02-V03)

End Point	Amendment Version	Visits Added	Visits Removed	Other Details
Echocardiography	V02		All	Performed only at EOT for patients in V01 with baseline data
FSH, LH, SHBG	V02		All	[REDACTED]
[REDACTED]	V02		All*	
[REDACTED]	V02		All	
[REDACTED]	V02		All	
[REDACTED]	V02		All	
Coagulation parameters	V02		All	
Physical Examination	V02		102, 103, 105 and 106	
Height			EOS	
Body temperature, blood pressure, pulse rate	V02		101	
Electrocardiogram	V02		101, 102, 103, 105, 106 and EOS	
Hematology	V02	104	101, 103, 105 and 106	
Clinical Chemistry	V02	104	101, 103, 105 and 106	

End Point	Amendment Version	Visits Added	Visits Removed	Other Details
Clinical Chemistry	V03	1015, 102, 103		
Testosterone	V02		All except visit 1	
Urinalysis	V02		All except visit 1	
Cardiac panel	V02		101, 102, 103	
Vitamin D	V02	104	103, 105 and EOS	
6MWT, [REDACTED]	V02		102, 103, 105, 106 and EOS	
SPPB	V02		102, 105 and EOS	
[REDACTED]				
[REDACTED]				
[REDACTED]				
Diet assessment	V02		102, 103, 104, 105, 106**	

** Diet assessments may still be measured in case there is a significant change in weight

2 Study objectives and design

2.1 Study objectives

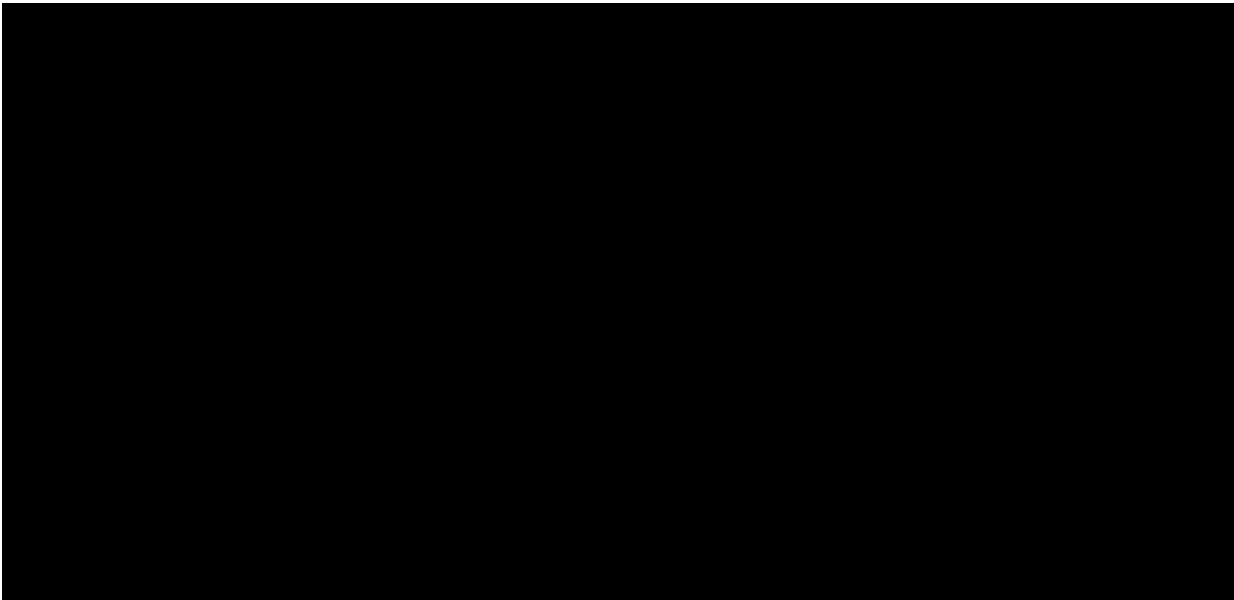
2.1.1 Primary objective

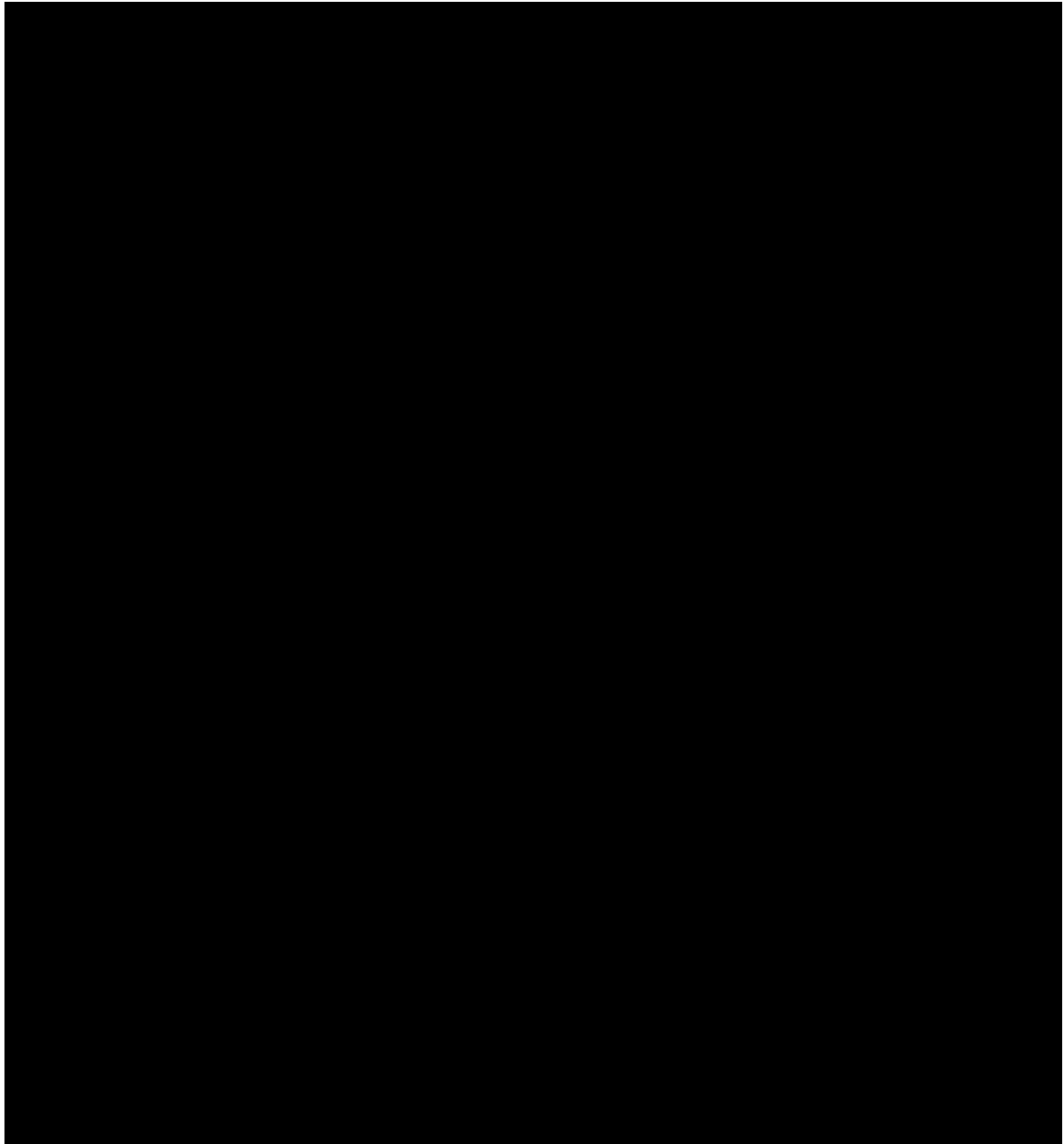
The primary objective is to assess the effect of 24-weeks of bimagrumab treatment on patient physical function assessed by a change in the Short Physical Performance Battery (SPPB) total score from baseline to week 25 relative to placebo in older adults with sarcopenia.

2.1.2 Secondary objective(s)

Secondary objectives are as follows:

- To assess the effect of bimagrumab compared to placebo on the safety and tolerability of multiple doses of bimagrumab administered over 24 weeks as assessed by measures such as vital signs, clinical laboratory variables, electrocardiogram (ECG), echocardiogram (in a limited number of patients), and adverse events (AE) in older adults with sarcopenia.
- To assess the effect of bimagrumab compared to placebo on improvement in physical performance as measured by change from baseline to week 25 in the 6 minute walk test (6MWT) distance in older adults with sarcopenia.
- To assess the effect of bimagrumab compared to placebo on improvement in mobility as measured by change from baseline to week 25 in usual gait speed (GS; measured as a component of the SPPB) over 4 meters in older adults with sarcopenia.
- To assess the effect of bimagrumab on total lean body mass and appendicular skeletal muscle index (ASMI) measured by DXA, as assessed by change from baseline to week 25 compared to placebo in older adults with sarcopenia.





2.2 Study design and treatment

This Phase II-b study is a two-part randomized, double-blind, placebo-controlled, study design with approximately 339 older adults with sarcopenia assigned to one of four treatment groups: placebo, bimagrumab 70mg, bimagrumab 210mg, or bimagrumab 700mg.

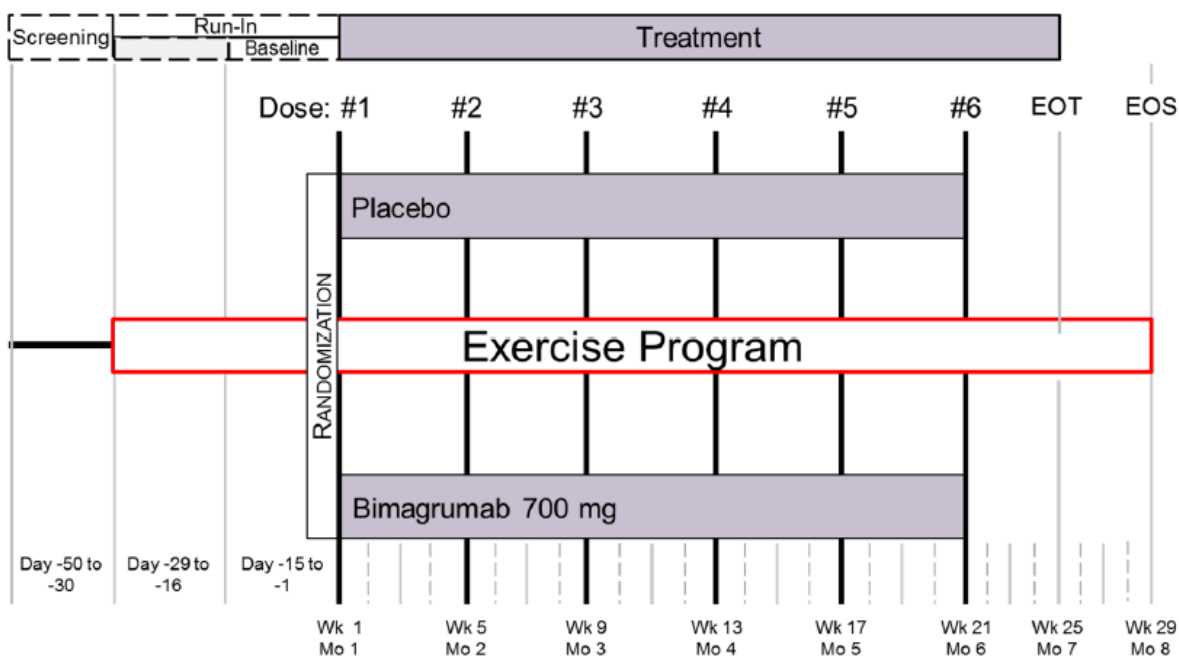
The study will consist of a 20-day screening period followed by a 28-day run-in period, and a 24 week treatment period followed by a 4 week follow-up period. During the run-in period, all patients will be introduced to a 3 times per week exercise program, daily vitamin D and oral nutritional supplementation (ONS), and the performance-based endpoints. Towards the end of the run-in period, patients will be re-assessed for eligibility (utilizing the baseline eligibility criteria) and qualified patients will enter the treatment phase to receive six monthly doses of

assigned study drug. Patients randomized prior to implementation of protocol amendment v02 will remain on their assigned treatment, but will be switched to the new assessment schedule at their next scheduled visit. It is estimated that approximately 18 patients will have been randomized into each of the four treatment groups at the initiation of this amendment (N= approx.72 through protocol amendment v01).

2.2.1 Part A

Patients will be enrolled and randomized to receive either bimagrumab 700 mg or placebo (see Figure 2-1), until approximately 100 patients will have been enrolled in the bimagrumab 700 mg arm and 60 patients in the placebo arm. At this point, recruitment into the study will be paused until Part A is completed and an interim analysis conducted.

Figure 2-1 Study design: Part A

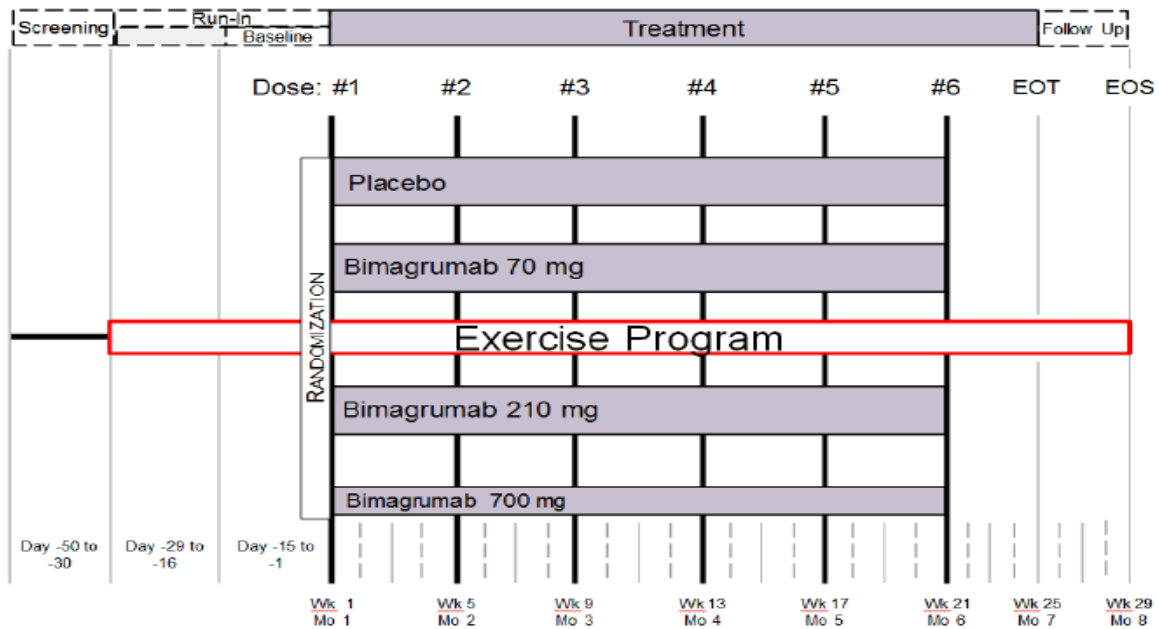


2.2.2 Part B

Part B will be performed based on Part A outcomes.

