

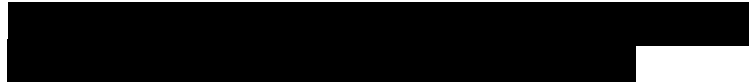
Novartis Institutes for BioMedical Research

BYM338/bimagrumab

Clinical Trial Protocol 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)

Authors:



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Notification of serious adverse events

A serious adverse event (SAE) is any event which is fatal or life-threatening, which requires or prolongs hospitalization, which is significantly or permanently disabling or incapacitating, which constitutes a congenital anomaly or a birth defect, or which is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE occurring in a subject from consent until 30 days after stopping the trial/study drug must be reported either on the paper SAE report form or via the electronic SAE form within the clinical data capture system (where available).

For SAEs reported using the paper SAE report form, the investigator will ensure that the form is completed and faxed by the investigator to the local Novartis Drug Safety and Epidemiology Department within 24 hours of learning of the occurrence of the SAE even if the SAE does not appear to be drug-related. The original SAE form, together with the fax confirmation sheet, must be kept with the case report forms at the study site.

For SAEs recorded *electronically* in the Novartis clinical data capture system, information should be entered, saved and e-signed within 24 hours of awareness of the SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology.

More details in [Section 7](#) of this protocol.

Fax numbers of local Novartis Drug Safety and Epidemiology Departments

Australia	Fax:	[REDACTED]
North America	Fax	[REDACTED]
France	Fax	[REDACTED]
Germany	Fax	[REDACTED]
Denmark	Fax	[REDACTED]
Belgium	Fax	[REDACTED]
Spain	Fax	[REDACTED]
Switzerland	Fax	[REDACTED]
Japan	Fax	[REDACTED]
Taiwan	Fax	[REDACTED]
Czech Republic	Fax	[REDACTED]
Russia	Fax	[REDACTED]
South Korea	Fax	[REDACTED]

In addition, the investigator will inform the following responsible person(s) of Novartis Translational Medicine:

[REDACTED]
[REDACTED]
(Sponsor's medical expert)

Tel. Business: [REDACTED] (direct)
Tel. Mobile phone: [REDACTED]
Email: [REDACTED]

Any update to the Novartis DS&E or personnel information required during the course of the study will be communicated directly to the relevant Investigator site(s); a specific protocol amendment should not be required.

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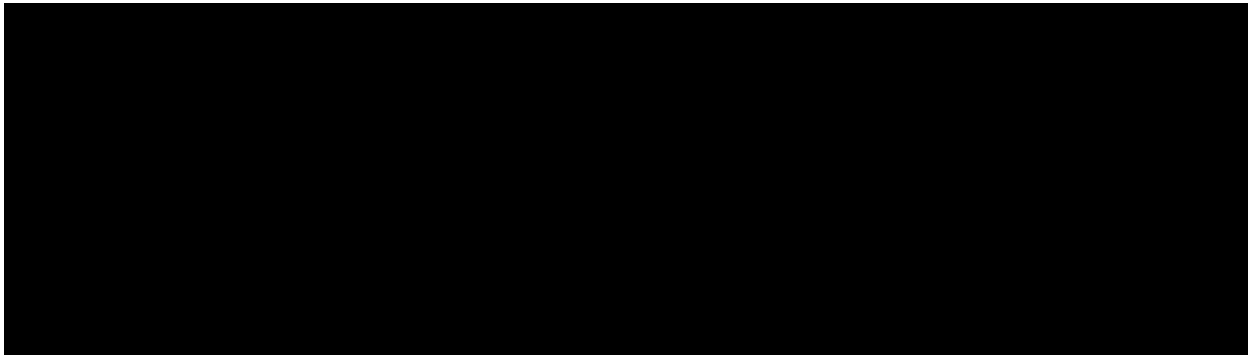
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List of abbreviations

6MWT	6 minute walk test
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	adverse event
AICD	Automated Implantable Cardioverter-Defibrillator
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ActRIIA/B	type II activin receptors A and B
ASMI	Appendicular skeletal mass/muscle index
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CMR	cardiac magnetic resonance imaging
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study
EoT	End of Treatment
EWGSOP	European Working Group on Sarcopenia in Older People
FAS	Full Analysis Set
FDA	Food and Drug Administration

FNIH	Foundation for the National Institutes of Health
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDF-11	Growth differentiation factor 11
γ -GT	Gamma-glutamyl transferase
GS	Gait speed
h	hour
HIV	human immunodeficiency virus
IA	interim analysis
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LBM	lean body mass
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LIVI	liquid in vial
LLQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
MI	Myocardial infarction
ml	milliliter(s)
MMSE	Mini Mental State Examination
ONS	Oral Nutritional Supplement
█	█
PD	pharmacodynamic(s)
█	█
█	█
█	█
█	█
PP	per protocol

PRO	Patient Reported Outcome
RBC	red blood cell(s)
REB	Research Ethics Board
RVR	Rapid ventricular rate / response
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHBG	Sex hormone-binding globulin
SI	Systems International
sIBM	Sporadic Inclusion Body Myositis
SPPB	Short Physical Performance Battery
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVT	Supraventricular tachycardia
TBL	total bilirubin
TGF- β	transforming growth factor beta
TMDD	target mediated drug disposition
TMV	thigh muscle volume
ULN	upper limit of normal
ULOQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization



Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”
Investigational treatment	<p>All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.</p> <p>This <i>includes</i> any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.</p> <p>Investigational treatment generally <i>does not include</i> protocol-specified concomitant background therapies when these are standard treatments in that indication.</p>
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy

Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal
Patient Number	A number assigned to each subject/patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 3 (October 2017)

Amendment rationale

The primary purpose of this amendment is to present [REDACTED] the resultant modifications to the protocol, and to adjust the sample size to enable program decision making at the completion of Part A. In addition, editorial revisions were made to clarify the terminology of the oral nutritional supplement and to improve understanding in other areas of the text.

[REDACTED]

The results from Part A will be used for strategic decision making within the bimagrumab program. To ensure an adequate sample size will be available for the interim analysis following Part A, the total number of patients randomized has been increased from 150 to 196. The additional patients will increase the predicted power for interpretable results based on the original calculation, using estimates of the minimum and maximum variability expected in the SPPB data.

The term “protein supplement” was used in prior versions of the protocol to describe a nutritional supplement that contained a certain amount of dietary protein and other macro- and micronutrients. In order to eliminate confusion by using more universally understood terminology, “protein supplement” has been replaced with “oral nutritional supplement” to more accurately reflect the product intended to be consumed by the patient. The actual product used should not be changed.

Changes to the protocol

[Assessment Schedule](#), [Section 3.1](#) Study design, [Section 6](#) Visit assessments [Section 13](#) Appendix 1: Sample log table – all matrices,

- Clinical chemistry samples added at Week 3, 5, and 9.

[Protocol synopsis](#)

- Updated to reflect changes throughout the protocol.

[Section 3.1](#) Study design, [Section 3.5](#) Purpose and timing of interim analyses/design adaptations, [Section 4](#) Population, [Section 5.2](#) Treatment arms, [Section 5.5](#) Treating the patient

- Total number of patients enrolled until the end of Part A was updated to 196, to include 100 patients randomized to BYM338 700 mg and 60 patients randomized to placebo.

- Total number of patients to be enrolled in Part B and randomization ratio of Part B was clarified.
- Total number of patients to be enrolled in the entire study (Parts A and B) updated to 339.
- Study Flow Diagram (Figure 3-2) clarified.

Section 3.1 Study design

- Updated to remove reference to electronic diaries.

Section 3.1.2 Interim Analysis and Section 9.4.2.1 Analysis for part-A

- The interim analysis may include additional endpoints of safety, efficacy, [REDACTED] and background treatments.

Section 3.2 Rationale for study design, Section 4.1 Inclusion criteria, Section 5.1.2 Additional study treatment, Section 5.5.3.2 Handling of other study treatments, Section 6.2 Dietary Requirement and throughout the protocol

- Protein supplementation terminology updated to oral nutritional supplementation.

[REDACTED]

Section 4.2 Exclusion criteria

- [REDACTED]
- Criterion #25 clarified to note that active infection results must be received prior to randomization.
- [REDACTED]

Section 5.5.6 Recommended treatment of adverse events

- [REDACTED].

Section 6.5.7 Mini Mental State Examination (MMSE)

- Clarified that MMSE is not required at baseline, as per the Assessment Schedule.

[REDACTED]

Section 9.4.2.1 Analysis for part-A

- Criterion 1 significant difference updated from one-sided 5% level to one-sided 2.5% level.
- The two-sided confidence interval of treatment vs placebo was updated from 90% to 95%.

Section 9.6 Sample size calculation

- Sample size calculations for Part A interim analysis updated.

Section 9.7 Power for analysis of key secondary variables

- Analysis of power for key secondary variables updated for gait speed and 6-minute walk test.

Section 15 Appendix 3: Clinically notable laboratory values

- 

Section 16 Appendix 4: Blinding and unblinding

- Footnote added to clarify that if the study is terminated following the interim analysis, blinding will follow the final database lock event guidelines.

Additional administrative clarifications and corrections have been made throughout the protocol for clarity.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (September 2016)

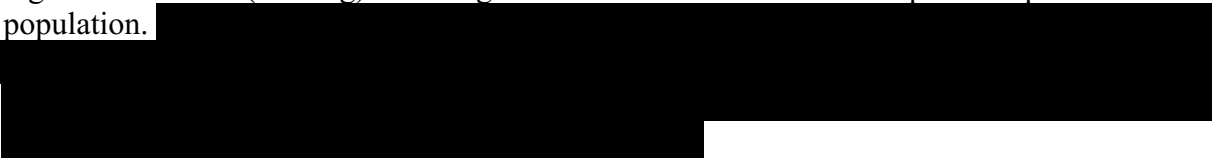
Amendment rational

The purpose of this amendment is to align the study design and endpoints with progress made in the field of sarcopenia and the bimagrumab program since the original protocol was submitted, integrate new safety data from recently completed bimagrumab studies, facilitate recruitment, and reduce patient and site burden where possible.

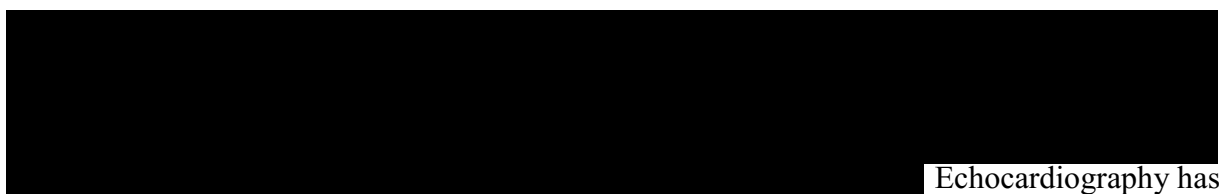
There are two key design changes in this amendment: change in the primary outcome and division of dose evaluations into two parts. The Short Physical Performance Battery (SPPB) will replace the 6-Minute Walk Test (6MWT) as the primary outcome, and the 6MWT will become a secondary outcome. This change is based on a combination of factors identified from the medical literature and observed in discussions with health authorities since the original protocol was written. The measurement properties of the SPPB are supported by an extensive history and body of literature that show a strong link between declining lower extremity functional status and adverse, clinically relevant outcomes in older adults, including falls, hospitalizations, incident disability and death ([Guralnik et al 1994](#), [Guralnik et al 1995](#), [Guralnik et al 2000](#), [Studenski et al 2011](#)). The 6MWT was chosen originally as the primary outcome based on the large, clinically relevant improvement observed in the sarcopenia proof of concept study (CBYM338X2201, unpublished data), where the SPPB was not included. In contrast to the SPPB, the 6MWT assesses mobility and is more clinically relevant in other patient populations, such as those with cardiovascular or pulmonary disease or multiple sclerosis ([Morris et al 2014](#); [ATS 2002](#); [Brown and Simnad 2016](#)).

The SPPB score and 4-meter gait speed have emerged as the predominant characteristics that define inadequate lower extremity function in older adults in general and in those with sarcopenia and frailty in particular ([Studenski et al 2014](#)). The SPPB has been used recently as the primary outcome variable in intervention trials examining functional recovery following hip fracture ([Latham et al 2014](#), [Prestmo et al 2015](#)). In a large US based study (LIFE Study) evaluating an exercise and diet intervention in older adults, the SPPB was a key outcome that demonstrated an improvement of ≥ 1 point was associated with a significant reduction in falls and the baseline score predicted onset of mobility disability ([Pahor et al 2014](#)).

The original four arm parallel design with three dose levels will become a two part study, to reduce the number of patients exposed to an experimental therapy until data are obtained that demonstrate the efficaciousness of bimagrumab to improve functional status in patients with sarcopenia, as assessed by the SPPB. This study is the first to assess the SPPB in patients with sarcopenia administered bimagrumab. Therefore, Part A will determine the effect of the highest dose level (700 mg) of bimagrumab on total SPPB score compared to placebo in this population.



Intensive (monthly) monitoring of certain safety parameters (physical exam, ECG, hematology, clinical chemistry, cardiac panel, vitamin D level, coagulation and urinalysis) is being replaced with a frequency aligned with standard clinical care, based on the absence of safety signals in the clinical program. As an example, coagulation monitoring, originally included because of observations of epistaxis with a competitor molecule using a different mechanism of action, is being reduced due to the absence of bleeding associated adverse events reported in the bimagrumab program.



Echocardiography has been used in studies with healthy volunteers and patients to monitor changes in cardiac structure and function in response to preclinical findings of a compensatory hypertrophy.



Requirement for adjudication of orthopedic complications has also been removed from the protocol. This adjudication process was designed for a parallel indication (hip fracture) and the events to be adjudicated do not apply to a sarcopenia population.

While adequate nutrition and body weight stability remain important, comprehensive diet assessment beyond qualification will only be required if there is an indication of malnutrition from another assessment or if there is a change in body weight of $\pm 5\%$ from baseline.

Revisions to the inclusion and exclusion criteria should broaden participant eligibility without compromising safety. Minimum body weight will be lowered from 40 kg to 35 kg to accommodate the normal lower body weight of older adults in Asian countries. Particular conditions often seen in older adults (e.g., depression) that are well-managed may be considered if the patient is able to comply with all study procedures. In addition, the Mini Mental State Examination (MMSE) score for inclusion into the study has been lowered from 24 to 21 to include patients with mild cognitive impairment who are able to comply with study activities and to accommodate a limitation of the instrument in people with lower education levels, experienced in several countries. Other criteria that were overlapping or not clearly described have been clarified.

[REDACTED]

[REDACTED] In line with decreasing the study burden for patients, the frequency of efficacy [REDACTED] assessments has also been reduced.

[REDACTED]

At the time of this amendment, approximately 65 patients have been enrolled in the study. All patients enrolled in the study prior to this amendment will continue on the treatment arm they were randomized to, but will be switched to the new assessment schedule at their next study visit (assessment schedule for Parts A and B are the same). Patients who have undergone a baseline echocardiogram under a prior version of the protocol will have a follow up assessment at study end of treatment (EOT). All patients who receive study drug will be included in the safety and efficacy analyses as described in the analysis plan in this protocol.

Changes to the protocol

Title Page

- Study branding (InvestiGAIT) added to study title.
- Removal of ‘parallel group’ in line with the new study design.

Protocol Synopsis

- Amended to reflect changes throughout the protocol.

Assessment Schedule

- Elimination of the following assessments:
 - Echocardiography (will only be performed at EOT for patients enrolled prior to this amendment who have received a baseline scan). A footnote (#12) has been added to specify the same.
 - FSH, LH and Sex hormone-binding globulin (SHBG)
 - Coagulation parameters
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]

- Reduction in frequency of the following assessments:
 - Physical examination (removed at visits 102, 103, 105 and 106).
 - Height (removed at EOS).
 - Body temperature, blood pressure / pulse rate removed at visit 101 in order to avoid duplication where visits are combined.
 - Electrocardiogram (removed at visits 101, 102, 103, 105, 106 and EOS).
 - Hematology and clinical chemistry (removed at visits 101, 103, 105 and 106 but added at visit 104).
 - Testosterone and urinalysis (now only performed at screening (visit 1) for eligibility).
 - Cardiac panel (removed at visits 101, 102 and 103).
 - Vitamin D quantification (removed at visits 103, 105 and EOS but added at visit 104).
 - 6 minute walk test (removed at visits 102, 103, 105, 106 and EOS).
 - [REDACTED]
 - SPPB (removed at visits 102, 105 and EOS).
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - Diet assessment (removed at visits 102, 103, 104, 105 and 106 unless malnutrition is indicated or a change in weight of $\pm 5\%$ occurs). A footnote (#11) has been added to specify this.
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Footnote #9 added to state that visits 2 & 3 (run-in) and visits 5 & 101 (baseline and Day 1) may be combined where feasible and considered safe for the patient, in order to reduce the study burden for patients.

Introduction (Background)

- Human safety and tolerability data updated with latest information.
- Human pharmacodynamic data with latest information.

Objectives

- Primary objective amended to SPPB and 6MWT moved to secondary objectives.
- [REDACTED]
- Minor changes or clarifications to other objectives.

Section 3.1 Study design

- Amended to provide details of Parts A and B purpose and design.
- Details of interim analysis added.
- Study design diagrams amended.
- Drug treatment assignment updated to include Parts A and B.
- Removal of reference to timing of specific assessments throughout to simplify and avoid inconsistencies with other protocol sections.
- Text added to state that visits 2 & 3 (run-in) and visits 5 & 101 (baseline and Day 1) may be combined.
- Adjustment of requirement for observation following dosing.

Section 3.2 Rationale for study design

- Updated with rationale for changes to population, 2-part study design and study outcomes.

Section 3.3 Rationale for dose/regimen, duration of treatment

- Updated with rationale for dose levels and changes in body weight requirements.

Section 3.5 Purpose and timing of interim analyses/design adaptations

- Added information on the purpose and details of the planned IA.

Section 3.6 Risks and benefits

- Updated risks in line with new study data, including readouts from [REDACTED] and hormone safety study (CBYM338X2108).

Section 4.1 Inclusion Criteria

- Inclusion criteria #4: clarification that Appendicular skeletal muscle index (ASMI) eligibility should be based on the central reading and update to allow possibility of other Asian countries in addition to the ones previously considered.
- Addition of inclusion criterion #5: SPPB score of ≤ 9 at screening, to reduce the risk of a ceiling effect on this endpoint.
- Inclusion criterion #6 (previously #5):
 - lower weight limit reduced to 35.0 kg based on feedback from sites in Japan and in order to align this criterion throughout the bimagrumab program.
 - BMI lower limit is reduced to 15.0 kg/m² based on feedback from sites in Japan and in order to align this criterion throughout the bimagrumab program.
 - BMI upper limit is raised to 32.0 kg/m² based on feedback from investigators.

Section 4.2 Exclusion Criteria

- Addition of statement allowing repeat of out of range values once prior to run-in and clarification that laboratory parameters are assessed centrally.
- [REDACTED]
- Exclusion criterion #1: clarified to ensure that subjects with well managed musculoskeletal pain are not excluded.

- Exclusion criterion #2: clarified that subjects with adequately treated depression are not excluded.
- Exclusion criterion #4 modified to incorporate muscle diseases from exclusion criterion #11 (e.g., myopathy), and exclusion #11 deleted.
- Exclusion criterion #6: addition of Systems International (SI) units
- Exclusion criterion #7: lower limit for hemoglobin at screening changed to 10.0 g/dL for women, to account for the difference in normal ranges between men and women and additional of SI units.
- [REDACTED]
- Exclusion criteria #11 (previously #13): clarified that subjects with well managed gastrointestinal diseases may be included.
- Exclusion criterion #14 (previously #17): amended to remove hypertrophic cardiomyopathy based on latest data on cardiac safety.
- [REDACTED]
- Exclusion criterion #15, 16, 17 and 18 (previously #'s 18, 19, 20 and 22): amended cardiac exclusions to reflect the latest safety information and to align with the most recent exclusion criteria in the bimagrumab program.
- Exclusion criterion #21 has been removed. This criterion had been utilized as a standard exclusion in healthy volunteer studies. [REDACTED]
- [REDACTED]
- Exclusion criteria #29 (previously #34): clarification that only regular (e.g. daily) assistance with basic activities of daily living (ADL) is excluded and that assistance with instrumental ADL is permitted.
- Exclusion criterion #30 (previously #36) amended to lower the MMSE cutoff to 21.
- Exclusion criteria #33 (previously #39): amended text to clarify that only systemic corticosteroids are excluded.
- [REDACTED]
- [REDACTED]

Section 5.1.2 Additional study treatment

- Updated to clarify that nutritional supplements are required for the study.

Section 5.2 Treatment arms

- Updated with details of Parts A and B.

Section 5.3 Treatment assignment

- Clarification that the randomization number is for internal use only.

Section 5.4 Treatment blinding

- Clarification of a fourth method to maintain the blind in the study, i.e. any potentially unblinding parameters will not be made available to the patient, site or study team.

Section 5.5.1 Patient numbering

- Amendment of randomization number text in line with the actual IRT process in use for the study.
- Addition of details on randomization schemes prior to amendment, and following amendment (Parts A and B).

Section 5.5.2 Dispensing the study treatment

- Updated to align with other bimagrumab studies and to remove duplication of text.

Section 5.5.3.2 Handling of other study treatments

- Added clarification of vitamin D supplementation

- [REDACTED]

Section 5.5.6 Recommended treatment of adverse events

- The recommendation for the treatment of acute allergic reactions has been moved to Section 5.5.6 (previously included in Section 5.5.7).

Section 5.5.8 Concomitant treatment

- Updated in line with the latest protocol template language

Section 5.5.10 Discontinuation of study treatment

- Update of study stopping rules to remove hypersensitivity reaction in alignment with other bimagrumab studies and to avoid overlap with the second stopping criteria.
- Update of individual subject withdrawal rules: [REDACTED]

Section 6 Visit assessments

- Expansion of the visit windows based on feedback from sites and in line with other studies in the bimagrumab program.
- Text added to state that visits 2 & 3 (run-in) and visits 5 & 101 (baseline and Day 1) may be combined.
- Order of assessments updated according to new assessment schedule.

Section 6.1 Dietary, fluid and other restrictions

- Removal of restriction on alcohol during the study as this is primarily a requirement in healthy volunteer studies.
- Removal of requirement for fluid intake due to reduced need for urine collection.

Section 6.2 Dietary Requirement

- Adjustment of the requirements for nutritional assessment and counselling – this will now only be required if a change in weight of $\pm 5\%$ is observed.

Section 6.5 Efficacy / Pharmacodynamic assessments

- Re-ordering of sections to reflect change in study outcomes.

Section 6.5.5 (previously Section 6.5.6) Total lean body mass and appendicular skeletal mass index (ASMI) assessed by DXA

- Clarification that the images acquired will be independently reviewed by a central reading vendor.

Section 6.5.7 Mini Mental State Examination (MMSE)

- Adjustment of the score required for eligibility to 21

Section 6.6.4 Laboratory evaluations

- Removal of coagulation parameters
- Removal of FSH, LH and SHBG from hormone panel

Section 6.6.6 Echocardiography

- Removal of section

[REDACTED]

Section 7.1 Adverse events

- Addition of new field on AE eCRF documenting the AE classification.
- Addition of text regarding collection of information on adverse events of special interest.

Section 8.4 Data Monitoring Committee

- Amendment of language due to new fully unblinded review of data by DMC.

Section 8.5 Adjudication Committee

- Removal of requirement for orthopedic adjudication which does not make sense in this population.

Section 9 Data analysis

- All sections updated in line with new study outcomes and associated analyses.

Section 12 References

- Addition of 19 new references

Appendix 1: Sample log table – all matrices

- [REDACTED]
- Removal of urinalysis sampling at V4, 101, 103, 105, EOT and EOS.
- [REDACTED]
- [REDACTED]

Appendix 3: Clinically notable laboratory values

- Addition of this new appendix to define the criteria to be used as a guidance for notable abnormalities of key laboratory tests.
- [REDACTED]

Minor changes have been made throughout the protocol to improve clarity.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the participating Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent Form (ICF) that takes into account the changes described in this protocol amendment. Novartis will provide an updated model ICF to sites.

Amendment 1 (May 2015)

Amendment rationale

The purpose of this amendment is to correct minor inconsistencies identified during health authority and ethics committee reviews, and to provide some clarifications on study assessments.

At the time of implementing this amendment, 3 patients had begun treatment; none were affected by changes made to the protocol. The changes described in this amendment do not affect the objectives of the study, impact the safety of the subjects or change the analysis of the study data. Some adjustments have been made to inclusion and exclusion criteria as a result of experience so far with the population required for this study.

Changes to the protocol

Protocol Synopsis

- Amended to reflect changes throughout the protocol

Assessment Schedule

- Addition of visit windows.
- Addition of Informed Consent to assessment schedule (already present in protocol but previously omitted from assessment schedule).
- [REDACTED]
- [REDACTED]
- Amendments due to change in follow-up period for patients continuing to the extension:
 - Movement of height measurement and [REDACTED] from EoS visit to EoT visit to provide data for extension study baseline.
 - Removal of footnote for prematurely discontinuing patients to only return for EoS visit.
 - Addition of footnotes stating that EoT visit will occur 4 weeks after last dose and will be the last visit for patients continuing to the extension study, and EoS visit will occur 4 weeks after EoT visit except for patients continuing to the extension study.
- ‘Study Completion information’ changed to ‘Phase Completion’ and assessment added at Baseline V2 and EoT to be in compliance with current database requirements.

Section 3.1 Study design

- Correction to add follow-up period to the diagram.
- Correction to assessments at Day 1 due to inconsistency with the Assessment Schedule.
- Addition of information on observation period following dosing on ‘Other Dosing Visits – Days 29, 57, 85, 113 and 141’.