New patients will be enrolled and randomized to receive either placebo, bimagrumab 70 mg or bimagrumab 210 mg (see Figure 2-2), until approximately 70 patients have been randomized into each arm. An additional 13 patients will be recruited into the 700 mg arm and additional 26 patients into the placebo arm to allow effective randomization and bridging between Parts A and B. This will complete enrollment of approximately 339 patients into the study. Following the last patient visit in Part B, the study will end and the final analysis will take place to address the study objectives.

Figure 2-2



Exercise program

During screening, the ability of patients to perform the exercise program will be determined by a trained study staff member, to ensure patients have the ability to perform the required physical tasks.



Drug treatment assignment

In initial versions of the protocol (V00-V01) eligible patients (~72) were randomized in a 1:1:1:1 ratio to receive i.v. doses of placebo or 70, 210, or 700 mg bimagrumab every 4 weeks until Week 21 for a total of 6 doses.

In protocol V02-V03, Part A: At the conclusion of the baseline period (Visit 5), newly recruited eligible patients will be randomized in a 2:1 ratio to receive i.v. doses of bimagrumab 700mg or placebo every 4 weeks until Week 21 for a total of 6 doses.

Part B: At the conclusion of the baseline period (Visit 5), eligible patients will be randomized in a 4:4:2:1 ratio to receive i.v. doses of bimagrumab 70mg, bimagrumab 210mg, bimagrumab 700mg, or placebo every 4 weeks until Week 21 for a total of 6 doses.

3 First interpretable results (FIR)

3.1 Interim FIR

Interim first interpretable results (FIR) will be provided for this trial.

The study FIR template can be found in CREDI in the study RAP folder

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be marked as “Key” in the M9.1 Tracking sheet output list.

Primary FIR will contain only overall summary; no subgroup analysis is needed.

- Summary of patients disposition by treatment
- Summary of patients under each analysis set by treatment
- Summary of population demographics (age, sex, race – Caucasian, Black, Asian) by treatment
- Summary of baseline characteristics (weight, height, BMI, ASMI, SPPB total score, gait speed, 6MWT, [REDACTED]) by treatment.
- Analysis of treatment-emergent adverse events (AE)
 - Summary of treatment emergent AEs by system organ class (SOC) and preferred term (PT) by treatment.
 - Overview of adverse events
- Analysis of primary endpoint: Statistical analysis of SPPB change from baseline at week 25 by treatment to evaluate the dual criteria as mentioned in [section 10.1.3.1](#).
- Supportive analysis of primary endpoint : Statistical analysis of SPPB change from baseline using MMRM model as described in [section 10.1.3.3](#) Arithmetic mean (SE) time profile: SPPB Total score, gait speed and 6MWT
- In addition to the primary endpoint, analyses of the change over time (baseline to Week 25) by treatment of the following endpoints will be included:
 - 6 minute walk test (6MWT)
 - Gait Speed (GS)
 - [REDACTED]
 - Appendicular skeletal muscle index
 - [REDACTED]

Contents for extended FIR:

- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]

4 Interim analyses

[REDACTED]

Primary analysis: To support the primary objective, the change in the Short Physical Performance Battery (SPPB) total score from baseline to week 25 will be compared between treatment groups.

Timing of interim analysis: An interim analysis is planned to evaluate the efficacy and safety of multiple doses of bimagrumab in patients with sarcopenia. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Based on the planned use of Part A data for decision making, additional endpoints of safety (e.g., AEs, lab values, ECG), [REDACTED] background treatments (e.g., exercise, Vitamin D, diet), and efficacy (e.g., gait speed, 6MWT, [REDACTED], [REDACTED], LBM and ASMI by DXA, [REDACTED]) may be included in the interim analysis.

Outputs for interim analysis FIR document are discussed under section 3.

5 Subgroups

Subgroup 1:

Country Specific

- Japan
- Non-Japan

Subgroup 2:

Geographical:

- Asian countries (Patients from study sites in Japan, Taiwan and South Korea).
- Non-Asian countries (Patients from study sites not in Japan, Taiwan and South Korea).

All of the summary reports for subgroup analysis will be summarized in three groups: Japan/ non-Japan, Asia/ non-Asia and overall.

6 Protocol deviations

The major protocol deviations observed during study will be discussed with core clinical trial team (CTT) and will be summarized before IA lock.

Table 6-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all analysis in case of these PDs:		
		Exclude subject completely from all analysis sets
No additional PD here		
Subjects are excluded from full analysis set in case of these PDs:		
		Exclude subject from full analysis set
No additional PD here		
Subjects are excluded from per protocol analysis set in case of these PDs:		
EXCL37	Subject is using therapies known to affect muscle mass, including androgens, androgen supplements.	Yes
COMD01	Subject took a prohibited medication while in the trial, however was not discontinued from the trial.	Yes
INCL04	"Time for 4 meters" should be greater or equal to 5 sec (which equates 0.8 m/sec) but less than 13.3 sec (which equates to 0.3 m/sec).	Yes

[REDACTED]

[REDACTED]

No additional PD here

After database lock and unblinding, the treatment allocation will be checked against the study drug actually received.

7 Statistical methods: Analysis sets

Assignment of patients to the different analysis sets [REDACTED] will be performed prior to the unblinding of the treatment code and start of the final data analysis.

The following analysis sets are defined for final analysis purposes:

Randomized analysis set: All randomized patients, regardless of whether the patient received study drug. Subjects will be analyzed according to treatment assigned at randomization.

Safety (SAF) analysis set: The SAF analysis set will consist of all patients who received at least one infusion of study drug. Patients will be analyzed according to the treatment actually received. If a patient received only part of the infusion (i.e. study drug infusion permanently discontinued), the patient will be regarded as having received study drug infusion and will be included in the SAF analysis set.

Full analysis set (FAS):

The full analysis set (FAS) comprises all subjects to whom study treatment has been assigned. Following the intent to treat principle, subjects will be analyzed according to treatment assigned at randomization. Patients who are randomized erroneously in IRT system and did not receive any treatment will be excluded. FAS is key analysis set to be used for most of the efficacy endpoints.

Per Protocol (PP) analysis set: The PP analysis set will include all FAS patients who complete the study without major deviations from the protocol procedures. Major protocol deviations and the definition of the PP analysis set will be identified and finalized based on blinded review of the data, prior to the final database lock. Patients will be analyzed according to the treatment they were assigned to at randomization. The following are common examples of such deviations:

- Subject entered the study even though they did not satisfy the entry criteria (INCL04)
- Subject developed study/treatment withdrawal criteria during the study but was not withdrawn (EXCL37)
- Subject took a prohibited concomitant medication (COMD01)
- Subjects with SPPB baseline score (Baseline visit 2) should be less or equal to 9

Per protocol set will be identified and finalized based on blinded review of data, prior data base lock.

For definitions of major protocol deviations see Section 6 (Protocol deviations).

[REDACTED]

7.1 Recommended visit windows:

Patients should be seen for all visits on the designated day within the recommended ‘visit window’ specified below, or as close to it as possible. If any visits are delayed or missed, the site personnel should ensure alignment of future visits according to the originally planned visit schedule:

- Randomization / Day 1: + 2 days
- Weeks 3: +/- 2 days
- Weeks 5-13: +/- 4 days
- Weeks 17-29: +/- 7 days

7.2 Patient disposition, background and demographic characteristics

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 treatment group, region, center and patient if not indicated otherwise.

Where relevant, “across all treatment groups” refers to the addition of a “Total” column within the planned presentation of the data. Similarly “overall” refers to overall levels of stratification of the relevant subgroup.

7.2.1 Patient disposition

All randomized patients will be summarized using number (n) and percentage (%) overall and by subgroups (refer to [Section 5](#)) for each treatment group and across all treatment groups combined. Furthermore, for each study epoch (screening and treatment) 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.

The number (n) and percentage (%) of randomized patients with protocol deviations will be summarized by category and deviation, overall and by subgroups (refer to [Section 5](#)), for each treatment group and across all treatment groups combined. Patients with protocol deviations will be listed.

The number (n) and percentage (%) of randomized patients included in each analysis set will be summarized. Reasons for exclusions from analysis sets will be tabulated overall for all patients and by subgroups for each treatment group and across all treatment groups combined. 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.

7.2.2 Patient demographics and other baseline characteristics

Descriptive statistics for demographics, baseline characteristics and disease history will be presented to describe the FAS. All summaries will be presented overall and subgroups (refer to [Section 5](#)) for each treatment group and across all treatment groups combined. Unless otherwise specified, percentages will be based on the number of patients in the FAS with data available.

7.2.2.1 Demographics

Demographic variables collected at screening include age in years (as recorded in the Demography eCRF), sex, race and ethnicity.

(see Section 5 [Subgroups])

7.2.2.2 Patient baseline characteristics

Unless otherwise stated, baseline is defined as the last available assessment performed prior to the start of the first infusion (except screening assessments) of study drug. All relevant pretreatment assessments, including baseline value will be summarized overall and subgroups (refer to [section 5](#)) using default descriptive statistics. Baseline characteristics will include physical descriptors of body size: height (cm), weight (kg), body mass index (BMI) (kg/m²) and ASMI; and functional measurements: 6MWT, SPPB total score, gait speed, [REDACTED].

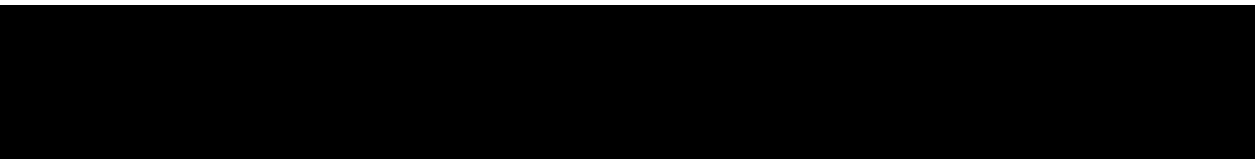
Disease history

Medical history

Relevant medical history/current medical conditions will be presented by number (n) and percentage (%) of all patients assigned to FAS according to the latest available Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT), regardless of whether the status is reported as ongoing or not ongoing. 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 SOC's and/or PT's with equal total frequencies, the relevant SOC's and/or PT's will be sorted alphabetically. The number (n) and percentage (%) of patients having at least one medical history/current medical condition, and having at least one medical history/current medical condition in each primary SOC, and for each PT will be presented. Hence if a patient reported more than one medical history/current medical condition with the same PT, the medical history/current medical condition will be counted only once. If a patient reported more than one medical history/current medical condition within the same primary SOC, the patient will be counted only once at the system organ class level.

Cardiovascular co-morbidities

Occurrence (yes/no/unknown) of cardiovascular diseases as pre-specified in the Cardiovascular History eCRF will be presented by number (n) and percentage (%) of all patients assigned to FAS. The disease status (ongoing/not ongoing/not applicable) will be listed.



Nutritional status

Nutritional status 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).

7.3 Efficacy/ Pharmacodynamic assessments

Total LBM, ASMI

Dual energy X-ray absorptiometry (DXA) will be used to assess changes in total lean body mass (LBM) and appendicular skeletal muscle index (ASMI). DXA instruments use an x-ray source that generates and is split into two energies to measure bone mineral mass and non-bone/non-fat mass generalized as fat-free mass (LBM). LBM of the arms and legs when collectively presented and normalized for the person's height is identified as appendicular skeletal muscle index (ASMI) and soft tissue from which fat mass (total body fat) and fat-free mass are estimated.

Baseline data (all relevant pre-treatment assessments, including Baseline value) of total LBM, ASMI will be summarized using descriptive statistics.

SPPB

The short physical performance battery (SPPB) contains three physical functional activities for the lower extremities divided into three functional components: balance test, usual gait speed and chair stand test. A score (0-4) will be calculated for each of the three components. In addition a total SPPB score will also be calculated. In each case the lowest possible value is zero (0).

Higher values correspond to better functional condition.

Balance test: 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 = 1 point, held for less than 3 sec or not attempted = 0 points.

Gait Speed: Gait speed will be assessed as part of the SPPB, over a 4 meter distance of a 6 meter course. Gait speed assesses a person's usual walking speed, which is defined as the speed a person normally walks from one place to another (e.g. walking from one store to another). The patient will perform two recorded trials of walking across the defined course. The fastest time in seconds (to the nearest 0.01 sec) a patient takes to complete the assessment will be scored and recorded in the Gait Speed section of the SPPB eCRF. 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.

Chair stand test: 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.

Baseline data (all relevant pre-treatment assessments, including Baseline value) of the total SPPB score with the corresponding scores of the three individual component tests: balance test, gait speed, and chair stand test 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 5 points.
- 6 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:

- Balance test: Side-by-side stand, semi-tandem stand and tandem stand, number of seconds held.
 - If the patient attempted the test and is indicated as “Held for 10 seconds” then a value of 10 seconds will be used.
 - If the patient attempted the test and is not indicated as “Held for 10 seconds” then the reported number of seconds will be used.
- Gait speed test: Times of the first and second gait speeds.
 - If the patient attempted the test successfully, time for 4 meters as reported in seconds.
- Chair stand test:
 - If the patient attempted the test successfully, the time to complete five stands as reported in seconds will be used.

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

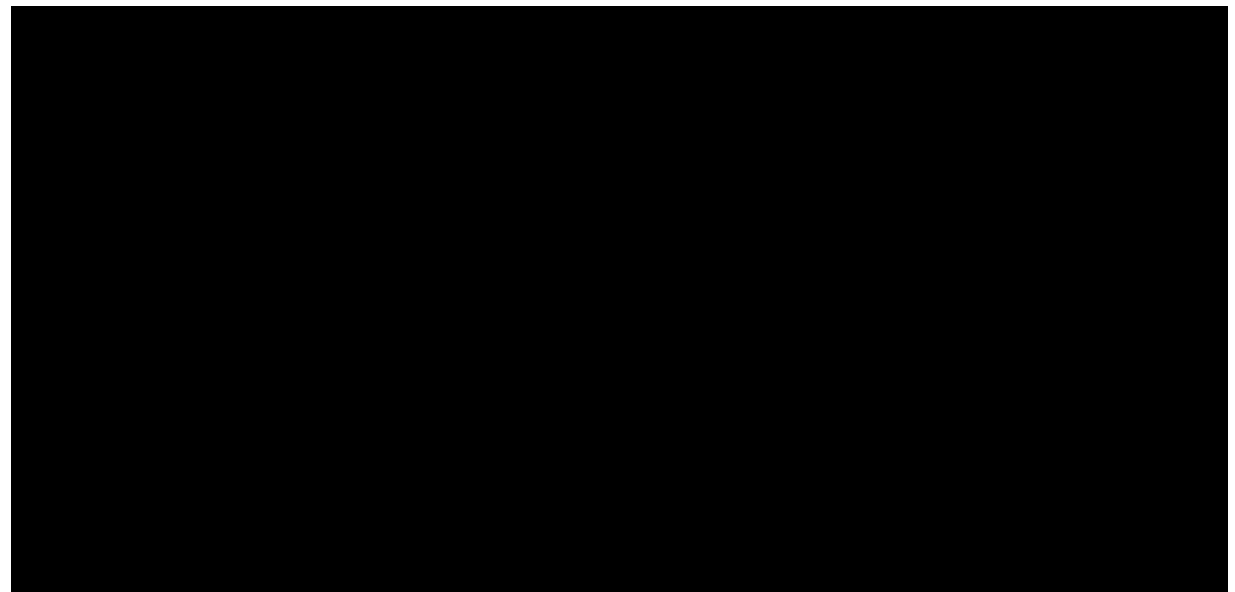
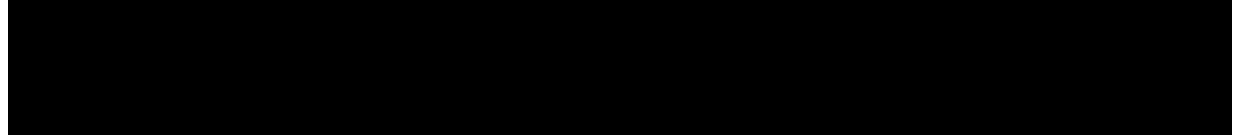
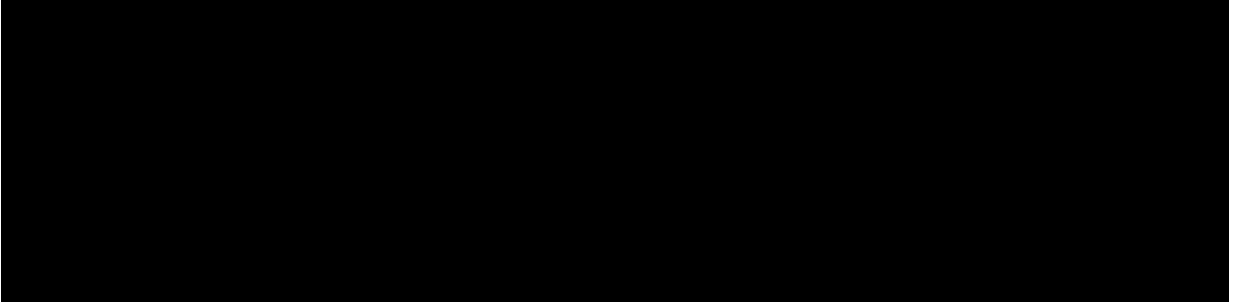
Six Minute Walk Test (6MWT)

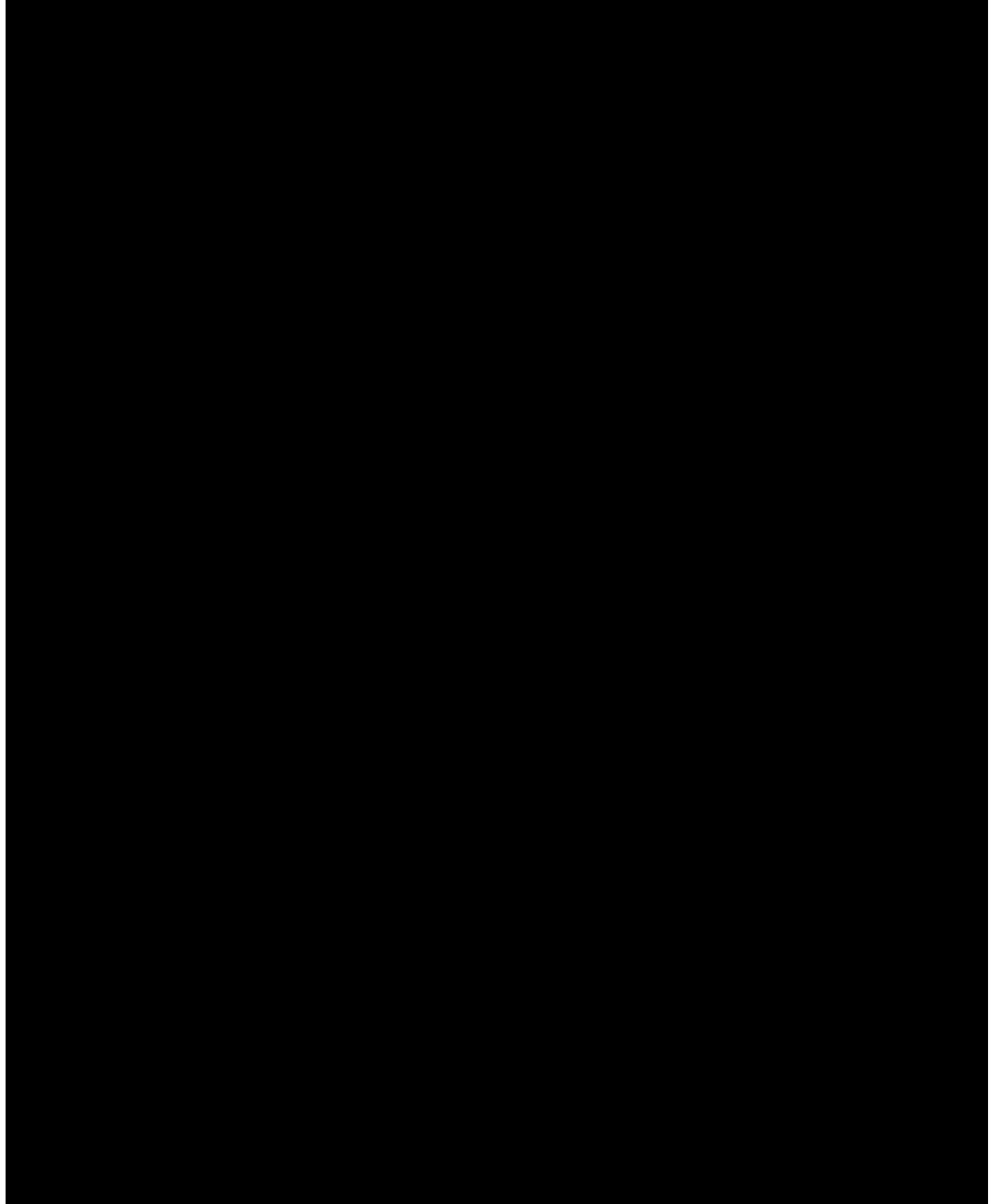
The 6 minute walk test (6MWT) is a simple, economical and reproducible test that measures how many meters a person can walk in 6 minutes. Total distance walked will be summarized by descriptive statistics. All subjects will be included in the descriptive statistics with the actual distance walked. In 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:

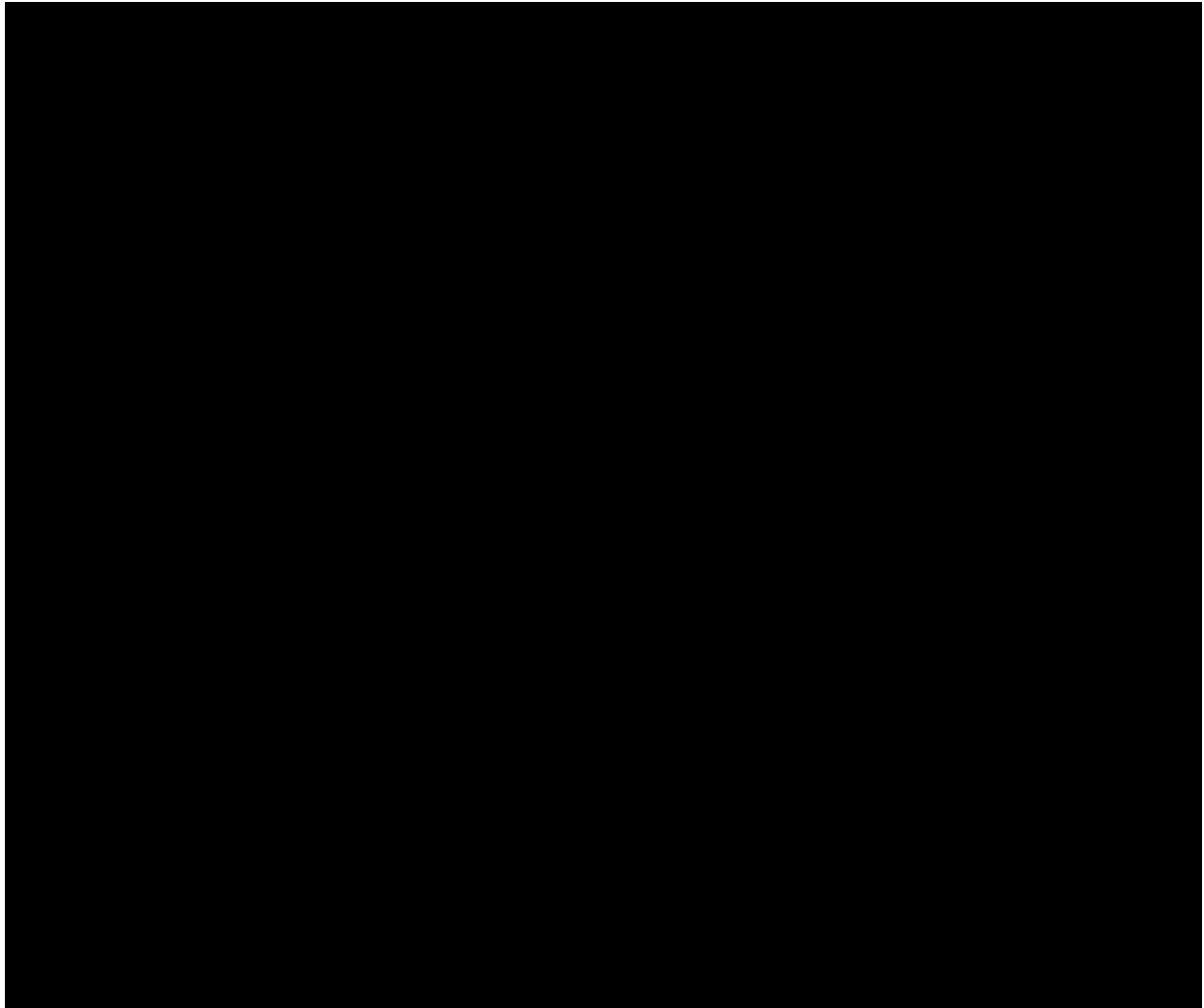
- Ankle foot orthotic
- Knee-ankle foot orthotic/long leg brace
- Cane with 1 point of floor contact
- Cane with >1 point of floor contact
- Crutch
- Hemi-walker
- Walker without wheels
- Wheeled walker
- Rollator

The number (n) and percentage (%) of patients who prematurely discontinued the test will be presented. Walking aids used for the test will be summarized by both descriptive measures for quantitative variables (number of aids used) and qualitatively for different devices used.









7.5 Other Assessments

Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. Further detail of this investigation is available in protocol.



8 Treatments (study drug, other concomitant therapies, compliance)

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, region, center and patient if not indicated otherwise.

Where relevant, “across all treatment groups” refers to the addition of a “Total” column within the planned presentation of the data. Similarly “overall” refers to overall levels of stratification of the relevant subgroup.

8.1 Study drug administration

Compliance is expected to be good since study drug will be administered by the investigator or study personnel, unless the patient misses clinic visits. Compliance will be calculated for each patient as follows:

- Compliance (%) = (Number of study drug infusions received/Number of treatment epoch visits) * 100

Here the number of treatment epoch visits is counted as the number of planned treatment visits until study treatment discontinuation or study treatment completion (i.e. last study drug infusion).

If a patient received only part of an infusion (i.e. infusion start time is recorded but study drug infusion permanently discontinued is indicated as “Yes” in the Dose Administration Record – Infusion eCRF), the patient will be regarded as having received study drug infusion at that visit for the purpose of compliance calculation.



8.2 Prior and concomitant medications

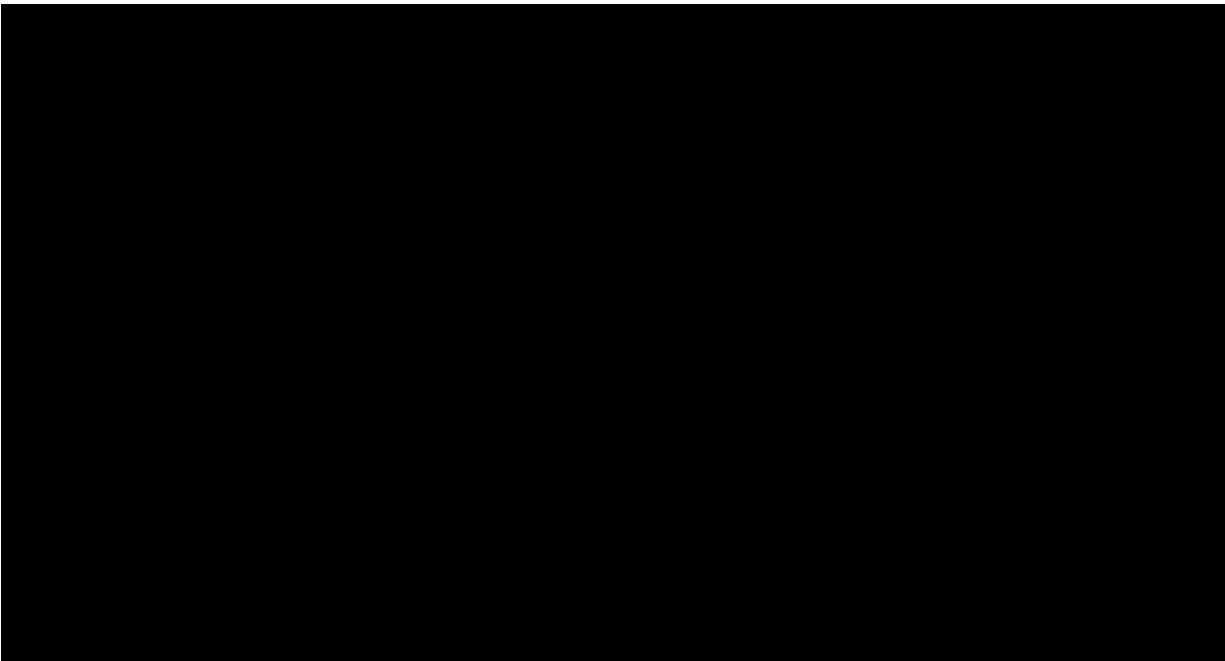
The number (n) and percentage (%) of patients taking prior and concomitant medications will be summarized in separate tables by Anatomical Therapeutic Chemical (ATC) classification and PT, by treatment group and across all treatment groups combined.