- Explanation that patients continuing to the extension study will move directly from EoT visit to Visit 1 of the extension.
- Clarification that EoS visit will occur only for those patients discontinuing from the study prematurely or those not continuing to the extension study.
- Addition of information on planned extension study.

Section 3.6.1 BYM-related risks

- Text describing a standardized dermatology assessment removed. This is no longer needed as adverse event recording is sufficient.

Section 4.1 Inclusion criteria:

- Inclusion criterion #6: Dietary criteria to apply only at baseline, allowing correction of nutritional deficiency during screening period if appropriate.

Section 4.2 Exclusion criteria:

- Exclusion criterion #5: Amendment to state that intraocular surgery or intraocular laser procedures for refractive corrections are excluded.
- Exclusion criterion #6: Vitamin D criteria to apply only at baseline, allowing correction of low vitamin D levels at screening if appropriate.
- Exclusion criterion #11: Addition of inclusion body myositis in the examples for exclusion.
- Exclusion criterion #12: Addition of other systemic autoimmune disease requiring immunosuppressive therapy or corticosteroids to exclusion.
- Exclusion criterion #35: Amendment to allow patients receiving testosterone replacement therapy.
- Exclusion criterion #39: Clarification that medication exclusion applies prior to screening.
- Exclusion criterion #40: Clarification to exclude patients taking a systemic VEGF inhibitor and the acceptability of intravitreal use.

Section 5.5.1 Patient numbering

- Correction and clarification of randomization process with IRT system.

Section 5.5.3 Handling of study treatment

- Adjustment of concomitant vitamin D requirements to allow for sourcing in all countries.



Section 5.5.10 Discontinuation of study treatment

- Amendment of study completion requirements for patients who discontinue treatment early to ensure compliance with required safety follow-up timelines and consistency with the planned extension study.

Section 6.2.2 Nutritional supplement

- Adjustment of concomitant vitamin D requirements to allow for sourcing in all countries.
- Addition of low vitamin D correction with a loading dose.

Section 6.5.3 6 minute walk test

- Text added to clarify the conditions under which a test could be repeated.

Section 6.5.6 Patient Reported Outcomes

- Clarifications of PRO terminology

- [REDACTED]

Section 6.6.2 Vital signs

- Clarification that vital signs should be measured on the same arm at each visit where possible.

Section 6.6.4 Laboratory evaluations

- Clarification of situations where repeat assessments can be performed.
- Addition of creatinine to the chemistry panel to support the evaluation of eGFR for inclusion/exclusion.

Section 6.6.7 Pregnancy

- Removal of requirement for sexually active men to use a condom during the course of the study in alignment with the rest of the bimagrumab program, as there is no associated risk with this antibody.

Section 8.5 Adjudication committee

- Addition of orthopedic event adjudication

Section 10.2 Informed consent procedures

- [REDACTED]

Appendix 1: Sample log table

- Corrections to blood volumes following final setup and reconciliation with the central lab, and correcting an error which occurred during insertion of the table. [REDACTED]

- [REDACTED]

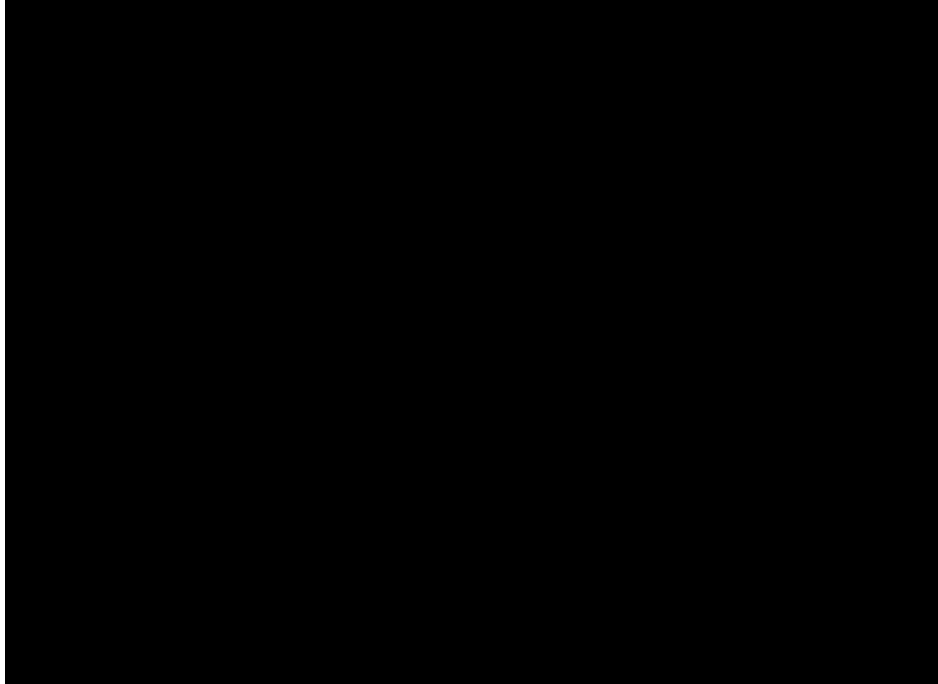
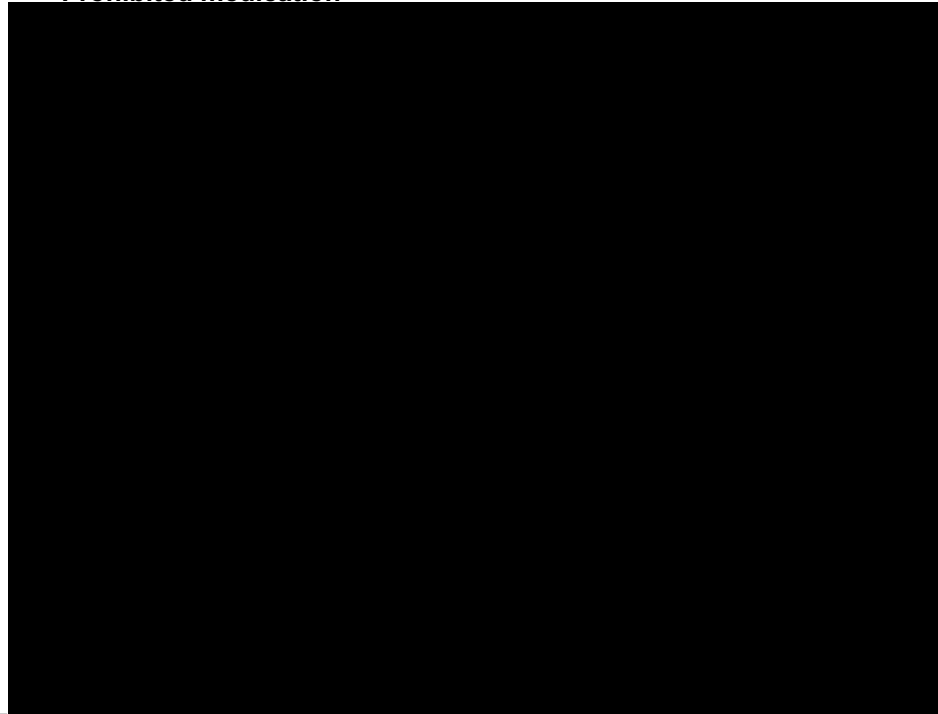

Protocol synopsis

Protocol number	CBYM338E2202
Title	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).
Brief title	Dose range finding study to assess multiple doses and evaluate safety and tolerability of bimagrumab in patients with sarcopenia.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>The purpose of this study is to determine the efficacy of repeat dosing with multiple dose levels of bimagrumab on patient function, skeletal muscle mass and strength in older adults with sarcopenia. In addition, this study will generate data on the safety, tolerability, [REDACTED] of bimagrumab in older adults with sarcopenia.</p> <p>The randomized, parallel group, placebo-controlled design will allow an unbiased comparison between 3 different dose regimens of bimagrumab and placebo on changes in muscle quantity and patient physical function in a population of older adults with sarcopenia</p>
Primary Objective(s)	<ul style="list-style-type: none"> 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.
Secondary Objectives	<ul style="list-style-type: none"> To assess the effect of multiple doses of bimagrumab on the safety and tolerability of bimagrumab administered over 24 weeks as measured by vital signs, clinical laboratory values, electrocardiogram (ECG), echocardiogram (in a limited number of patients), and adverse events (AE) compared to placebo 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) 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, assessed by the change from baseline to week 25 compared to placebo in older adults with sarcopenia.

Study design	<p>A two-part, randomized, double-blind, placebo-controlled, parallel group study design with approximately 339 older adults with sarcopenia assigned to one of four treatment groups: placebo, bimagrumab 70 mg, bimagrumab 210 mg, or bimagrumab 700 mg.</p> <p>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 subjects will be introduced to a 3 times per week exercise program, daily vitamin D and oral nutritional supplementation, and the performance-based endpoints. Towards the end of the run-in period, subjects will be re-assessed for eligibility (utilizing the baseline eligibility criteria) and qualified subjects will enter the treatment phase to receive six monthly doses of assigned study drug.</p>
Population	<p>The study population will be community-dwelling men and women ages 70 years and older meeting the criteria for sarcopenia as defined by the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al 2010) and Asian Working Group for Sarcopenia (Chen et al 2014).</p>
Inclusion criteria	<ol style="list-style-type: none"> 1. Written informed consent must be obtained before any assessment is performed; 2. Men and postmenopausal women aged 70 years or older at screening with self-reported mobility limitations such as difficulty standing up from a chair, walking for longer than 10 minutes on a flat surface or climbing a flight of stairs; <ul style="list-style-type: none"> • Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 3. Gait speed over 4 meters of <0.8 m/s but ≥ 0.3 m/s at screening and baseline; 4. Appendicular skeletal muscle index (skeletal muscle in kg/ height in m^2) by DXA based on central reading: <ul style="list-style-type: none"> • ≤ 7.26 kg/m^2 for men and ≤ 5.5 kg/m^2 for women to be assessed during screening. • ASIAN COUNTRIES ONLY: ≤ 7.0 kg/m^2 for men and ≤ 5.4 kg/m^2 for women to be assessed during screening; 5. Total SPPB score of ≤ 9 at screening and baseline; 6. Weigh at least 35.0 kg to participate in the study and have a body mass index (BMI) within the range of 15.0 – 32.0 kg/m^2; 7. Usual dietary intake ≥ 20 kcal/kg body weight and ≥ 0.8 g protein/kg per day over the 4 weeks prior to baseline estimated by an established method of diet assessment (i.e. 24 hour recalls, food records or similar)

Exclusion criteria	<p>Medical conditions limiting performance of physical assessments</p> <ol style="list-style-type: none">1. History of a lower limb fracture (e.g. femur, tibia) within the past 6 months with persistent negative impact on lower extremity function or any significant impairment or disease adversely impacting gait (e.g. intermittent claudication in advanced peripheral vascular disease, spinal stenosis, or severe osteoarthritis of the knee or hip with joint pain not controlled with medication/injections that adversely impacts mobility);2. Confirmed diagnosis of significant psychiatric disease (e.g. dementia/Alzheimer's disease, schizophrenia, depression or bipolar disorder). Individuals with adequately treated depression are eligible for enrollment;3. A Patient Health Questionnaire – 9 (PHQ-9) score ≥ 10 at screening;4. Neurological injury/disorder with significant persistent functional deficit (e.g. stroke with hemiparesis, spinal cord injury, muscular dystrophy, polymyositis, dermatomyositis, myopathy/myositides, myasthenia gravis, Parkinson's disease, peripheral polyneuropathy);5. Intraocular surgery and laser procedures for refractive correction within 6 months prior to screening;6. Vitamin D deficiency defined as 25-OH-vitamin D levels < 12.0 ng/mL (30nmol/L) at baseline;7. Hemoglobin concentration below 11.0 g/dL (110g/L) for men or below 10.0 g/dL (100g/L) for women at screening. <p>Medical conditions associated with muscle loss</p> <ol style="list-style-type: none">8. Chronic kidney disease [estimated glomerular filtration rate (GFR) < 30 mL/min];9. History of confirmed chronic obstructive pulmonary disease with a severity grade > 2 on the Medical Research Council Dyspnea Scale;10. Confirmed rheumatoid arthritis or other systemic autoimmune disease requiring immunosuppressive therapy or corticosteroids > 10mg/d prednisone equivalent, acquired immunodeficiency syndrome (AIDS), or type 1 diabetes mellitus;11. History of or ongoing gastrointestinal diseases known to cause malabsorption of protein or energy, such as inflammatory bowel disease, celiac disease, short bowel syndrome, pancreatic insufficiency. Individuals in which the disease is well controlled with medication/enzyme supplements (e.g., pancreatic insufficiency) or dietary modification (e.g., celiac disease) are eligible for enrollment; <p>Liver [REDACTED] related conditions</p> <ol style="list-style-type: none">12. Abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin (except Gilbert's Disease), [REDACTED]. The investigator should be guided by the following criteria:<ul style="list-style-type: none">• Any single transaminase may not exceed 3x the upper limit of normal (ULN). A single parameter elevated up to and including 3x ULN should be re-checked as soon as possible, and always prior to enrollment/randomization, to rule out any lab error.• If the total bilirubin concentration is increased above the ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27μmol/L).• [REDACTED]
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	<p>[REDACTED]</p> <p>13. Known history or presence of severe active acute or chronic liver disease (e.g., cirrhosis) or conditions with hepatotoxic potential (e.g. known gallbladder or bile duct disease, acute or chronic pancreatitis);</p> <p>Cardiovascular conditions</p> <p>14. Confirmed diagnosis of heart failure classified as New York Heart Association Class III and IV (e.g. dilated cardiomyopathy);</p> <p>15. Myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention (e.g. angioplasty or stent placement), or deep vein thrombosis/pulmonary embolism within 12 weeks of screening. Patients with current/active unstable angina are excluded;</p> <p>16. Severe cardiac valve disorders or defects (e.g. aortic or mitral stenosis);</p> <p>17. Severe pulmonary hypertension uncontrolled with medication;</p> <p>18. Clinically significant cardiac arrhythmia requiring medical intervention in the past 3 months (e.g. SVT, atrial fibrillation with RVR, AICD with discharge);</p> <p>Other medical or living conditions</p> <p>19. History of hypersensitivity to therapeutically administered antibodies.</p> <p>20. Chest pain, severe shortness of breath, or occurrence of other safety concerns during the screening or baseline assessments.</p> <p>21. Lack of peripheral venous access</p> <p>22. Active cancer (i.e., under current treatment), or cancer requiring treatment in the last 5 years excluding nonmelanoma skin cancers or cancers with excellent prognosis (e.g., early stage prostate or breast cancer, carcinoma in situ of the uterine cervix);</p> <p>23. Significant coagulopathy, platelet count less than 75,000/mm³;</p> <p>24. Active systemic infection requiring hospitalization or treatment with i.v. anti-infectives or antibiotics within 4 weeks of screening;</p> <p>25. Any chronic active infection (e.g., HIV, hepatitis B or C, tuberculosis, etc), to be confirmed prior to randomization. Subjects receiving chemoprophylaxis for latent tuberculosis infection are eligible for the study;</p> <p>26. Active alcohol/drug abuse, or alcohol/drug treatment < 12 months prior to screening; subjects having successfully completed an alcohol/drug treatment program >12 months prior to screening with sustained abstinence are eligible;</p> <p>27. Subject has any medical condition or laboratory finding during screening (e.g. an unexplained or clinically significant lab result), which, in the opinion of the investigator may interfere with participation in the study, might confound the results of the study, or pose an additional safety risk in administering bimagrumab;</p> <p>28. Subject plans to move out of the study area within 12 months or be out of study area for > 4 weeks continuously;</p> <p>29. Individuals who require routine and regular (e.g., daily) assistance from another person to complete one or more basic activities of daily living (basic ADL; bathing, dressing, toileting, feeding, grooming) regardless of where they reside. Assistance with instrumental ADL (i.e., shopping, meal preparation, housework) is permitted;</p>
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	<p>30. Subjects with a Mini Mental State Examination score < 21 at screening;</p>  <p>Prohibited medication</p> 
Investigational and reference therapy	Placebo, bimagrumab 70 mg, bimagrumab 210 mg, or bimagrumab 700 mg
Efficacy assessments	<ul style="list-style-type: none">• Short Physical Performance Battery (SPPB) to assess functional status• 6 minute walk test (6MWT) to assess functional status• 

	<ul style="list-style-type: none"> • Gait speed (GS) to assess functional status • Total lean body mass (LBM) and appendicular skeletal mass index (ASMI) assessed by DXA to measure lean body mass and skeletal muscle mass of the arms and legs, respectively. • Patient reported outcome questionnaires
Safety assessments	<ul style="list-style-type: none"> • Physical examination • Vital signs (heart rate, blood pressure) • Height and weight • Laboratory evaluations • Urinalysis • ECG • Echocardiography (at EOT only for patients enrolled prior to this amendment who have a baseline scan) • [REDACTED] • [REDACTED] • [REDACTED]
Other assessments	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED]
Data analysis	<p>[REDACTED]</p> <p>This is a two part study. Part-A will investigate the presence of a positive effect of maximum bimagrumab dose (700 mg) over placebo in change from baseline SPPB score at week 25. A positive effect of bimagrumab will be defined as a statistically significant effect over placebo and a clinically relevant improvement of ≥ 1 unit increase from baseline compared to week 25.</p> <p>[REDACTED]</p>
Key words	<p>Dose range finding study, effect, safety and tolerability, bimagrumab, sarcopenia, muscle, physical function</p>

Assessment schedule

Study Phase	Screening	Run-In					Treatment												Follow-up								
		Baseline																	EoT	EoS							
Visit Numbers ¹	1	2*	3*	4	5*	101*	1015	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	
Month	-2			-1		1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Week	-	-	-	-	-	1		3	5	9	13	17	21	25	29												
Day	-50 to -30	-29 to -23	-22 to -16	-15 to -10	-5 to -1	1	15	29	57	85	113	141	169*	197**													
Visit Window	-	-	-	-	-	+ 2 days	+ 2 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	+ 4 days	
Hours	-	-	-	-	-	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0
Informed Consent	X*																										
Inclusion / Exclusion criteria ²	X				X																						
Relevant med. hist. / Current med. cond. ²	X				X	X		X		X		X		X		X		X		X		X		X		X	
Concomitant Meds / Therapies		as required												as required													
Demography	X																										
Physical examination	X				X					X				X						X				X		X	
Body weight	X				X			X		X			X		X			X		X			X		X		
Body height	X																							X			
Body temperature	X				X			X		X			X		X			X		X			X		X		
Blood pressure / Pulse rate (sitting)	X	X			X			X		X			X		X			X		X			X		X		
Electrocardiogram (ECG)	X				X								X											X			
Echocardiography ¹²																								X*			
Hepatitis and HIV screen	X																										
Alcohol test	X																										
Drug screen	X																										
Hematology	X				X*								X										X		X		
Clinical Chemistry	X				X*		X	X		X			X										X		X		
Testosterone	X																										
TSH	X																										
Cardiac Panel	X												X										X		X		
Vitamin D quantification	X				X*								X										X				
Urinalysis	X																										
Supervised exercise		as required												as required													
Home-based exercise		as required												as required													

¹ Visit structure given for internal programming purpose only

² Review of inclusion and exclusion criteria and current medical conditions is required at Screening AND Baseline

³ In case of a suspected allergic hypersensitivity reaction sampling will be conducted as required (i.e. at any study visit)

*For randomized patients: from the time of signing informed consent until EoS

**Time of signing informed consent until 30 days after subject has stopped study participation

⁴ Laboratory results must be confirmed prior to dosing on Day 1

⁷ Blood sample to be drawn pre-dose and at the end of infusion after flushing

* Adjacent visits may be combined where feasible and considered safe

¹² Only for patients who have received a baseline scan under protocol v01

¹¹ Informed consent may be obtained prior to V1

* EoT visit should be scheduled approx. 4 weeks after last dose. This is the final visit for patients continuing to the extension study

** EoS visit should be scheduled approx. 4 weeks after EoT visit unless patient is continuing to the extension study

Study Phase	Screening	Run-In					Treatment										Follow-up								
		Baseline					101*		105		102		103		104		105		106		EoT		EOS		
Visit Numbers ¹	1	2*	3*	4	5*	101*	105	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	
Month	-2	-1					1		3		5		9		13		17		21		25		29		
Week	-	-					1		3		5		9		13		17		21		25		29		
Day	-50 to -30	-29 to -23	-22 to -16	-15 to -10	-5 to -1	1		15		29		57		85		113		141		169*		197**			
Visit Window	-	-	-	-	-	+ 2 days		+/- 2 days		+/- 4 days		+/- 4 days		+/- 4 days		+/- 7 days		+/- 7 days		+/- 7 days		+/- 7 days			
Hours	-	-	-	-	-	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0	pre-DOSE	0
6 minute walk test	X		X		X								X										X		
Short physical performance battery	X		X		X							X		X					X				X		
Lean Body Mass and Appendicular skeletal mass index by DXA	X			X									X										X		
Randomization						X																			
Drug administration						X		X		X		X		X		X		X		X		X		X	
Diet assessment / nutritional status	X			X				X ^{††}		X ^{††}		X ^{††}		X ^{††}		X ^{††}		X ^{††}		X ^{††}		X ^{††}		X ^{††}	
Adverse Events ⁴																									
Serious Adverse Events ⁵																									
Comments																									
Phase Completion					X																		X	X	

¹ Visit structure given for internal programming purpose only

² Review of inclusion and exclusion criteria and current medical conditions is required at Screening AND Baseline

³ In case of a suspected allergic hypersensitivity reaction sampling will be conducted as required (i.e. at any study visit)

⁴ For randomized patients: from the time of signing informed consent until EOS

⁵ Time of signing informed consent until 30 days after subject has stopped study participation

[†] Laboratory results must be confirmed prior to dosing on Day 1

^{††} Blood sample to be drawn pre-dose and at the end of infusion after flushing

^{†††} Adjacent visits may be combined where feasible and considered safe

^{††††} Only if indicated by a change in weight (± 5%)

* EoT visit should be scheduled approx. 4 weeks after last dose. This is the final visit for patients continuing to the extension study.

** EoS visit should be scheduled approx. 4 weeks after EoT visit unless patient is continuing to the extension study

1 Introduction

1.1 Background

Muscle regulation and the ActRII Receptors

Several members of the transforming growth factor beta (TGF- β) superfamily, including myostatin, activin A, and growth differentiation factor 11 (GDF11), negatively regulate skeletal muscle mass in animals and humans throughout the lifecycle. Ligand signaling occurs via type II activin receptors (both ActRIIA and B; and the Smad 2/3 pathway), to inhibit muscle protein synthesis and myocyte differentiation and proliferation. The absence of any of these ligands in developing animals and humans results in a hypermuscular phenotype with an increased number and size of muscle fibers. A postpartum reduction of myostatin levels results in the hypertrophy of skeletal muscle due to an increase in the size of existing myofibers (Lee et al 2005; Lee et al 2010; Trendelenburg et al 2012). Thus, the capacity for modulating muscle growth by perturbing this signaling pathway at the receptor level is much more substantial than previously appreciated by direct anti-myostatin approaches.



Scientific rationale

Sarcopenia, the age-associated loss of skeletal muscle mass and physical function (Cruz-Jentoft et al 2010; Fielding et al 2011), affects approximately 30% of American men and women over the age of 60 and 50% older than 80 years (Baumgartner et al 1998). Sarcopenia is thought to result in mobility disability in 2-5% of elderly adults (Dam et al 2014). Loss of skeletal muscle mass and strength are common consequences of many chronic diseases, hospitalizations and normal aging and are strongly associated with morbidity, disability, mortality and loss of independence (Janssen et al 2004). A decline in muscle mass and strength in the elderly often manifests as reduced physical functional

capacity leading to lower quality of life and an increased risk of adverse health events (e.g., falls and fractures subsequent to falls). Currently, there is no standard treatment for the loss of skeletal muscle mass and function seen with aging.

Multiple consensus groups have proposed definitions for sarcopenia based upon changes in muscle mass and strength and physical function. Thus, diagnosis depends on documentation of low muscle mass plus low muscle strength or the presence of low physical performance (Cruz-Jentoft et al 2010; Muscaritoli et al 2010; Fielding et al 2011; Studenski et al 2014). The European Working Group on Sarcopenia in Older People (EWGSOP) recommended thresholds for defining sarcopenia that were based on the mean muscle mass in a normative healthy young adult population, with cutoff points calculated as two standard deviations below the mean reference value. This threshold is operationalized using an ASMI (skeletal muscle of the upper and lower limbs in kg/height in m²) by dual energy X-ray absorptiometry (DXA) of ≤ 7.26 kg/m² for men and ≤ 5.5 kg/m² for women. A similar consensus definition on sarcopenia was recently published from five other collaborative special interest groups – “Cachexia-anorexia in chronic wasting diseases”, “International Working Group on Sarcopenia”, “Nutrition in Geriatrics”, the “Asian Working Group for Sarcopenia” and the Foundation for the National Institutes of Health Sarcopenia Project – that recommended low muscle mass plus usual gait speed as the preferred measure of physical function (Muscaritoli et al 2010; Fielding et al 2011; Chen et al 2014; Studenski et al 2014).

The Short Physical Performance Battery (SPPB) is a series of six activities involving three domains of physical function – balance, usual walking speed and rising from a chair – and commonly used globally to assess and quantify (score 0-12) lower extremity function. The SPPB has been shown to predict future adverse health events. The SPPB has been translated into many languages in Europe and Asia and has been administered more than 30,000 times throughout the world with no known serious adverse consequences. Recently, the SPPB has emerged as an outcome of interest to health authorities and others as a means to assess the efficacy of drugs to improve physical function in populations of older adults.