Medications will be presented by anatomical main group (the 1st level of the ATC codes), sorted by descending frequency of the total number of patients with at least one medication in each ATC Level 1 category. Within each 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 present the overall number (n) and percentage (%) of patients receiving at least one medication and receiving at least one medication of a particular ATC code.

Prior medications are defined as medications started and stopped prior to the start of the first infusion of study drug. Concomitant medications are defined as any medication which started

or stopped on or after the start of the first infusion of study drug up to the last infusion of study drug + 56 days or are ongoing.

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. If it cannot be established that the use of a prior medication has ended prior to the start of the first infusion of study drug 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).



10 Statistical methods for Pharmacodynamic (PD) parameters

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 treatment group, region, center and patient if not indicated otherwise.

Where relevant, “overall” refers to overall levels of stratification of the relevant subgroup.

Table 10-1 Analysis set to be used for different endpoints

Endpoint	Type of Analysis	
	Summary (Table / Graph)	Statistical Analysis
SPPB (Primary)	FAS	PPS/FAS
Gait Speed	FAS	PPS/FAS
6MWT	FAS	FAS
LBM	FAS	FAS
ASMI	FAS	FAS
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

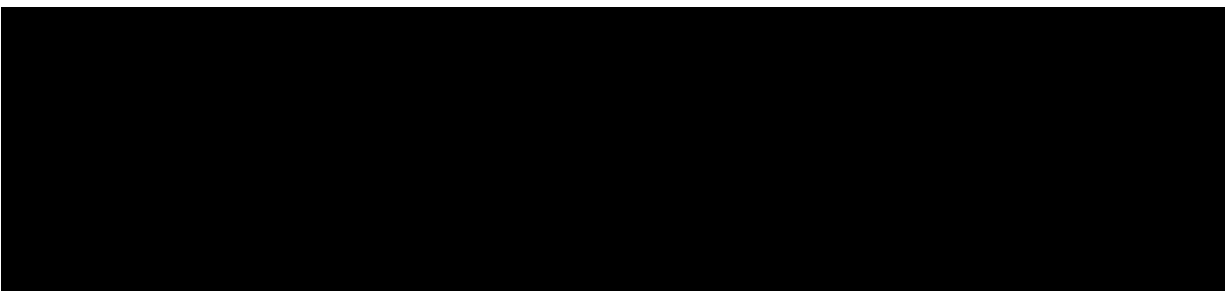
Endpoint	Type of Analysis	
	Summary (Table / Graph)	Statistical Analysis
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
All Safety endpoints	Safety analysis set	Safety analysis set
[REDACTED]	[REDACTED]	[REDACTED]
Listings* [REDACTED]	All subjects	All Subjects

*Unless specified otherwise

Summary of continuous endpoints:

All continuous endpoints (SPPB total score, 6MWT, Gait Speed, LBM, ASMI, [REDACTED]) will be summarized using descriptive statistics, overall and subgroups (refer to [section 5](#)) per treatment and visit for change from baseline.

Measurements for all available visits will be taken into consideration.



10.1 Analysis of the primary variable(s)

The primary objective of this study is to assess the effect of 24 weeks of bimagrumab treatment on patient physical function assessed by a change in Short Physical Performance Battery (SPPB) total score from baseline to week 25 relative to placebo in older patients with sarcopenia.

10.1.1 Variable

The primary endpoint is SPPB change from baseline to week 25. The baseline value should be the one obtained at Visit 5 whenever possible. If Visit 5 data is not available, the SPPB data from Visit 3 should be used. If the individual participant does not have SPPB data from either Visits 3 or 5, then the person should be excluded from the analysis.

10.1.2 Descriptive statistics

SPPB total score as well as score in different domains will be summarized using table and graphics as explained in section 10 ‘summary of continuous endpoints’. Additionally a shift table will be prepared to reflect the patient count under each absolute SPPB total score category from baseline to week 25.

10.1.3 Statistical model, hypothesis and method of analysis

This study is planned to be conducted in two parts.

10.1.3.1 Analysis for Part A

Part A is focused on proof of concept of BYM338 on SPPB change from baseline score in older adults with sarcopenia. In this part maximum dose of BYM338 (700mg) will be compared with placebo to establish the following criteria:

[REDACTED]

Analysis plan: Change from baseline SPPB total score at 25 week will be analyzed using an analysis of variance model (ANCOVA) with treatment and subgroup1 (Japan / non-Japan) as fixed effects and baseline SPPB total score as covariate. A 95% two sided confidence interval (CI) of treatment vs placebo will be estimated for treatment vs placebo contrast. To establish ‘statistical significance’, the lower CI is required to be positive.

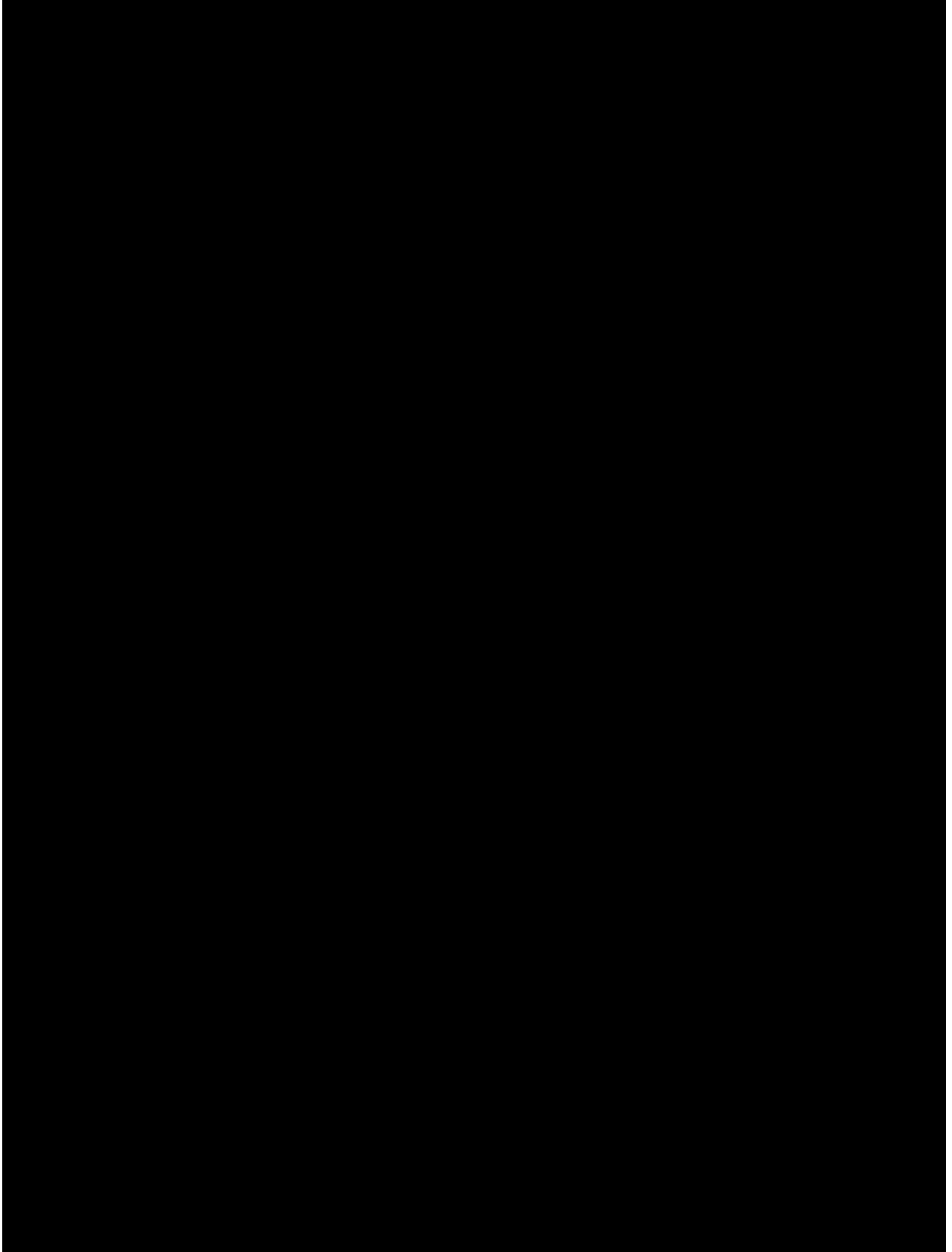
[REDACTED]

Analysis plan: Change from baseline SPPB total score at 25 week will be analyzed using an analysis of variance model (ANCOVA) with treatment and subgroup 1 (Japan/ non-Japan) as fixed effects and baseline SPPB total score as covariate. In order to establish ‘clinical significance’, the point estimate of treatment vs placebo is required to be more than 1 unit.

[REDACTED]

Primary analysis will be performed on PPS (per protocol set).

[REDACTED]



10.1.3.3 Supportive analysis

As a supportive analysis, a mixed repeated measures analysis of variance (MMRM) will be done on absolute change from baseline with a covariate for treatment (placebo or bimagrumab dose group), visit, baseline, visit*baseline, visit*treatment and subgroup1 (Japan/ non-Japan) (Japan, non-Japan). If Japanese subjects are enrolled, then Japan will be considered a separate region and give rise to a separate fixed covariate in the analysis. A saturated covariance structure for observations within the same subject will be used. Treatment to placebo comparison (70 mg vs. placebo, 210 mg vs. placebo, and 700 mg vs. placebo) at the 6 month time point will be estimated along with 95% two sided confidence interval and one sided p-value for treatment superiority over placebo will be reported. No adjustment for multiplicity will be done. If convergence problems are noted due to a sparse number of Japanese subjects, then the analysis may be redone while omitting this covariate. For MMRM analysis following visits will be considered: baseline, V103, V104, V106, V107.

Additionally for Part A, in order to investigate the overall occurrence of 1 unit increase in different treatment arms; responders will be modelled using treatment and subgroup1 (japan/ non-japan) as covariates to compare the relative responder rate. A patient will be identified as responder if SPPB change from baseline score at week 25 ≥ 1 .

10.1.4 Sensitivity analysis

In case the PP analysis is different from the FAS set, the primary analyses will be repeated for the full analysis set (FAS) as confirmation of the primary analysis results.

10.1.5 Handling of missing values/censoring/discontinuations

The above analysis will be performed using all available data under the assumption that the probability of missing values of SPPB are independent of unobserved measurements (missing at random [MAR]). Therefore the missing values will not be imputed for primary analysis.

10.2 Analysis of secondary [REDACTED] variables

10.2.1 Secondary variables

Secondary endpoints are:

- Gait speed measured as a component of the SPPB over 4 meters change from baseline:

Gait speed will be reported in two ways.

- a. Average gait speed.
- b. Fastest gait speed which is accounted for under SPPB scoring.

The change in gait speed from baseline at V103, V104, V106, and V107 will be analyzed using a MMRM model with treatment, visit, baseline, visit*baseline, visit*treatment and subgroup1 (Japan/ non-Japan) as covariates. Treatment to placebo comparison (70 mg vs. placebo, 210 mg vs. placebo, and 700 mg vs. placebo) at the each visit will be estimated along with 95% two sided confidence interval and one sided p-value for treatment superiority over placebo will be reported. No adjustment for multiplicity will be done.

A MCP-MOD (only V107, for Part B) analysis will be performed with same candidate families as used for the primary end point will be used (linear, convex, concave families).

The underlying assumptions of the repeated mixed model (homogeneity of slopes and normality) may be assessed by QQ plots of the studentized residuals. In case of departure from normality, the log of the ratio to baseline will be analyzed instead the change from baseline

- 6 minute walk test (6MWT) change from baseline.

The change in 6 minute walk test from baseline at V104 and V107 will be analyzed in a similar manner to the gait speed with an MCP-MOD (only V107 at Part B) analysis as well as MMRM model.