The quantitative properties of the SPPB are supported by a long history and large body of literature. Substantial data documents test-retest reliability (Studenski et al 2003, Freire et al 2012); construct validity (Guralnik et al 1994, Latham et al 2008); predictive validity for mortality (Guralnik et al 1994, Perera et al 2005), incident disability (Guralnik et al 1995, Guralnik et al 2000, Gill 2010), institutionalization and hospitalization (Guralnik et al 1994, Studenski 2009), functional decline after hospital discharge (Corsonello et al 2011); and sensitivity to clinically important change (Ostir et al 2002, Latham et al 2008, Perera et al 2006, Perera et al 2014). The SPPB has been used as the primary (Pahor et al 2006, McAuley et al 2013, Latham et al 2014, Prestmo et al 2015) and key secondary (Pahor et al 2014) outcome in a number of randomized clinical trials.

Easy to perform in both clinical and research environments, gait speed is a component of the SPPB and commonly included in comprehensive geriatric assessment and care in many countries. There is a substantial body of epidemiologic and intervention based literature demonstrating a strong association between slowed and declining gait speed and future adverse physical status and health outcomes, including mortality (Studenski et al 2011). In addition, a gait speed of <0.8 m/s categorizes a person as “mobility impaired.” (Studenski et al 2014). The two gait speed cutoff points recommended in the consensus statements for the diagnosis of sarcopenia

are < 0.8 m/s and 1.0 m/s in the 4 m walking test to include patients at increased risk of functional decline (Cruz-Jentoft et al 2010; Fielding et al 2011). The largest analysis to date, of 26,000 patients in observational data from multiple studies, further supports the 0.8 m/s cutoff to define the population at increased risk for adverse health events (Dam et al 2014).

[REDACTED]

[REDACTED]

1.1.1 Relevant data summary

All information currently available on pharmacology, toxicology, [REDACTED], and pharmacodynamics has been obtained from in vitro experiments, animal trials, toxicology studies, and previous human studies. To date, bimagrumab has been generally safe and well tolerated and efficacious at increasing muscle mass in adults 19-86 years of age. Findings and relevant data from prior studies are briefly described below and detailed in the bimagrumab Investigator's Brochure (Investigator's Brochure).

1.1.2 Human safety and tolerability data

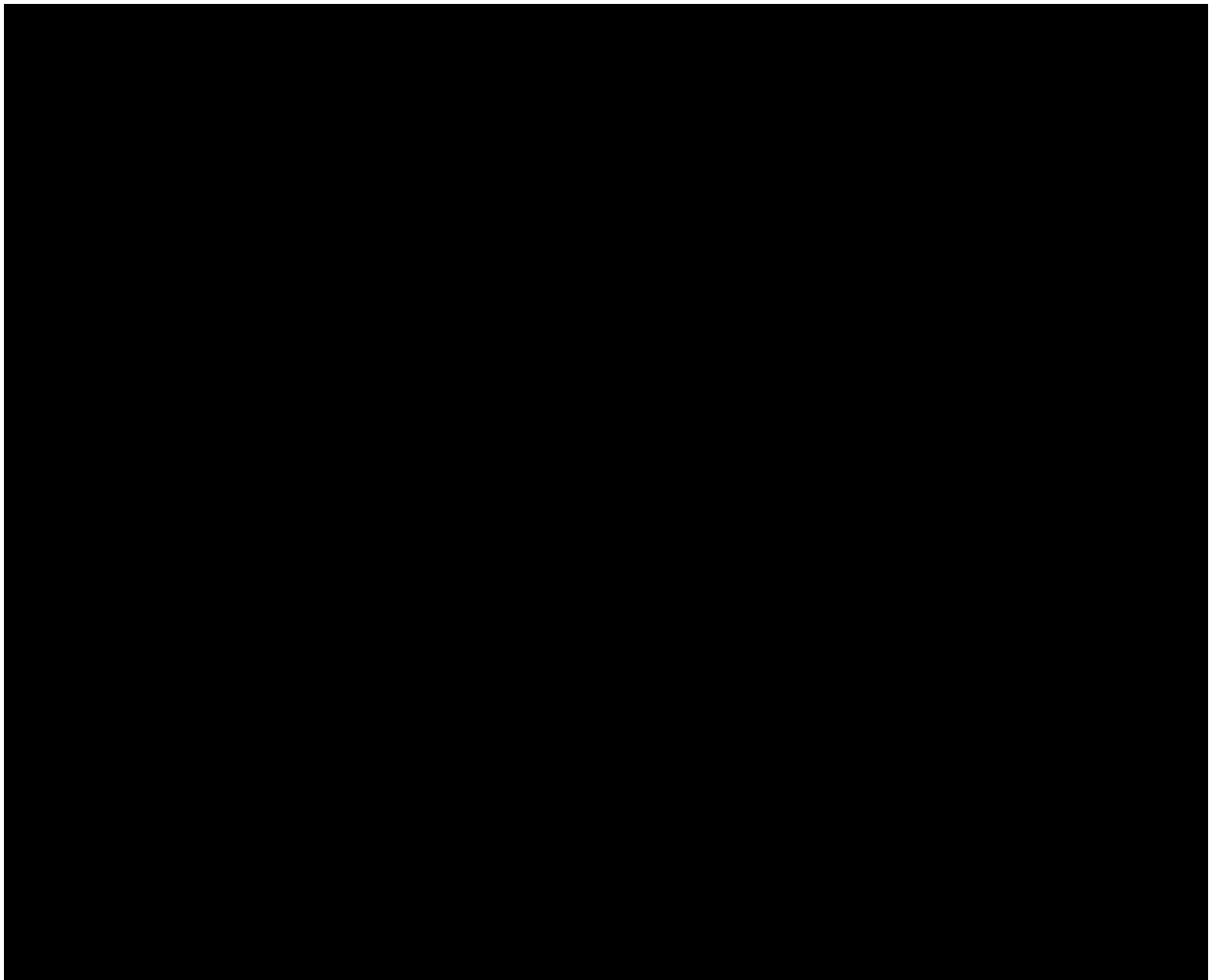
[REDACTED]

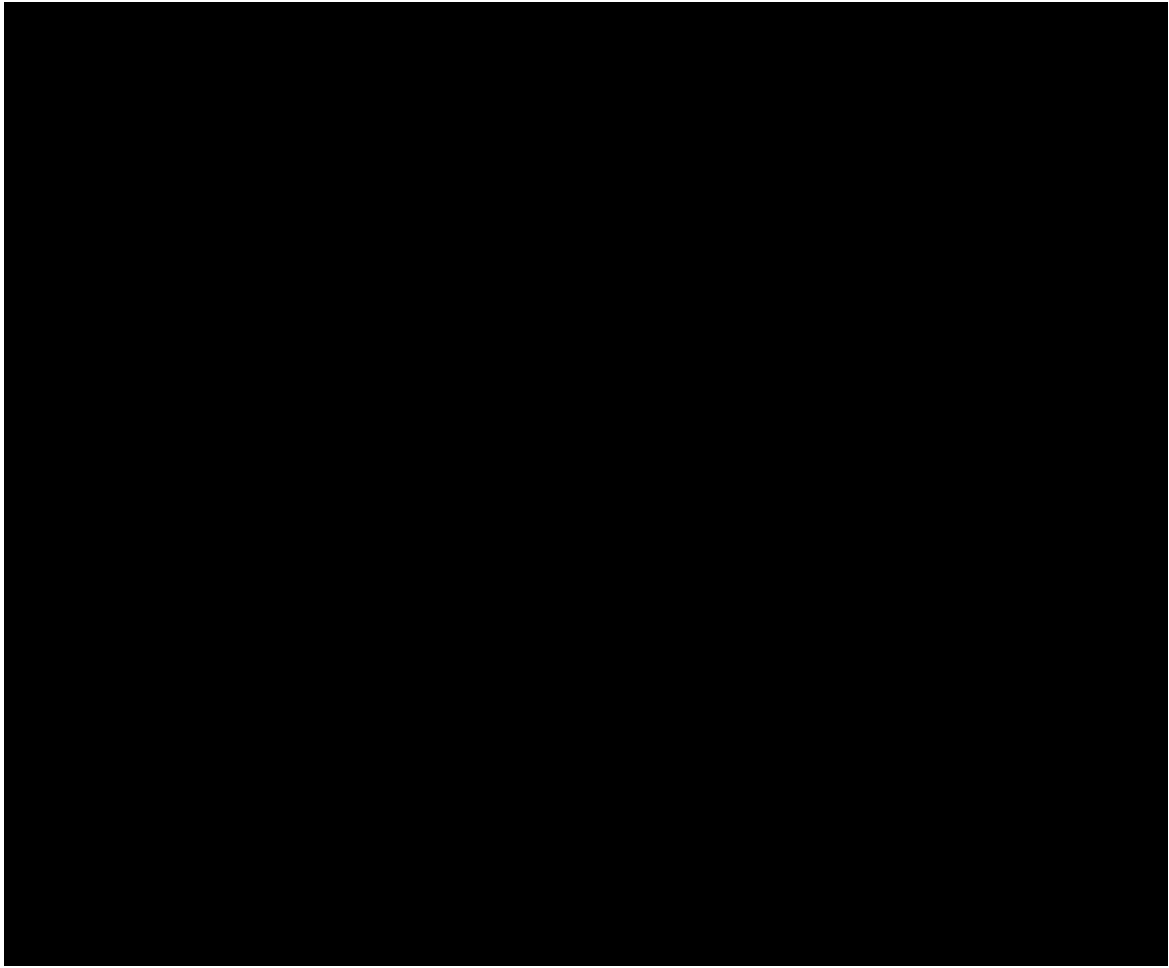
Study results to date indicate that bimagrumab is safe and well tolerated. The current safety profile is favorable, with adverse events limited to several minor, transient clinical symptoms. Transient cases of episodic, involuntary muscle contractions (referred to as "cramps or spasms"), acne and diarrhea of mostly mild intensity have been observed in study participants