- DXA parameters: total lean body mass and appendicular skeletal muscle index (ASMI) change from baseline

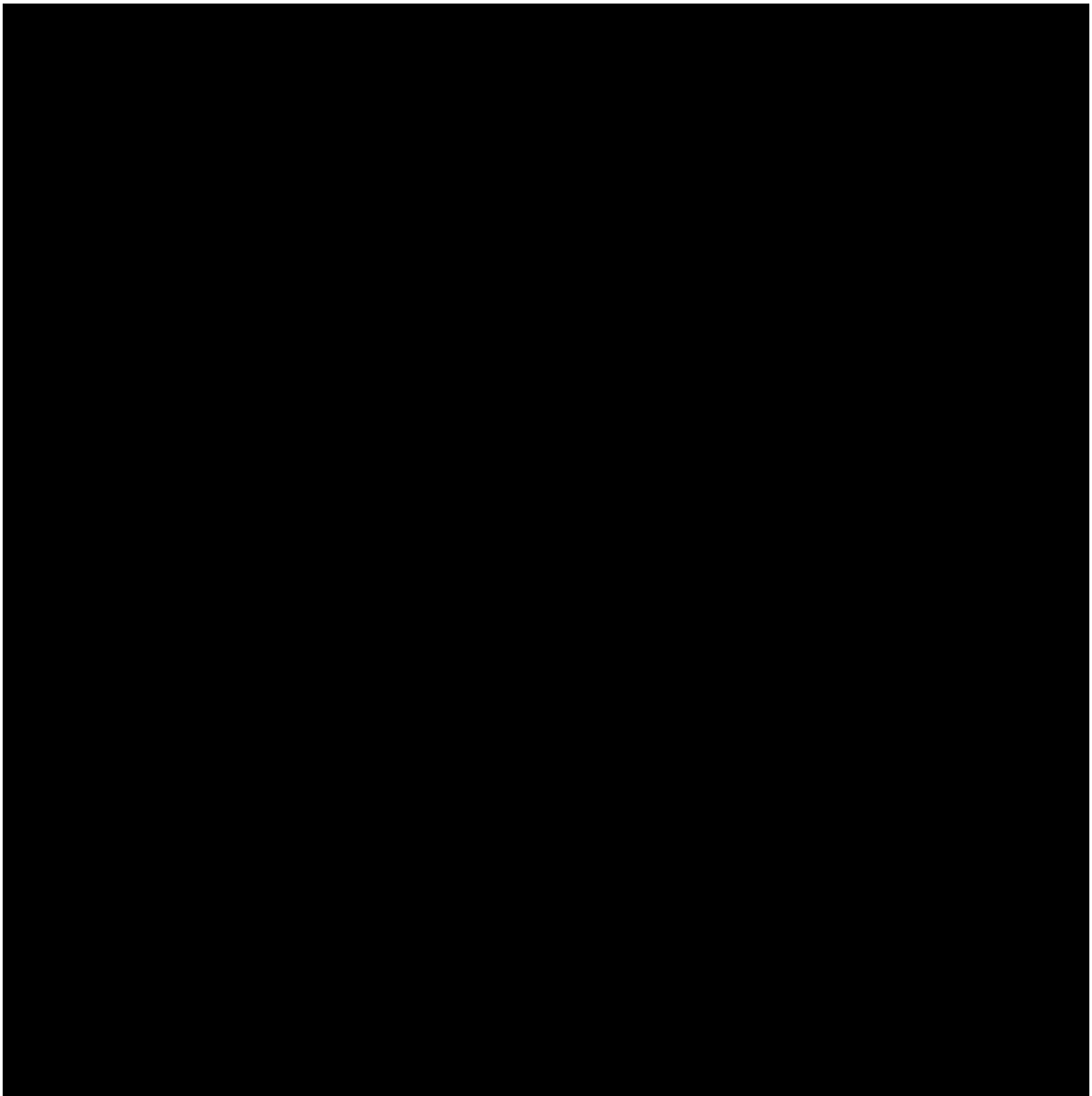
The ratio to Baseline in total LBM and appendicular skeletal muscle index (ASMI) will be analyzed with MMRM model. Data will be transformed using natural logarithm before analysis. Log transformed ratio to baseline DXA parameters (LBM / ASMI) will be analyzed using an MMRM model with log baseline, treatment, subgroup1 (Japan/

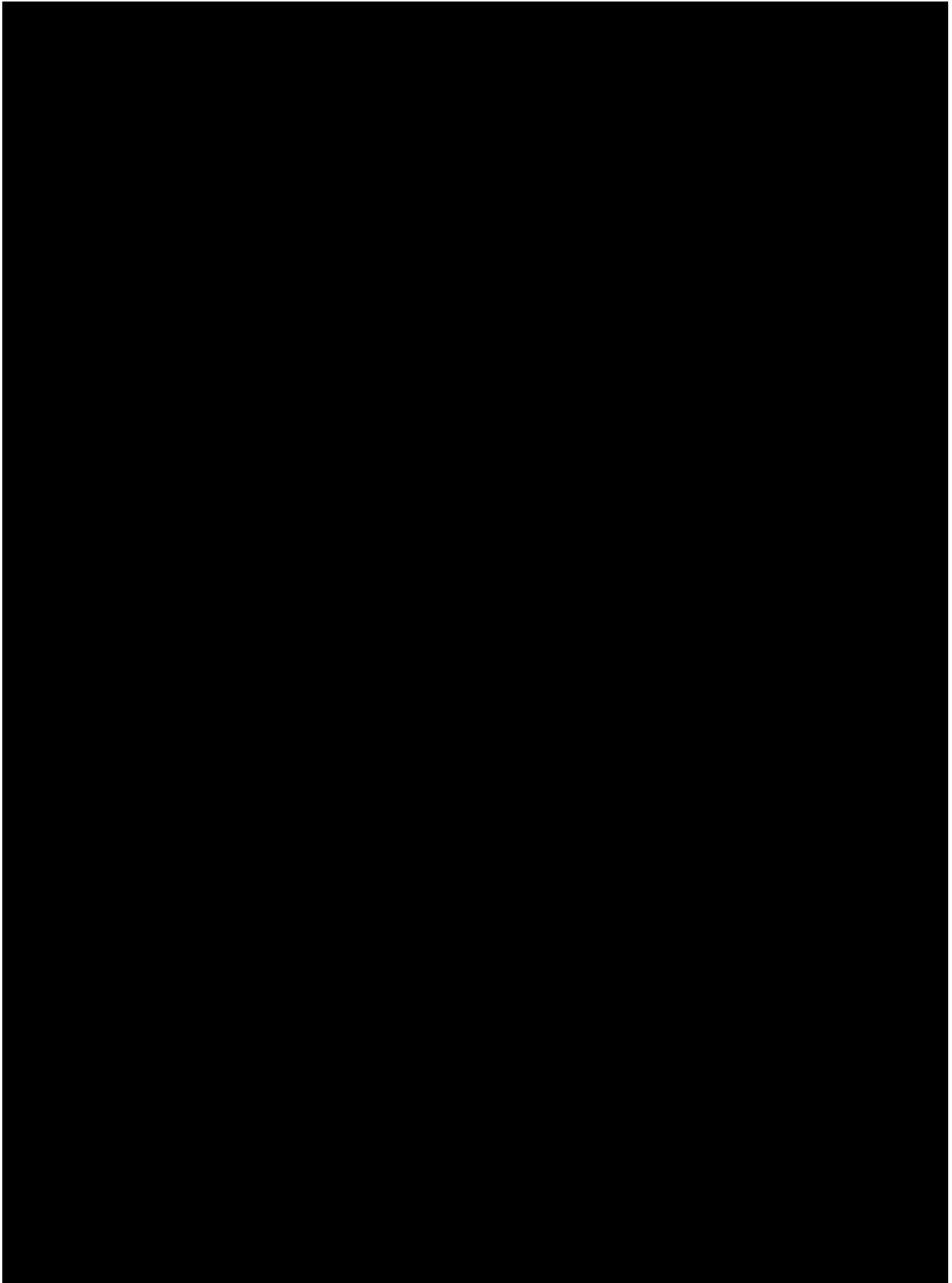
non-Japan), visit, visit*baseline, visit*treatment. A saturated covariance structure will be used for observations coming from same subject. All results for treatment vs placebo contrast will be back transformed to the original scale to present adjusted geometric mean ratio with two sided 95% CI and one sided p-value for treatment superiority over placebo will be reported.

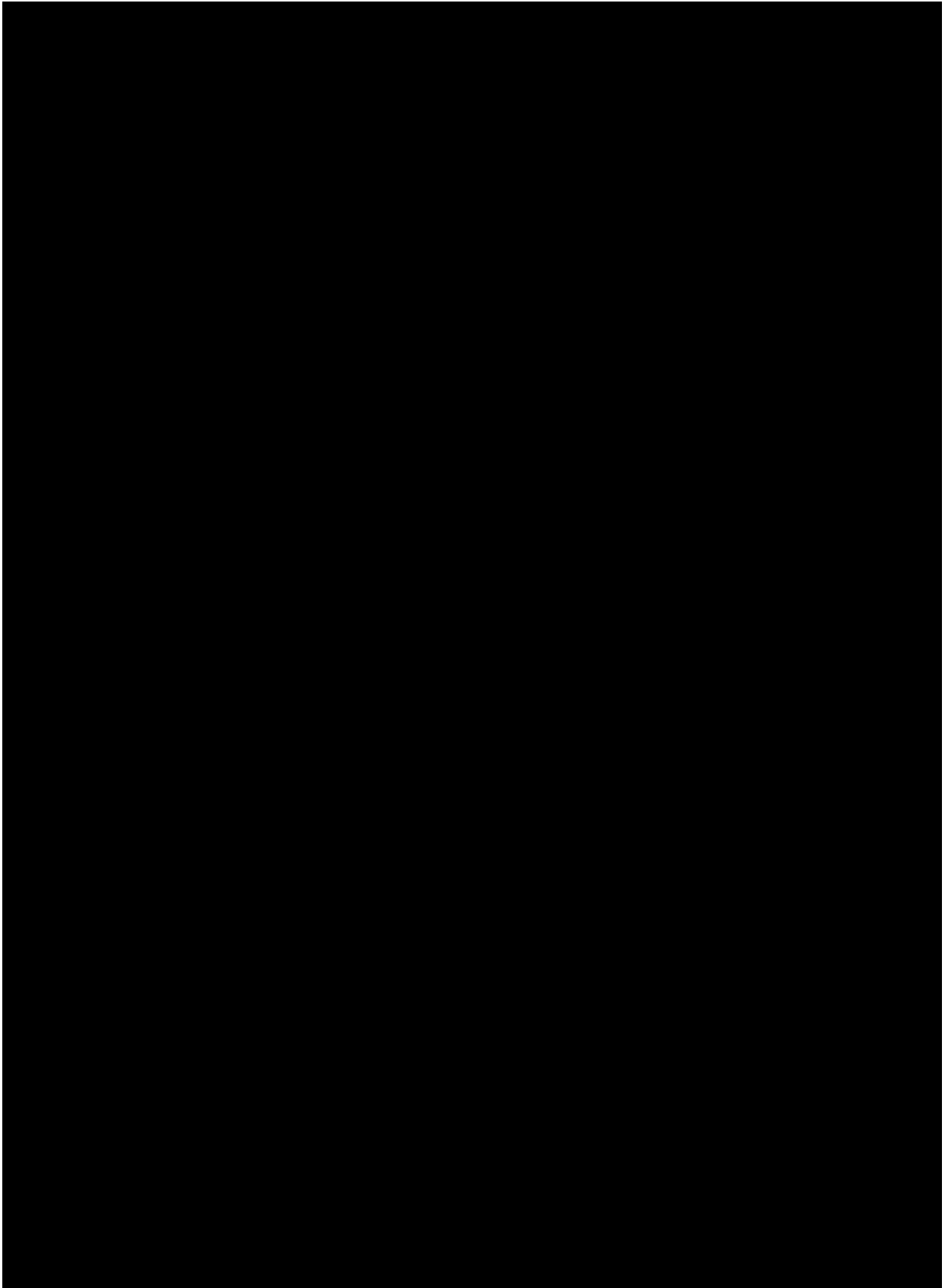
Visits to be considered for this analysis: Baseline, V104, V107.

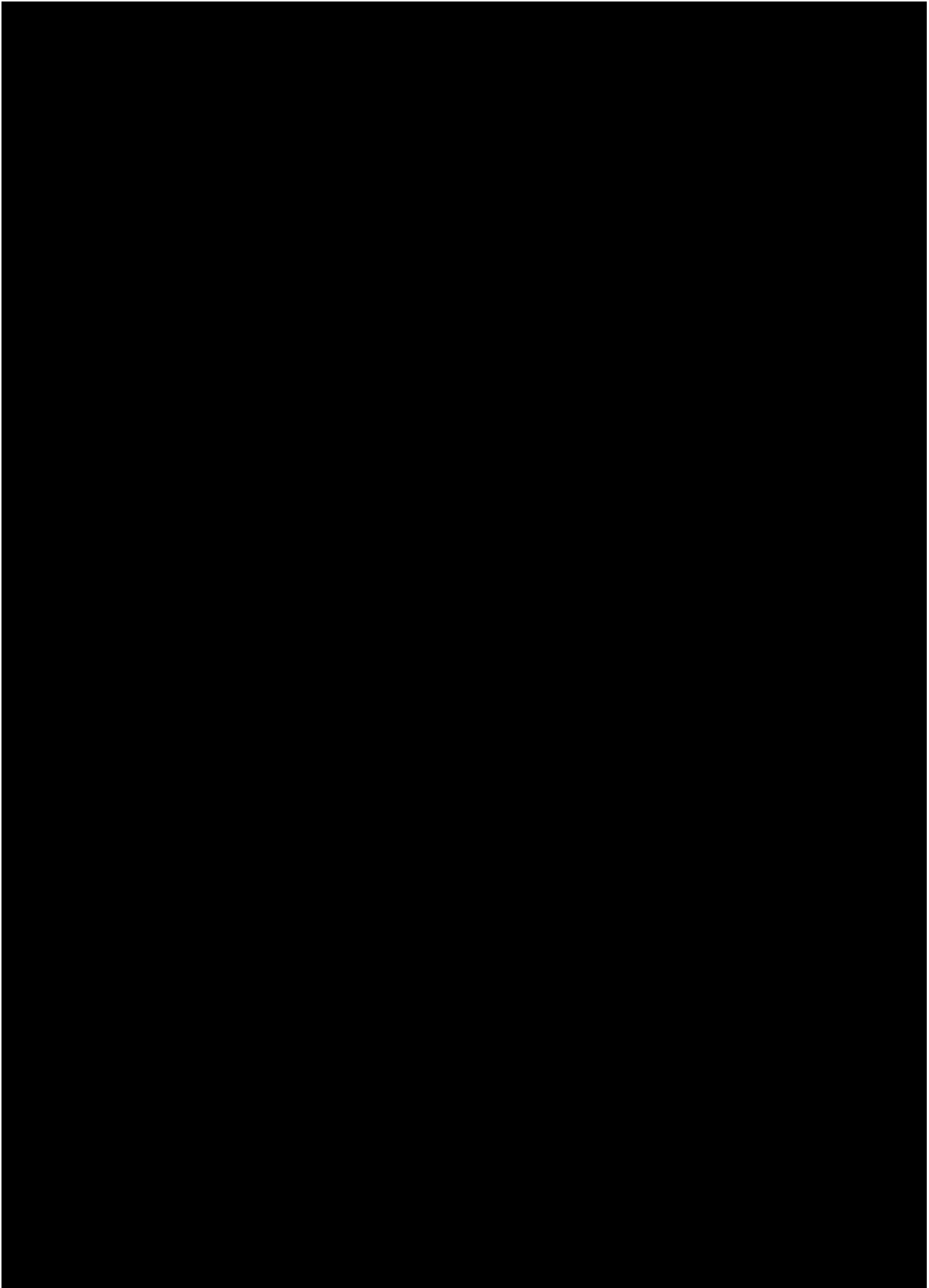
Scatter plot matrix will be produced to explore the association between mean change in total LBM and aLBM and other efficacy variables (gait speed, total SPPB and 6MWT) by treatment, subgroup1 (Japan/ non-Japan) and visit.