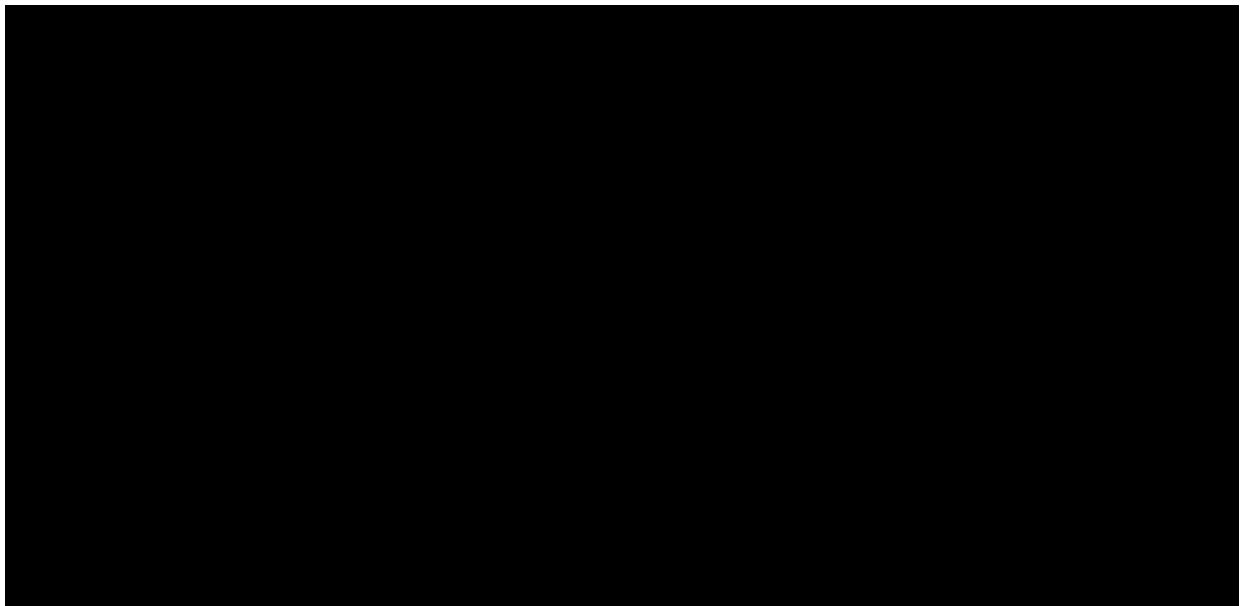
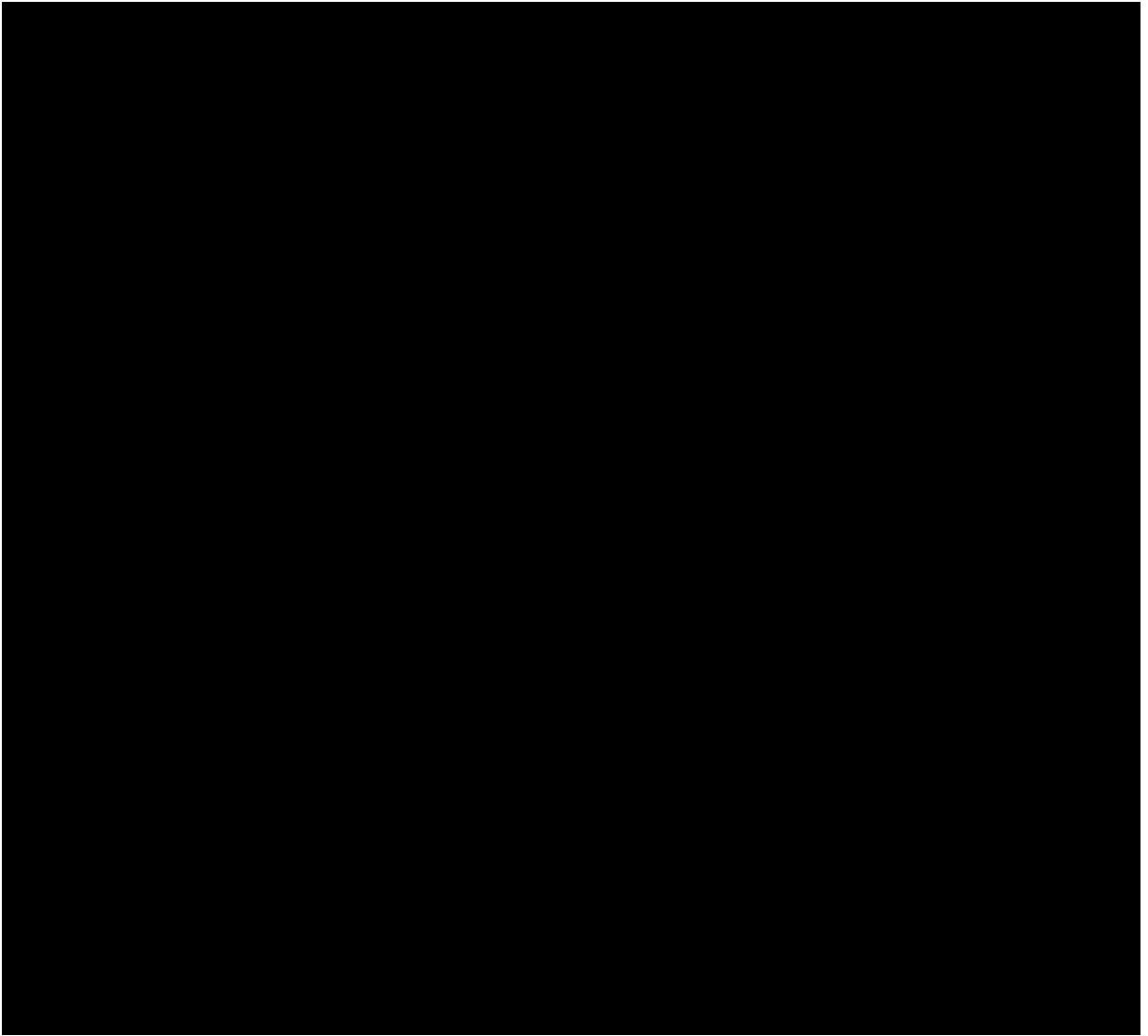
[REDACTED]

However, no one in the Proof of Concept (PoC) study (CBYM338X2201) in participants with sarcopenia and mobility limitations dropped out due to an AE.

Based on preclinical, toxicology and clinical findings to date the benefit-risk profile remains positive and supports continued development in patients with skeletal muscle loss who would benefit from increased lean tissue. The reference safety information for bimagrumab can be found in the Investigator's Brochure.







1.2 Study purpose

The purpose of this study is to determine the efficacy of repeat dosing with multiple dose levels of bimagrumab on patient physical function, skeletal muscle mass and strength in older adults with sarcopenia. In addition, this study will generate data on the safety, tolerability, [REDACTED] of bimagrumab in this patient population.

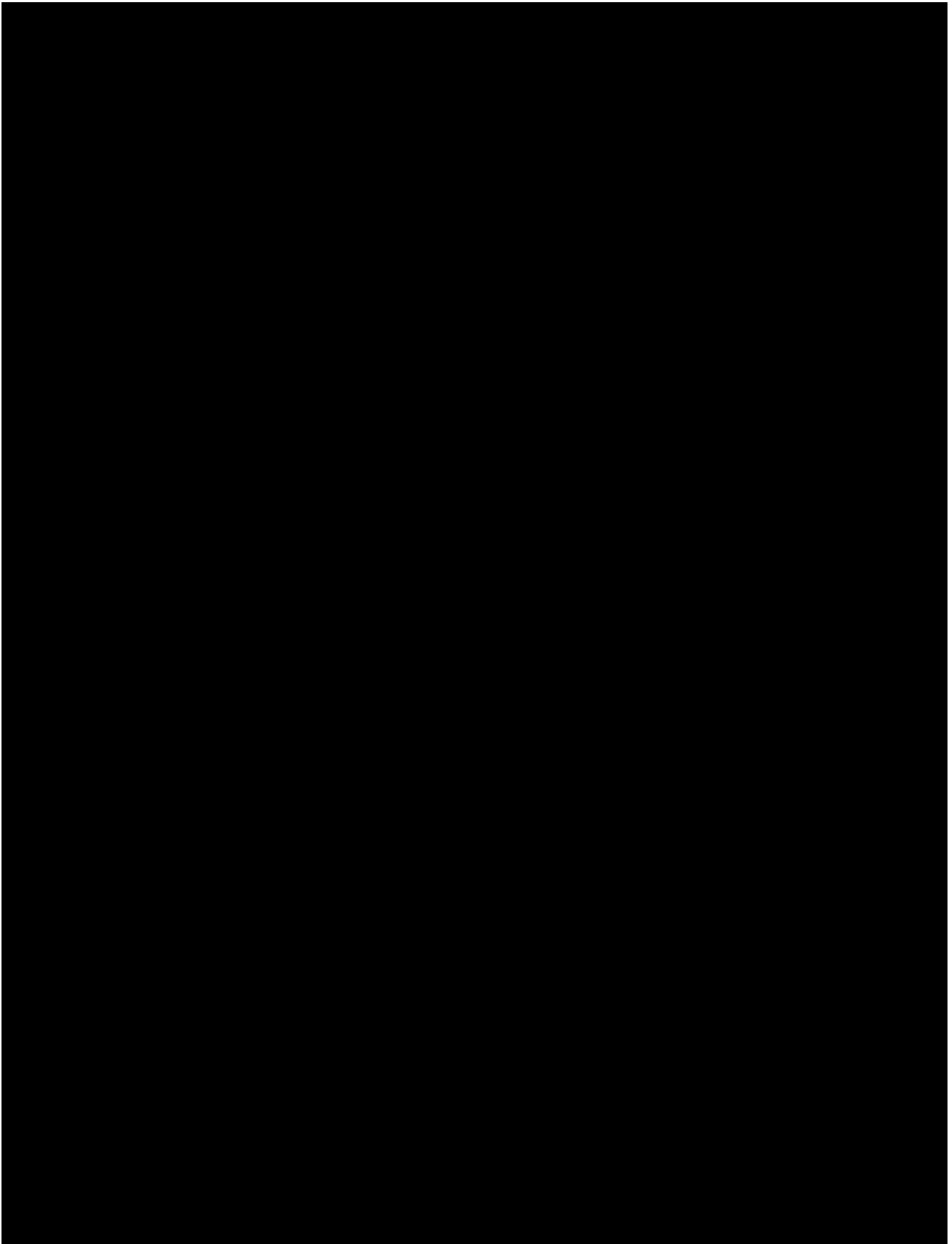
2 Study objectives

2.1 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.

2.2 Secondary objective(s)

- To assess the effect of bimagrumab compared to placebo on the safety and tolerability of multiple doses of bimagrumab administered over 24-weeks as measured by vital signs, clinical laboratory values, 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 function as measured by a 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) 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, assessed by the change from baseline to week 25 compared to placebo in older adults with sarcopenia.



3 Investigational plan

3.1 Study design

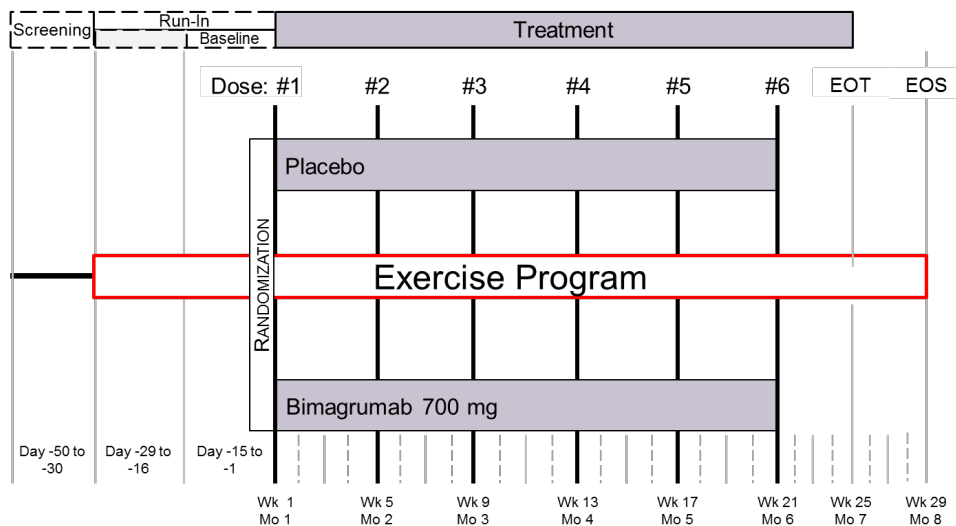
This Phase IIb study is a two-part, randomized, double-blind, placebo-controlled study design with approximately 339 older adults with sarcopenia assigned to one of four treatment groups: placebo, bimagrumab 70mg, bimagrumab 210mg, or bimagrumab 700mg,

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 [REDACTED] 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. [REDACTED]

3.1.1 Part A

Patients will be enrolled and randomized to receive either bimagrumab 700 mg or placebo (see Figure 3-1), until approximately 100 patients will have been enrolled in the bimagrumab 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 3-1 Study Design: Part A



3.1.2 Interim Analysis

An interim analysis will be performed on the bimagrumab 700mg and placebo groups at the completion of Part A to determine treatment efficacy. [REDACTED]

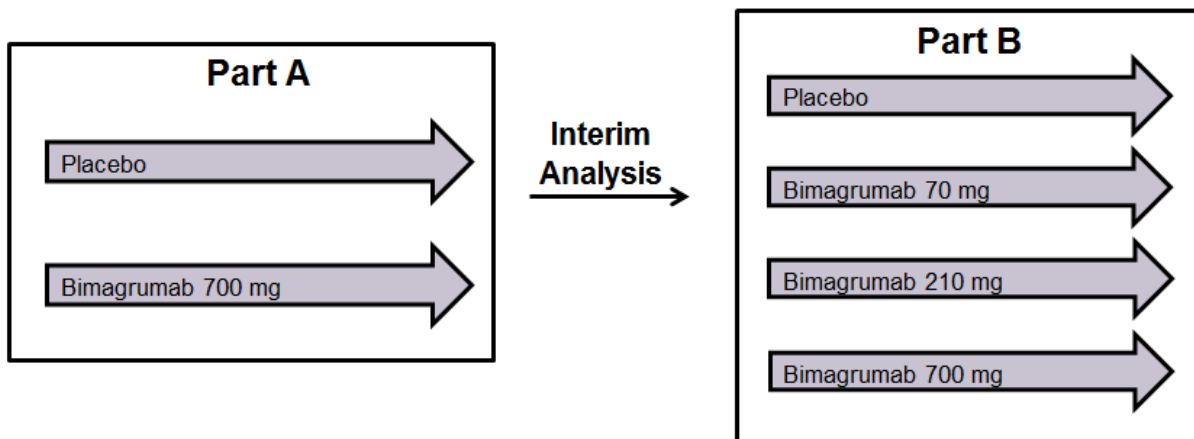
Primary analysis: To support the primary objective, the change in the Short Physical Performance Battery (SPPB) total score from baseline to week 25 will be compared between treatment groups.

Following criteria will be evaluated at the end of Part-A

- [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.