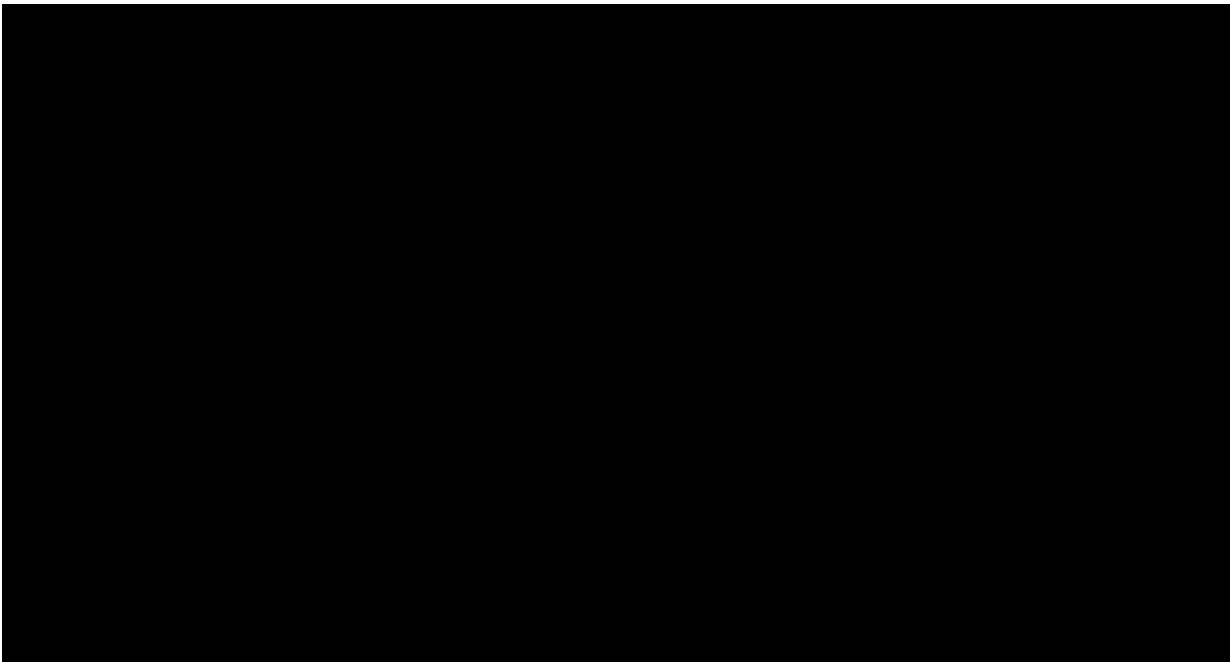
MMRM results will be reported at IA.











10.2.3 Additional analysis

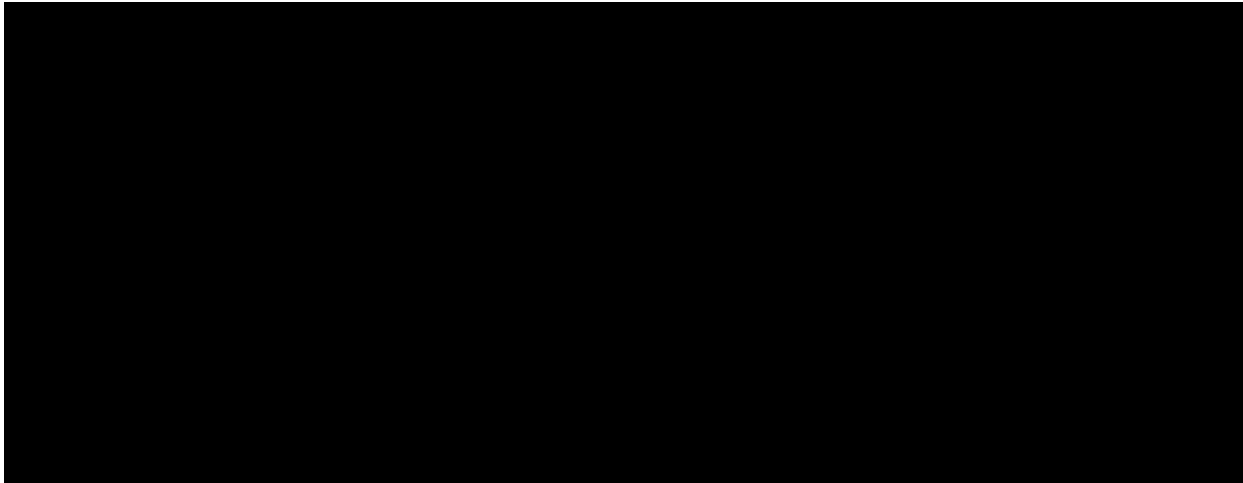
HA questions

Sarcopenia Assessment:

All randomized patients will be evaluated by treatment groups based on their baseline and week 25 performances under each of the following categories to assess sarcopenia status based on different assessment criteria:

1. Assessment of lean mass using ASMI (for protocol):
 - Non-Asian countries: $\leq 7.26 \text{ kg/m}^2$ for men and $\leq 5.5 \text{ kg/m}^2$ for women to be assessed during screening.
 - Asian countries: $\leq 7.0 \text{ kg/m}^2$ for men and $\leq 5.4 \text{ kg/m}^2$ for women to be assessed during screening
2. Alternative method for measuring lean mass (for FNIH):
 - ALM/BMI (appendicular lean mass from DXA / [weight in kg/ ht in m²]) qualifying cut off points <0.789 for men and <0.512 for women (Studenski et. al. 2014)
3. [Redacted]
4. GS $<0.8\text{m/sec}$
5. Protocol-defined sarcopenia: Meets criteria #1 and #4
6. FNIH-defined sarcopenia: Meets criteria #2 and #4
7. EWGSOP-defined severe sarcopenia: Meets criteria #1, #3 and #4

A single table representing n and percentages of subjects meeting each individual criterion at baseline and week 25 will be reported by treatment groups.



Analysis of AEs of special interest:

Number and percentage of AEs under each of the following categories will be summarized by treatment groups:



Treatment adherence:

Per protocol 6 doses are planned for each patient.

Treatment adherence of patients will be represented by summarizing patients by number of doses using the definition explained in section 8.1.

11 Safety analysis

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, region, center and patient if not indicated otherwise.

Descriptive statistics for safety variables will be presented for the safety analysis set.

Where relevant, “overall” refers to overall levels of stratification of the relevant subgroups.

11.1 Cardiac toxicity – cardiomyopathy analysis

The odds ratio (to placebo) of experiencing at least one cardiac toxicity event (based on events identified by the investigator in the cardiomyopathy eCRF) will be calculated together with 2-sided 95% confidence intervals for each of the bimagrumab treatment groups versus placebo treatment group. A p-value comparing each bimagrumab regimen (70 mg, 210 mg and 700 mg) versus pooled placebo will be calculated using Fisher’s exact test. The odds ratio, 95% confidence interval for the odds ratio will be presented for each independent comparison. The

results of these analyses will be presented in tabular form. Kaplan-Meier estimate for time to the first confirmed event with 95% confidence intervals will be presented for each treatment group. Differences between placebo and each of the bimagrumab treatment groups will be quantified by log-rank test. If a patient does not have a cardiac toxicity event the data will be censored to the study discontinuation/premature discontinuation date (see section 13.6.2 for more details).

The same analysis may be also performed by subgroups in case of enough events of interest are observed in both groups or if the rates seem to be different in both groups. Alternatively, Cox regression analysis may be performed including subgroups as a covariate in case of imbalance between patients is observed

Cardiac toxicity events (based on events as identified by the investigator and evaluated by the adjudication committee) will be listed in by-patient data listings. All by-patient data listings will be sorted by treatment group, region, center and patient if not indicated otherwise.

11.2 Adverse events

Adverse events data analysis will be based on the safety analysis set. Adverse events will be deemed treatment-emergent if the date of onset or worsening of the AE is on or after the date of first infusion of study drug until the end of the study (as per protocol end of study defined as approximately 56 days after last infusion of study drug). Percentages will be calculated relative to the number of patients in the safety analysis set. Only treatment-emergent AEs (TEAEs) will be summarized but all AEs reported will be listed in by-patient data listings. All by-patient data listings will be sorted by treatment group, region, center and patient if not indicated otherwise. Separate summaries would be created for:

- TEAEs regardless of study drug relationship.
- TEAEs with suspected study drug relationship.
- Other significant TEAEs leading to dose adjustment or discontinuation of study drug.

Missing or incomplete TEAE onset dates will be imputed; algorithms for date imputations will be provided in RAP Module 8 (Programming Specifications). No imputation will be applied to TEAE end dates. Hence, if the end date is missing, the duration of the TEAE will be “continuing”.

The most current MedDRA dictionary version will be used for coding and will be described in a footnote.

Where relevant, “overall” refers to overall levels of stratification of the relevant subgroup.

TEAEs by primary system organ class and preferred term

The number (n) and percentage (%) of patients with TEAEs will be summarized by primary SOC, PT by overall and subgroups 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. The number (n) and percentage (%) of patients having at least one TEAE, and having at least one TEAE in each primary system organ class, and for each PT will be presented. Hence if a patient reported more than one TEAE with the

same PT, the TEAE will be counted only once. If a patient reported more than one TEAE within the same primary system organ class, the patient will be counted only once at the system organ class level.

TEAEs by study drug relationship

The number (n) and percentage (%) of patients with TEAEs will be summarized by relationship, primary system organ class, PT by overall and subgroups and treatment group. If a patient reported more than one TEAE with the same PT, the AE with the strongest relationship (related) will be presented. If a patient reports more than one TEAE within the same primary system organ class, only one TEAE will be counted for that patient at the strongest relationship (related) in the total row for each primary system organ class. If TEAE “relationship” is missing, this variable will be listed as missing and treated as missing in summaries.

TEAEs by severity

The number (n) and percentage (%) of patients with TEAEs will be summarized by severity, primary system organ class, PT by overall and subgroups and treatment group. If a patient reported more than one TEAE with the same PT, the TEAE with the greatest (maximum) severity will be presented. If a patient reports more than one TEAE within the same primary system organ class, only one TEAE will be counted for that patient at the highest severity level in the total row for each primary system organ class. If TEAE “severity” is missing, this variable will be listed as missing and treated as missing in summaries.

Overview of serious adverse events

An overview of treatment-emergent AE/SAEs will be generated for

- TEAEs
- TESAEs
- TESAEs leading to death.
- TESAEs with suspected relationship to study drug.
- TESAEs leading to discontinuation or dose adjustment of the study drug

The number of patients with at least one TESAE in each category (patients with multiple TESAEs in each category are counted only once in each category) will be presented by treatment group, overall and by subgroups.

11.3 Deaths

All the deaths in the clinical database will be listed.

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

SAEs for screen failure subjects

Serious adverse events of screen failure subjects will be reported in a separate by-patient listing with key available information, (e.g., subject number, age/sex/race, preferred term, system organ class and action taken).

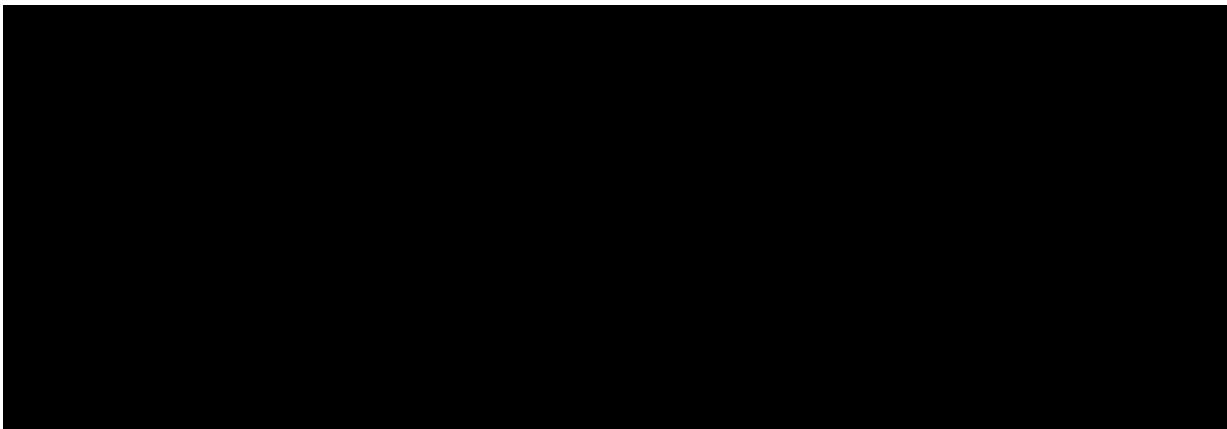
11.4 Laboratory data

All laboratory data will be listed by treatment, region, center, patient, and visit/time and if normal ranges are available abnormalities will be flagged. If ranges are available abnormalities and clinically notable values will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment by overall and subgroups 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 or pancreatic enzyme abnormalities will be summarized similarly to those of vital signs. Notable criteria for the table:
 - ALT or AST > 3 x ULN
 - ALT or AST > 5 x ULN
 - ALT or AST > 8 x ULN
 - TBL > 1.5 x ULN
 - TBL > 3 x ULN
 - ALP > 2 x ULN
 - ALP > 5 x ULN
 - ALT or AST > 5 x ULN & TBL > 2 x ULN
 - ALP > 5 x ULN & TBL > 2 x ULN Hy's law

Hormone panels (follicle stimulating hormone (FSH), luteinizing hormone (LH), Sex hormone-binding globulin (SHBG) and testosterone, thyroid stimulating hormone (TSH). free thyroxine if available) will be summarized by gender separately.

Notable laboratory values will be considered “newly occurring” if they had not been present at Baseline. If assessments cannot be made at Baseline due to missing value(s), post-baseline values meeting the notable criterion will be considered as newly occurring.

Boxplots to visualize trends in longitudinal safety data will be created.

11.5 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 and mean standing 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 for vital sign variables at each scheduled visit and for the change from Baseline in vital signs at each scheduled post-baseline visit and End of Treatment/End of Study as relevant, will be presented using descriptive statistics. Change from Baseline will be derived only for patients with both Baseline and post-baseline measurements.

Notable vital signs values will be considered “newly occurring” if they had not been present at Baseline. If assessments cannot be made at Baseline due to missing value(s), post-baseline values meeting the notable criterion will be considered as newly occurring.

- Systolic blood pressure:
 - >150mmHG or increase at Week 25 of ≥ 20 mmHg
 - <90mmHG or decrease at Week 25 of ≥ 20 mmHg
- Diastolic blood pressure:
 - >90mmHG or increase at Week 25 of ≥ 15 mmHg
 - <50mmHG or decrease at Week 25 of ≥ 15 mmHg
- Pulse rate:
 - >100bpm or increase at Week 25 of ≥ 15 bpm
 - <60bpm or decrease at Week 25 of ≥ 15 bmp
- Body weight:
 - +5% from Week 1 to 25 in kg
 - -5% from Week 1 to 25 in kg

Notable newly occurring vital sign abnormalities will be summarized by count and percentages by treatment group, overall and by subgroups.

All vital signs data will be listed by treatment, region, center, patient, and visit and if ranges are available abnormalities will be flagged.

Boxplots to visualize trends in longitudinal safety data will be created.

11.6 ECG

All ECGs must be recorded after 10 minutes rest in the supine position. The Fridericia QT correction formula (QTcF) will be used for clinical decisions.

Summary statistics will be presented for ECG parameters by visit and the change from Baseline will be presented at each scheduled post-baseline visit and End of Treatment/End of Study as relevant, for each treatment group. Change from Baseline will be derived only for patients with both Baseline and post-baseline measurements.

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

Data of patients with newly occurring or worsening ECG abnormalities at any scheduled or unscheduled visit after Baseline will be listed.

All ECG data will be listed by treatment, region, center, patient and visit, abnormalities will be flagged.

Boxplots to visualize trends in longitudinal safety data will be created.

11.7 Echocardiography

The following echocardiography measurements will be collected:

- Left ventricular end-diastolic volume (mL)
- Left ventricular end-systolic volume (mL)
- Left ventricular ejection fraction (%)
- Interventricular septum thickness (mm)
- Left ventricular end-diastolic diameter (mm)
- Left ventricular end-systolic diameter (mm)
- Left ventricular posterior wall thickness (mm)
- Left ventricular anterior wall thickness (mm)
- Left ventricular mass (g)
- Left ventricular mass index (g/m²)
- Relative wall thickness (ratio)
- Fractional shortening (%)
- Left atrial area (cm²)

- Left atrial volume (mL)
- Right ventricular wall thickness (mm)
- Right ventricular diameter in mid cavity (mm)

Summary statistics for echocardiography measurements and for the change from Baseline at each scheduled post-baseline visit and End of Treatment/End of Study as relevant, will be presented for each treatment group.

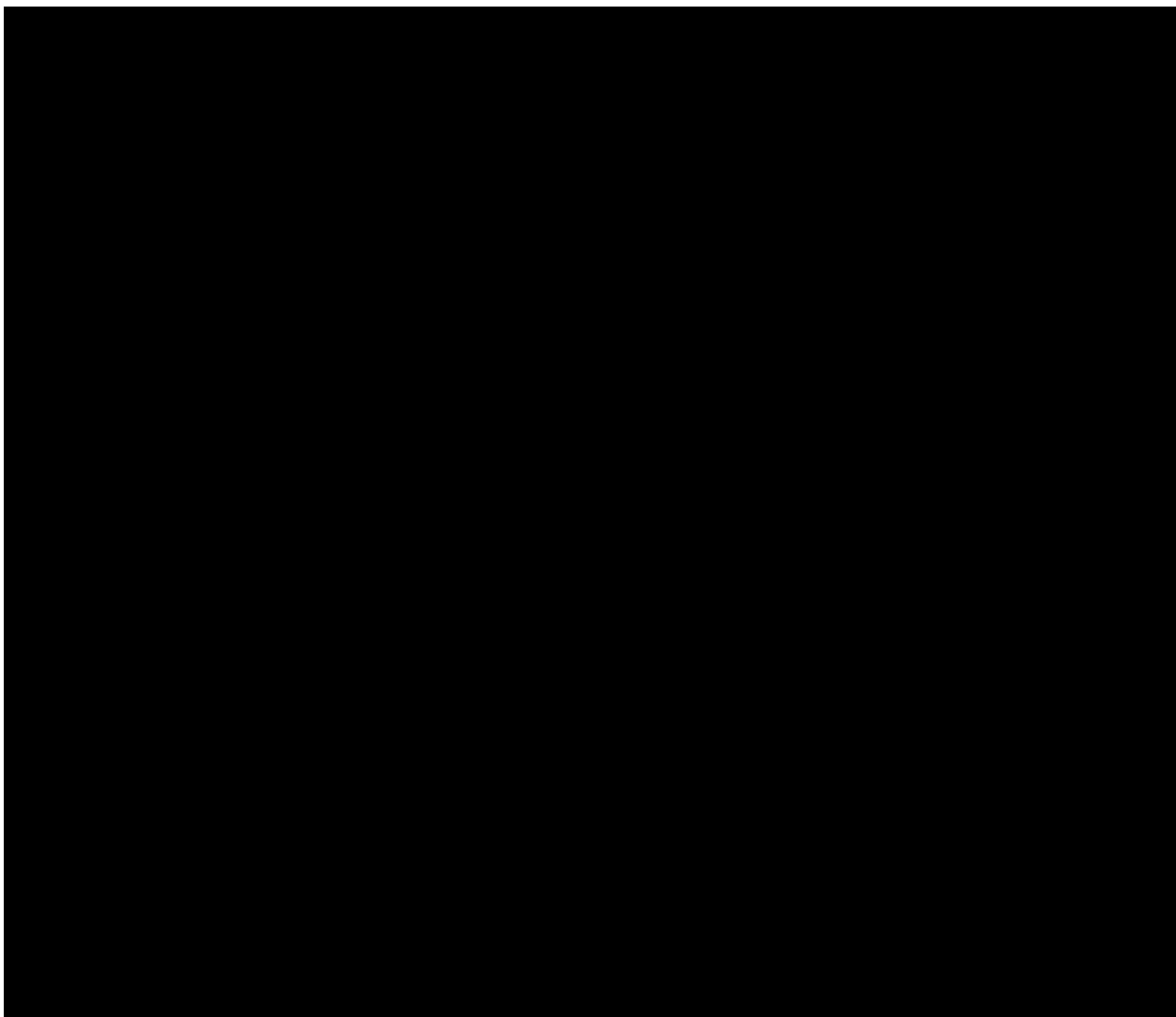
Change from Baseline will be derived only for patients with both Baseline and post-baseline measurements.

All echocardiographic data will be listed by treatment group, region, center, patient and visit.

11.8 Other safety variables

Other safety variables will be summarized descriptively by visit and treatment group and will be listed by treatment group, patient, and visit. Other safety variables include:

- [REDACTED]



13 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

13.1 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.

13.2 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

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.

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.

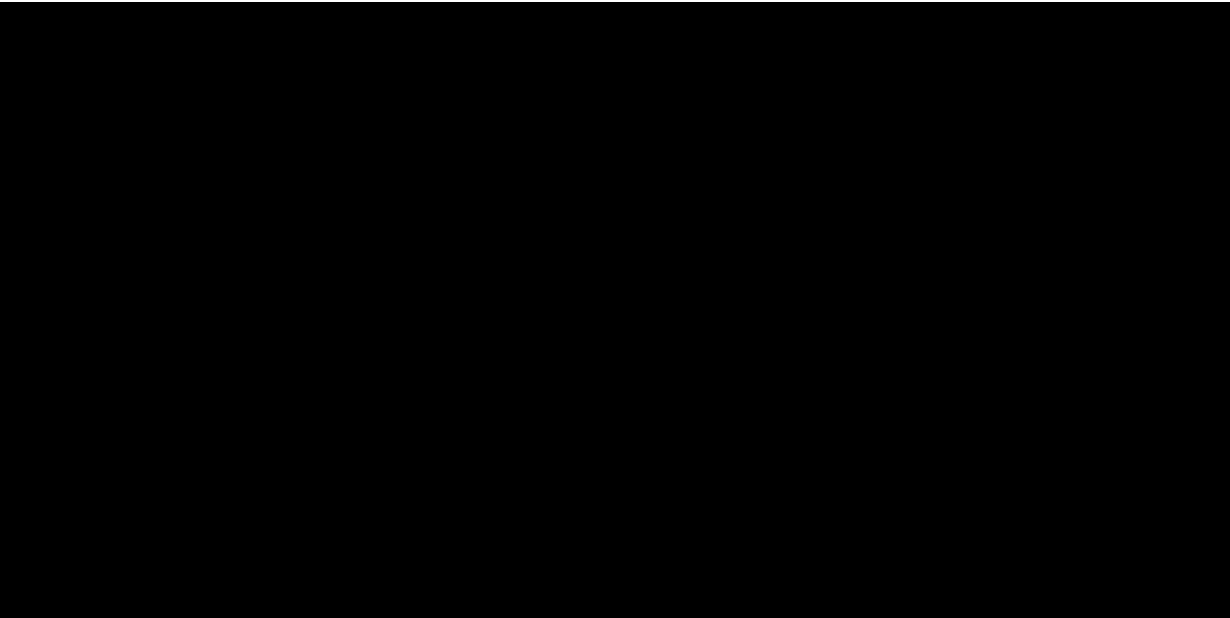
For application of inferential statistics, the least squares (LS) means and corresponding confidence intervals (CIs) will be reported with one extra decimal relative to the individual raw data. The odds ratios and corresponding CIs will be reported with two decimal places where relevant.

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.



13.3 Study Day 1 and other study days

The date of first infusion of study drug 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 date) + 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 date), 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.

13.4 Definition of Baseline and post-baseline measurements

Baseline is defined as the last available assessment prior to the start of the first infusion of study drug, including pre-dose assessments from Day 1. However this should not include any screening assessment. If all the pre dose values except screening are not available in data base then baseline should be considered as missing.

Assessments performed after the start of the first infusion are considered post-baseline assessments.

Change from Baseline is calculated where Baseline and post-baseline values are both available:

- Change from Baseline = (post-baseline value – Baseline value).
- Percentage Change from Baseline at each post-baseline visit:
- Percentage Change from Baseline = [(post-baseline value – Baseline value)/Baseline value] * 100
- Ratio from Baseline = (post-baseline value /Baseline value) (used in log transformed model)

13.5 Protocol-defined visits

Visit Number	Visit Name	Days
1	Screening	-50 to 30
2	Run-In Visit 1	-29 to -23
3	Run-In Visit 2	-22 to -16
4	Run-In Baseline 1	-15 to -10
5	Run-In Baseline 2	-5 to -1
101	W1D1	1 + 2 days
1015	W3D1	15 +/- 2 days
102	W5D29	29 +/- 4 days
103	W9D57	57 +/- 4 days
140	W13D85	85 +/- 4 days
105	W17D113	113 +/- 7 days
106	W21D141	141 +/- 7 days
107	W25D169 (End of treatment)	169 +/- 7 days
199	EOS	197 +/- 7 days

13.6 Analysis visits

13.6.1 Visit naming

Visit Number	Visit Name	Target visit day	Start day of visit window	Midpoint	End day of Visit window
1	Screening	-50 to 30		Not remapped	
2	Run-In Visit 1	-29 to -23		Not remapped	
3	Run-In Visit 2	-22 to -16		Not remapped	
4	Run-In Baseline 1	-15 to -10		Not remapped	
5	Run-In Baseline 2	-5 to -1		Not remapped	
101	W1D1	1		Not remapped	

1015	W3D1	15		15	22
102	W5D29	29	2	29	43
103	W9D57	57	44	57	71
140	W13D85	85	72	85	99
105	W17D113	113	100	113	127
106	W21D141	141	128	141	155
107	W25D169 (End of treatment)	169	156	Not remapped	Not remapped
199	EOS	197		Not remapped	

By-visit presentations will be presented according to the nominal visit number, no visit windowing will be applied.

13.6.2 Early discontinuation visit remapping

Patients who prematurely withdraw from the study for any reason, will be scheduled for an End of Treatment visit approximately 28 days following their last study drug infusion, at which time all of the assessments listed for that visit will be performed.

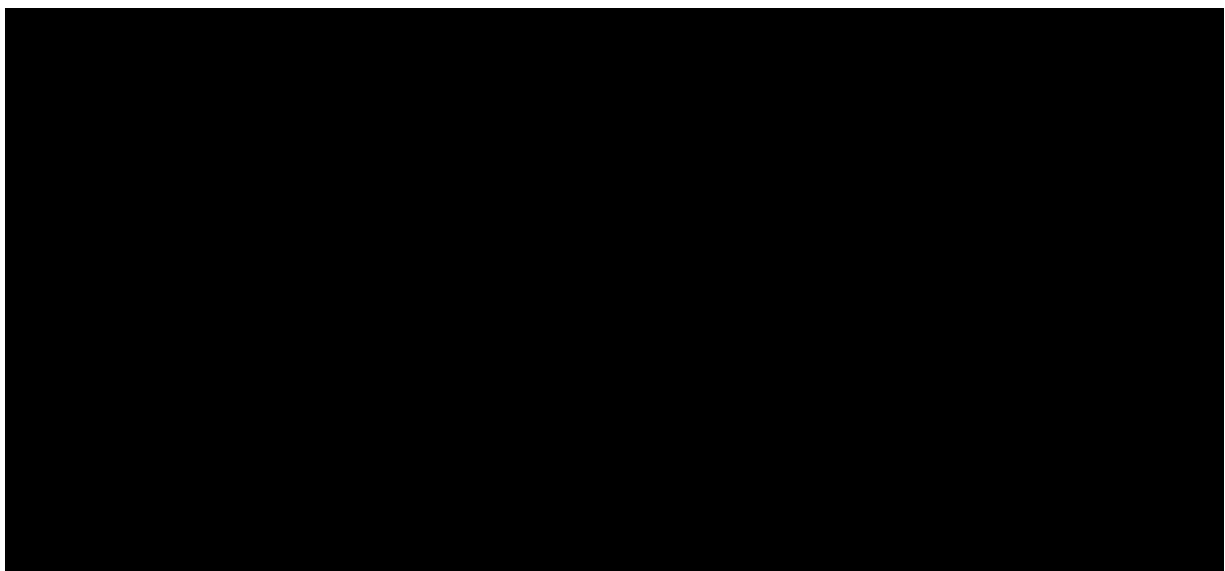
After the End of Treatment visit is completed, patients should return after an additional 4 weeks (28 days) for an End of Study visit.