Figure 3-2 Study Flow Diagram



3.1.3 Part B

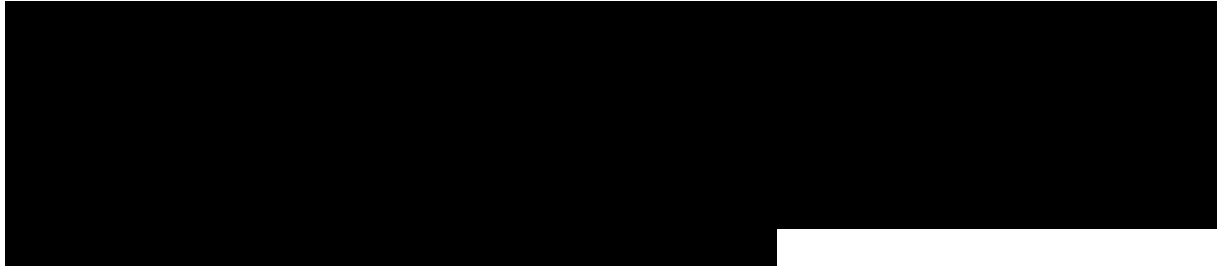
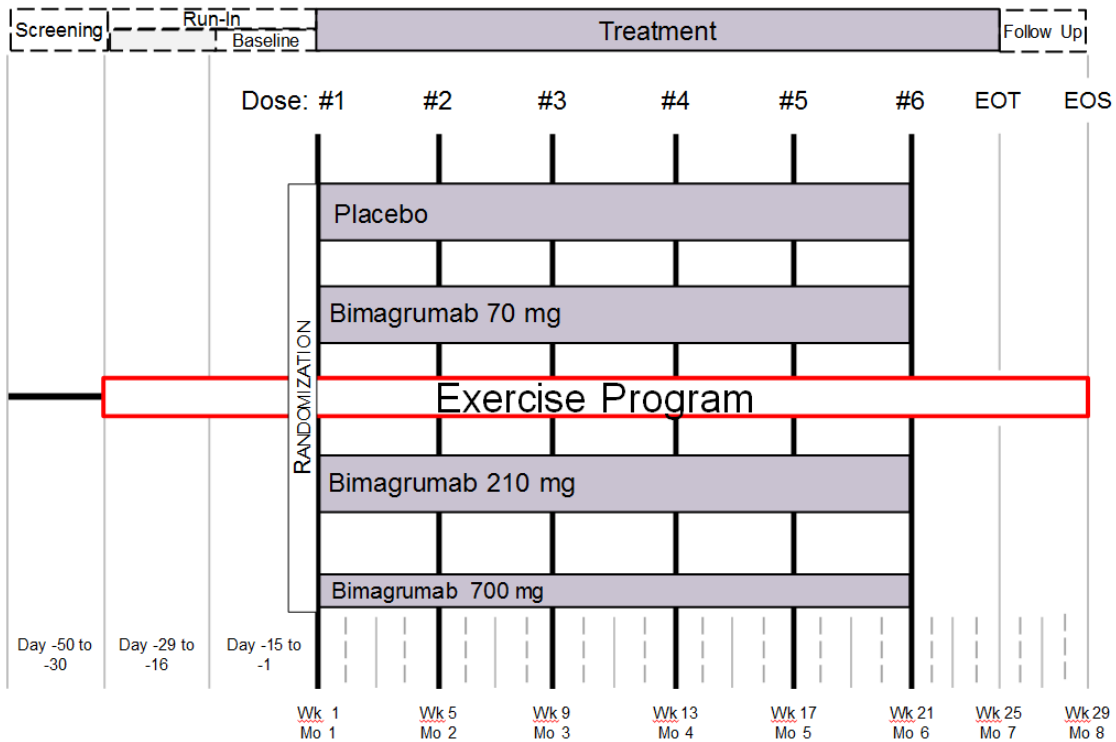


Figure 3-3 Study Design: Part B



Assessments performed under Part A and Part B are the same (see [Assessment Schedule](#)).

3.1.4 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 movements.



[REDACTED]

[REDACTED]

3.1.5 Drug treatment assignment

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

[REDACTED]

End of infusion will be considered as the time of the end of the line flush. **All times stated within this protocol are from the start of study drug administration (unless otherwise stated).** The assessments that will be carried out at each visit are presented in the study [Assessment schedule](#).

[REDACTED]

[REDACTED]

Study Phases

Screening

Visit 1 - Day -50 to -30

Patients will be required to attend the investigator center for the screening visit (for logistical reasons more than 1 visit may be planned) where qualification for the study will be assessed by the investigator. Informed consent will be obtained prior to implementing any study specific procedures.

Patients not meeting the minimum vitamin D or nutritional requirements at initial evaluation can be offered dietary counseling and/or receive vitamin D supplementation through their physician. If they are able to achieve required levels by the baseline visit, they may be enrolled, otherwise they will be listed as a screen failure and may be re-screened at a later time.

The ability and willingness of the patient to perform the exercise program should be evaluated by the investigator or a team member during this visit. [REDACTED]

Only patients who meet the inclusion/exclusion criteria at screening will be eligible to proceed to the run-in period of the study. However:

- Central laboratory assessments or ECG interpretations which fall outside of the **protocol-specified range** at screening can be repeated once at an unscheduled visit during the screening period to confirm patient eligibility prior to run-in.
- Patients excluded for one of the temporary medical conditions listed in section 4.2 may be rescreened after a period that is considered clinically relevant by the investigator.

For a full list of assessments, please refer to the [Assessment schedule](#).

Run-in Period

Visits 2-5 - Day -29 to -1

Patients are requested to visit the clinical site in the morning, under fasted conditions for the blood collections.

[REDACTED]

As reported above, [REDACTED]

[REDACTED]
[REDACTED]. Dietary supplements will be initiated during the run-in period as well.

[REDACTED] based on the Investigators judgement [REDACTED], Visits 2 and 3 may be combined and performed on one day. Each visit will be recorded separately in the eCRF with the same visit date.

For a complete list of assessments, please refer to the [Assessment schedule](#).

Baseline

Visits 4 and 5 - Day -15 to -1

These Baseline visits will occur towards the end of the run-in period. Patient eligibility will be rechecked, including current medical conditions and medications.

[REDACTED]
Patient eligibility must be confirmed by the investigator via repeat evaluation of the inclusion/exclusion criteria prior to randomization and progression into the treatment period. [REDACTED]

All other baseline assessments should be performed during the final week of the run-in period.

For a complete list of assessments, please refer to the [Assessment schedule](#).

Where the investigator deems it safe to do so, visits 5 (baseline) and 101 (Day 1) may be combined and performed on one day after the completion of the run-in period. All visit 5 (baseline) assessments must be performed pre-dose. Each visit will be recorded separately in the eCRF with the same visit date.

Treatment Period

First dosing Visit – Day 1

Once all blood draws have occurred at this visit, the subjects can be given breakfast (if the patient has not already eaten). [REDACTED]
[REDACTED]

The above mentioned assessments must be performed prior to administration of the first dose of bimagrumab. This visit may be combined with the previous visit (Visit 5).

Time of dosing will be collected in the eCRF and appropriate documentation of the patient specific dispensing process must be maintained. Wherever possible, it is recommended that infusions occur at approximately the same time of day at each dosing visit (e.g., morning or afternoon).

[REDACTED]
[REDACTED]

Following dose administration, patients should be observed for a period of time to ensure they are feeling well enough to be discharged from the study site. The duration of observation can be approximately 10-20 minutes or longer at the discretion of the investigator.

For a complete list of assessments, please refer to the [Assessment schedule](#).

Non-dosing Visit – Day 15

Subjects should return to the clinic site for collection of clinical chemistry labs as per the [Assessment Schedule](#).

Other Dosing Visits – Days 29, 57, 85, 113, and 141

Dosing visits must occur on the day \pm the visit window specified in [Section 6](#).

All assessments [REDACTED] should be performed prior to dosing. Please refer to [Section 6](#) and the Outcomes Manual for more details regarding the sequence of assessments.

Time of dosing will be collected in the eCRF and appropriate documentation of the patient specific dispensing process must be maintained. Infusions should occur at approximately the same time of day at each dosing visit.

[REDACTED]

Following dose administration, patients should be observed for a period of time to ensure they are feeling well enough to be discharged from the study site. The duration of observation can be approximately 10-20 minutes or longer at the discretion of the investigator.

For a complete and detailed list of assessments, please refer to the [Assessment schedule](#).

End of Treatment (EoT)

Day 169

This visit will take place approximately 4 weeks after the last study drug administration and must occur on the day \pm the visit window specified in [Section 6](#).

For a complete list of assessments, please refer to the [Assessment schedule](#).

Patients participating in the extension study will move immediately to Visit 1 of the extension trial following this End of Treatment visit.

End of study (EOS)

Day 197

This is the last planned visit in the study. The visit will take place approximately 8 weeks after the last dose for patients who discontinue from the study prematurely or who are not continuing to the extension study, and must occur on the day \pm the visit window specified in [Section 6](#).

Patients will be discharged from the study if they are in good general health as assessed by the Investigator. If deemed not appropriate for discharge, the Investigator (or the responsible medical delegate) will arrange for transfer of medical care to the patient's primary physician or another appropriately qualified medical practitioner. For a complete list of assessments, please refer to the [Assessment schedule](#).

Study Extension

An extension trial to evaluate the durability of effect of bimagrumab upon discontinuation of drug treatment is currently on-going. At the completion of this study, in participating sites, eligible patients may be invited to join the extension trial to evaluate the durability of effect of bimagrumab.

3.2 Rationale for study design

The two-part, randomized, double-blind, placebo-controlled design of this phase IIb study will allow a comparison of repeat dosing of three dose regimens of bimagrumab and placebo on changes in muscle quantity and patient physical function in a population of older adults with sarcopenia.

Patient population

The study population will be comprised of men and women aged 70 years or older with sarcopenia and muscle-associated slow gait speed (GS). The population enrolled in this study should reflect the general heterogeneity of elderly people with low skeletal muscle mass and mobility limitation with regard to co-morbidities, polypharmacy, physical functional status, physiological reserve, and physical activity patterns. Data on drug safety, tolerability, [REDACTED] and pharmacodynamics from this design and population, should provide an assessment of possible beneficial or adverse effects of bimagrumab in the larger global population of elderly adults with similar co-morbidities, functional status and mobility limitations. The exclusion criteria aim to omit individuals whose health condition(s) or status could put them at unwarranted safety risk from participation in study activities; those patients in whom their muscle related dysfunction is not the primary reason for low functional capacity; patients likely not to improve due to non-muscle issues, e.g. unmanaged osteoarthritis pain; or patients with conditions that could confound the study objectives. To better clarify the potential effects of bimagrumab and to minimize within and between country differences in standard of care of older adults with mobility limitations, all study participants will receive oral nutritional supplements (ONS) and vitamin D and participate in a personalized exercise program.

Design

A randomized, placebo-controlled, double-blind design will be used to ensure the comparison of active vs. placebo treatments. Due to the subjective and effort-based nature of many study endpoints (e.g., AEs, SPPB, 6MWT, [REDACTED], [REDACTED]), randomization to treatment and investigator and patient blinding will minimize the potential bias of patients and assessment personnel on key safety and performance-based endpoints.

The original four arm parallel design with three dose levels will become a two part study as of protocol amendment v02, to better address key study goals and to reduce the number of patients potentially exposed to an ineffective therapy until there is more evidence that bimagrumab is useful in treating sarcopenia. This study is the first to assess the SPPB in patients with sarcopenia administered bimagrumab. Therefore, Part A will determine the effect of the highest dose level (700 mg) of bimagrumab on total SPPB score compared to placebo in this population. At the completion of Part A, an interim analysis will be performed to determine efficacy and a sample size re-estimation to confirm original enrollment plan.

[REDACTED] Patients randomized to 70 mg and 210 mg bimagrumab before amendment v02 [REDACTED] will complete the study following the assessment schedule of this amendment and their data will be combined with other patients who receive the same dose level in Part B. Completion of Parts A and B will achieve the same objectives as the original design, just in a staggered manner.

Randomization will be used to account for the expected heterogeneity of the geriatric sample population and to minimize selection, age, gender and baseline differences between groups. It is expected that patients administered bimagrumab will demonstrate a greater increase in muscle mass (LBM and ASMI) after receiving the drug compared to patients receiving placebo and that this increase in muscle will translate into an increase in physical function seen as an improvement in the SPPB score and other outcomes.

Outcome variables

A key design change in this amendment is that the SPPB will become the primary outcome. This switch of the SPPB from a key secondary outcome in earlier versions of the protocol and the change of 6MWT distance from the primary to a key secondary outcome is based on a combination of factors identified from the medical literature and observed in discussions with health authorities since the original protocol was written. Created to assess physical function in longitudinal aging studies in the 1970's, the measurement properties of the SPPB are supported by an extensive history and body of literature. These data show a strong link of declining lower extremity functional status to adverse, clinically relevant outcomes in older adults, including falls, hospitalizations, institutionalization, incident disability and death (Guralnik et al 1994, Guralnik et al 1995, Studenski et al 2011, Perera et al 2006). Comparatively, the 6MWT is more clinically relevant in other patient populations, such as congestive heart failure, pulmonary disease and multiple sclerosis (Morris et al 2014; ATS 2002; Brown and Simnad 2016).