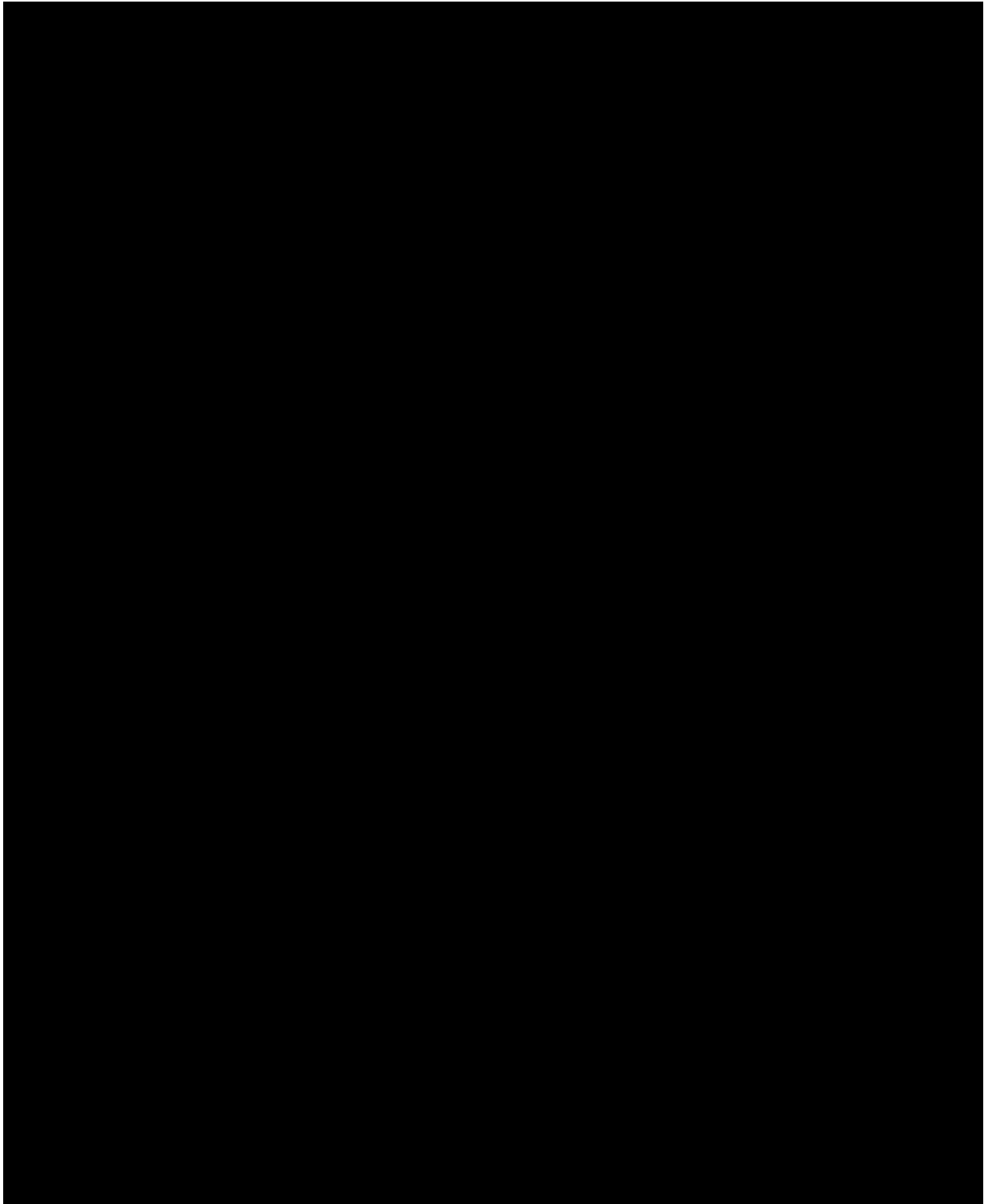
13.7 Handling of missing values/censoring/discontinuations

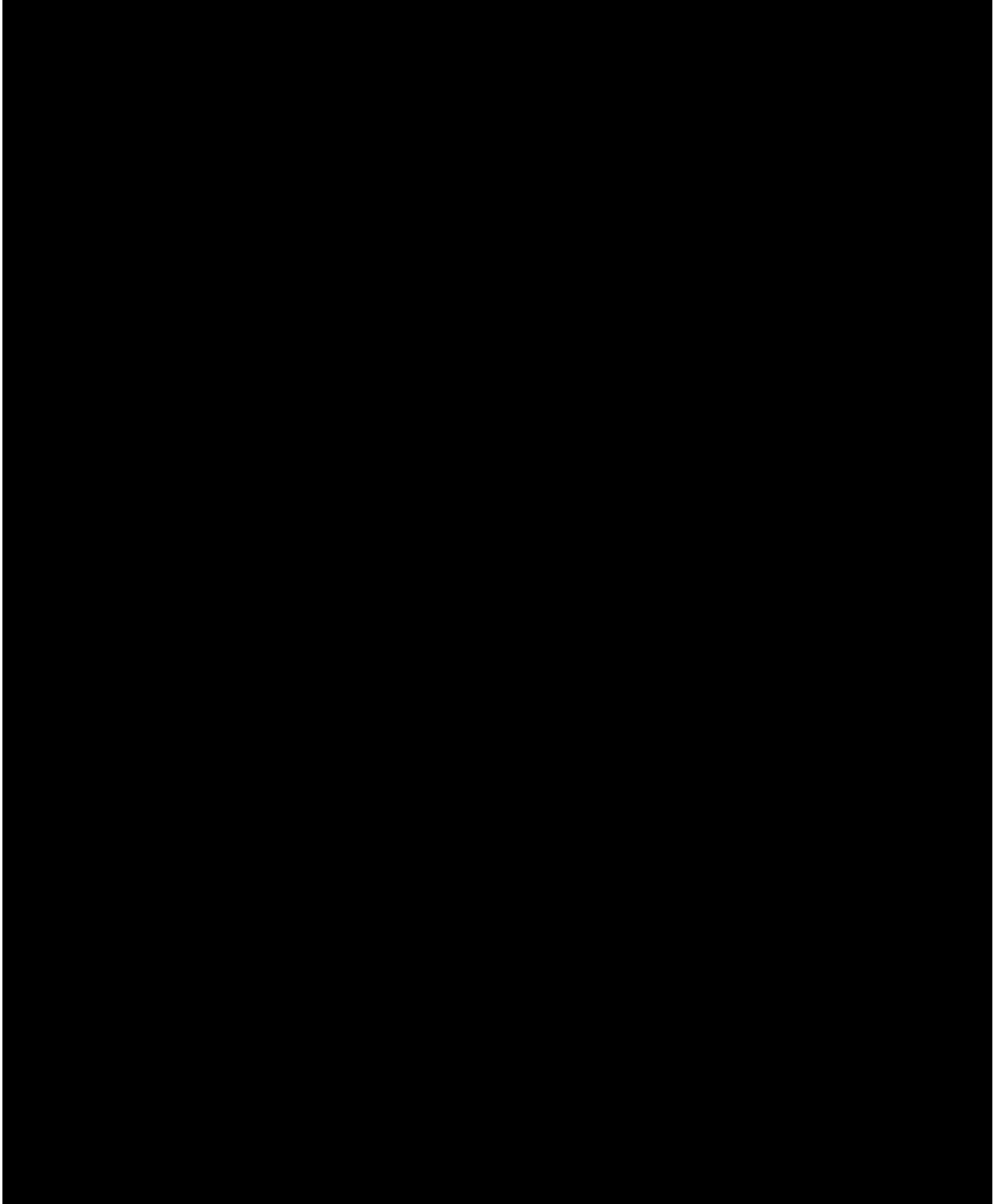
In general, unless otherwise indicated, no data imputation will be done for the missing values.

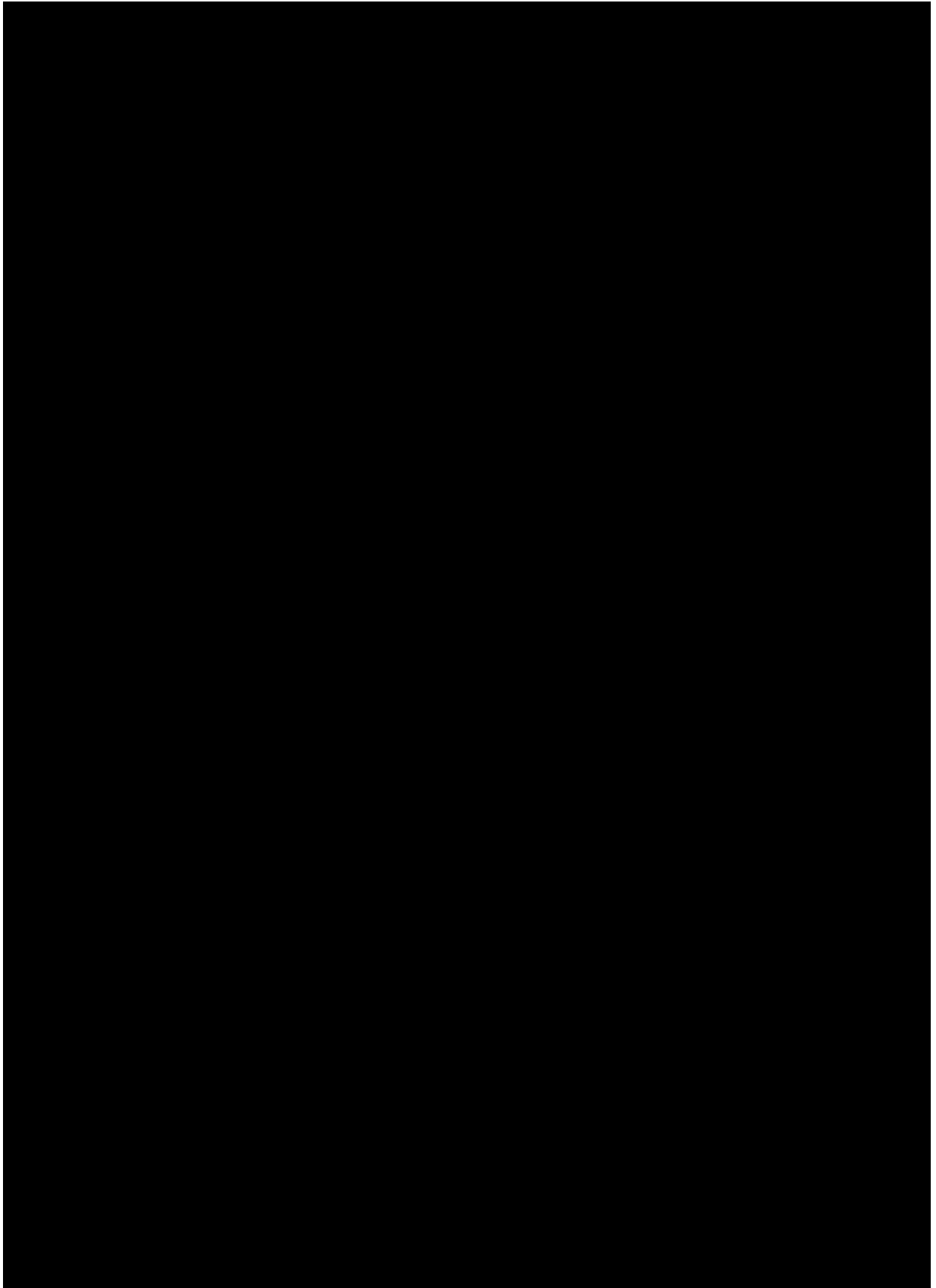
13.8 Imputation of missing and incomplete dates

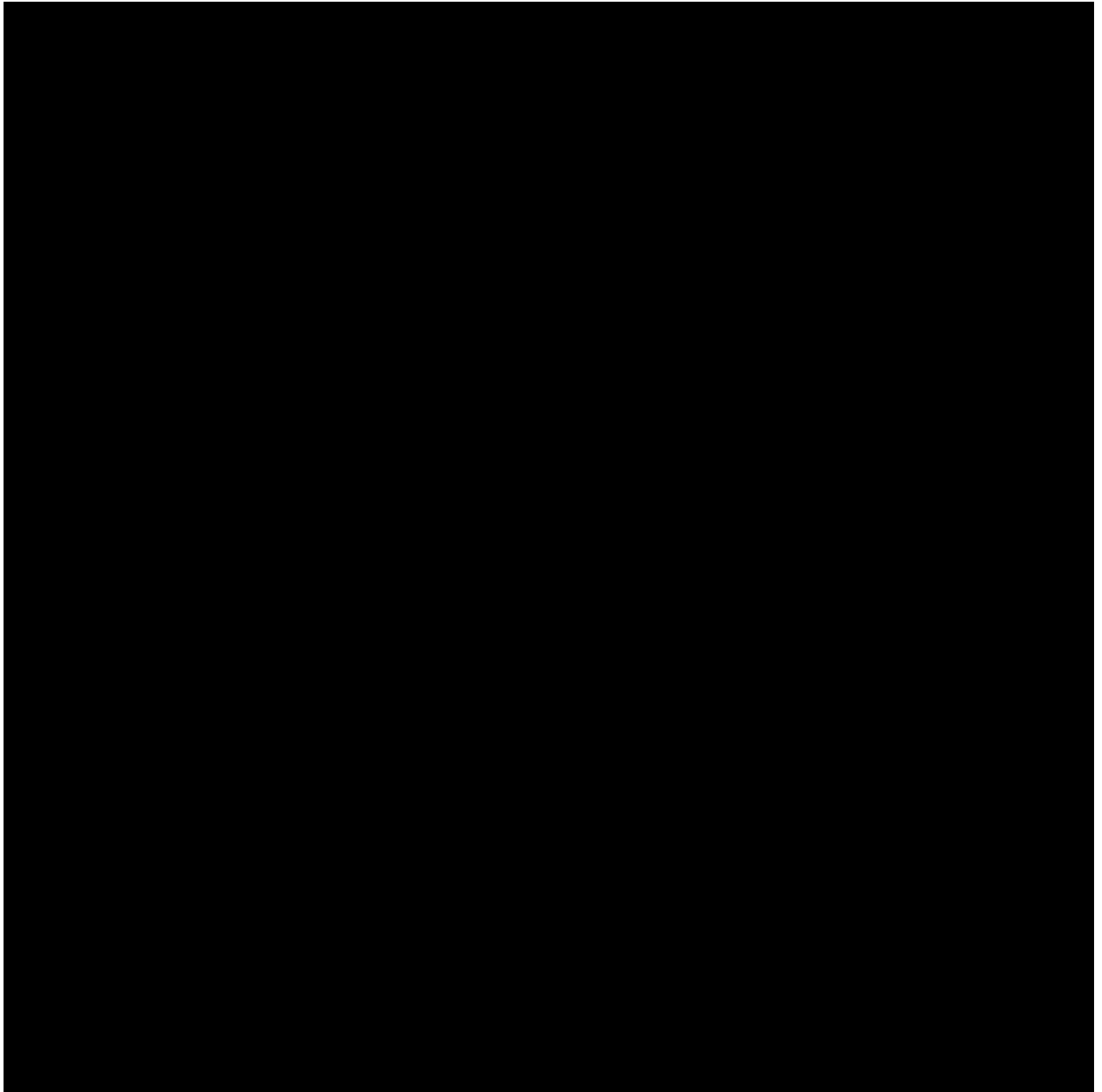
Adverse event and concomitant medication dates will be imputed per the Novartis standard tables, listings and figures (TLFs) conventions as detailed in the RAP Module 8 (Programming Specifications). All missing or incomplete dates shall however be listed in by patient data listings as recorded in the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











14 References

References are available upon request.