The SPPB score and 4-meter gait speed have emerged as the predominant characteristics that define impaired lower extremity function in older adults in general and in those with sarcopenia and frailty (Studenski et al 2014). The SPPB has been used as the primary outcome variable in two recent intervention trials examining functional recovery following hip fracture (Latham et al 2014, Prestmo et al 2015). In addition, the SPPB was a key outcome in a large US based study (LIFE Study), evaluating an exercise and diet intervention in older adults that demonstrated an improvement of ≥ 1 point on the SPPB score was associated with a significant reduction in falls, and the baseline score predicted onset of mobility disability.

Health authorities have identified the SPPB as a candidate for a registration endpoint. Novartis is collaborating with the FDA and the American Federation for Aging Research to validate the SPPB as a regulatory outcome.

[REDACTED]

To standardize the exercise program across all patients, the schedule of 2-3 exercise sessions per week will be maintained throughout the study.

The 6MWT, [REDACTED] will provide data to assess the potentially broader clinical impact of a change in muscle quantity on improvements in patient perceived functional status (see [Section 6.5](#)).

3.3 Rationale for dose/regimen, duration of treatment

3.3.1 Dose and frequency

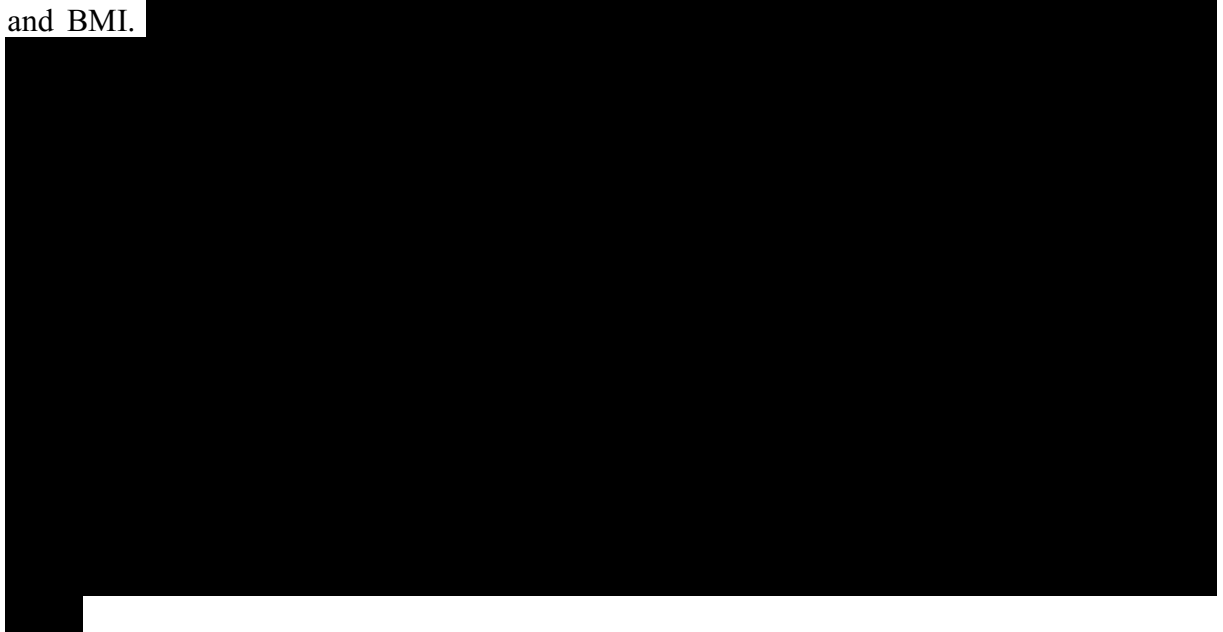
Part A of the study will evaluate the fixed i.v. dose of 700 mg bimagrumab administered every 4 weeks over a 20-week period for a total of six doses.

Part B of the study will evaluate fixed i.v. doses of 70 mg, 210 mg, or 700 mg bimagrumab every 4 weeks over a 21-week period for a total of six doses.

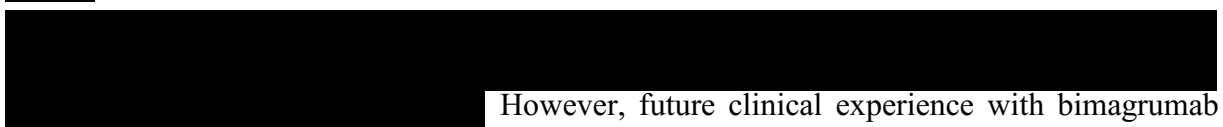
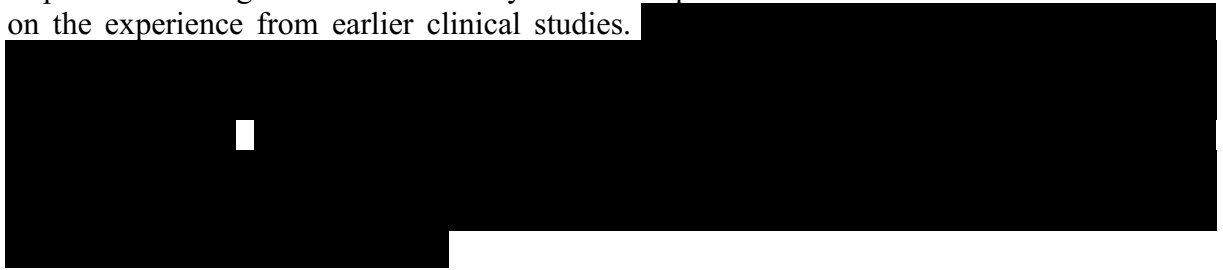
[REDACTED]

Fixed i.v. dosing rather than body weight based dosing will be used in the current study [REDACTED], allowing the exploration of dose-exposure-response relationship estimation and supporting final dose selection and

subsequent clinical development of bimagrumab for patients with sarcopenia. Based on the definition of sarcopenia and experience in this and prior studies, the lower limit of body weight has been lowered by 5 kg to 35 kg to be more inclusive of older adults in Asian countries. It is unlikely that a person will weigh more than 100 kg based on the limits of ASMI and BMI.



Exposure to bimagrumab for 6 monthly doses is expected to be safe and well tolerated based on the experience from earlier clinical studies.



However, future clinical experience with bimagrumab may clarify more precisely where the limits of efficacy and tolerability are. Therefore, this study proposes to investigate a wider rather than narrower range of bimagrumab exposures by administering a fixed dose of 700 mg, 210 mg and 70 mg.

Six doses will be used to evaluate the durability of treatment on the expected improvement in physical function and the time course for multiple performance assessments and to avoid

being misled by early changes that are not maintained with continued dosing ([Papanicolaou et al 2013](#)).

3.4 Rationale for choice of comparator

A placebo infusion will be used as the comparator in this placebo-controlled study; no drug comparator will be used. A placebo is used because several of the outcome measures are behavioral in nature and dependent on a patient's or observer's beliefs and perceptions. Therefore, knowing treatment assignment may bias outcome measures and other important results (i.e., AEs). In addition, placebo-controlled studies provide the optimal situation to distinguish adverse events caused by a drug from those resulting from underlying conditions or "background noise". As there is no approved pharmacotherapy for sarcopenia and it is not known if bimagrumab is efficacious, the use of placebo is ethically appropriate.

3.5 Purpose and timing of interim analyses/design adaptations

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

[REDACTED] The analysis will assess the effect of bimagrumab by the change from baseline to week 25 for efficacy in SPPB total and component scores, 6MWT distance and [REDACTED]. Safety will also be examined based on the incidence of adverse events and clinically relevant changes in certain clinical laboratory variables.

[REDACTED]

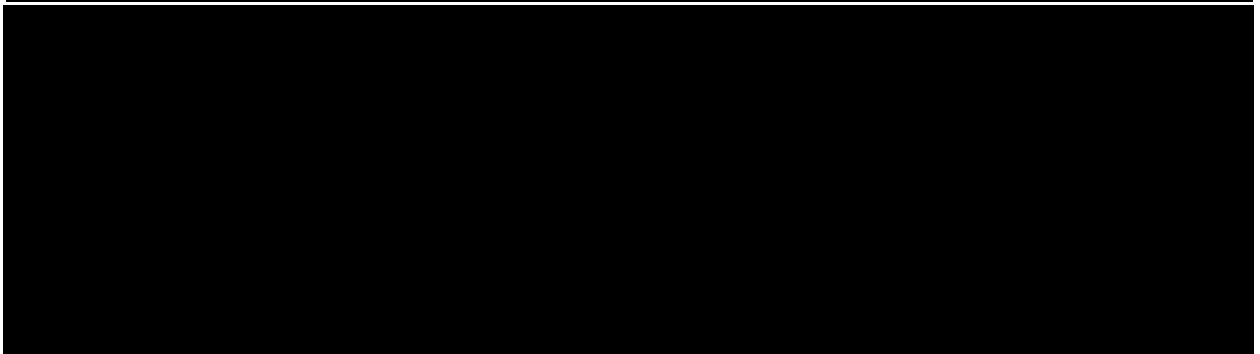
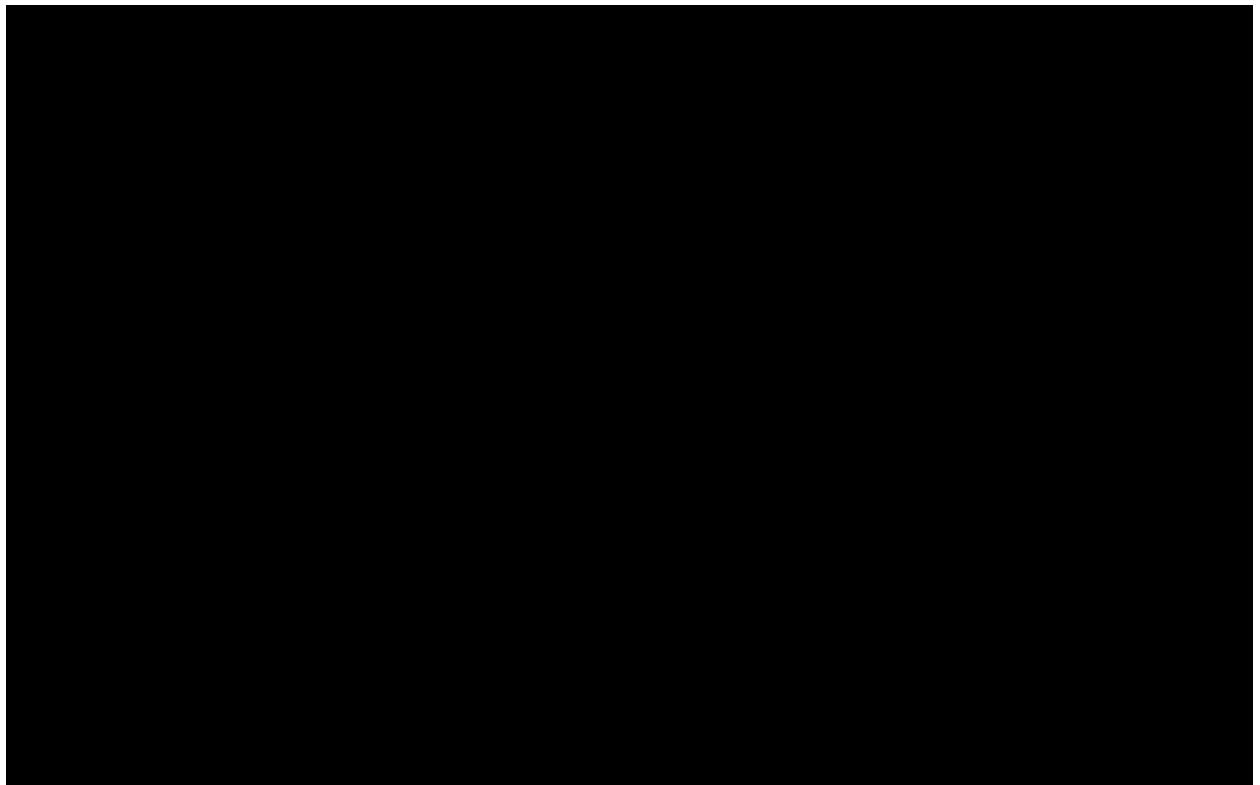
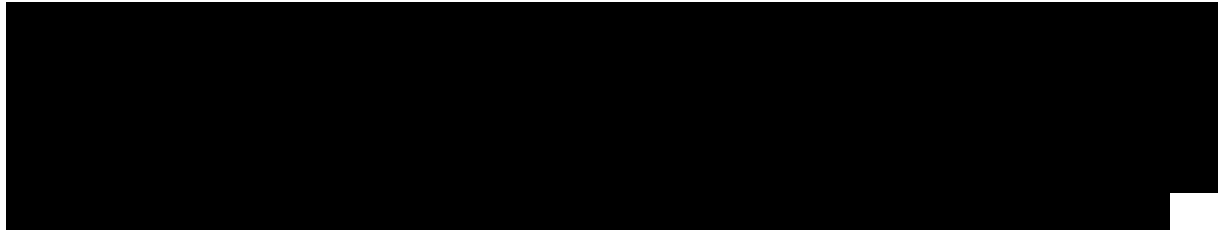
[REDACTED]

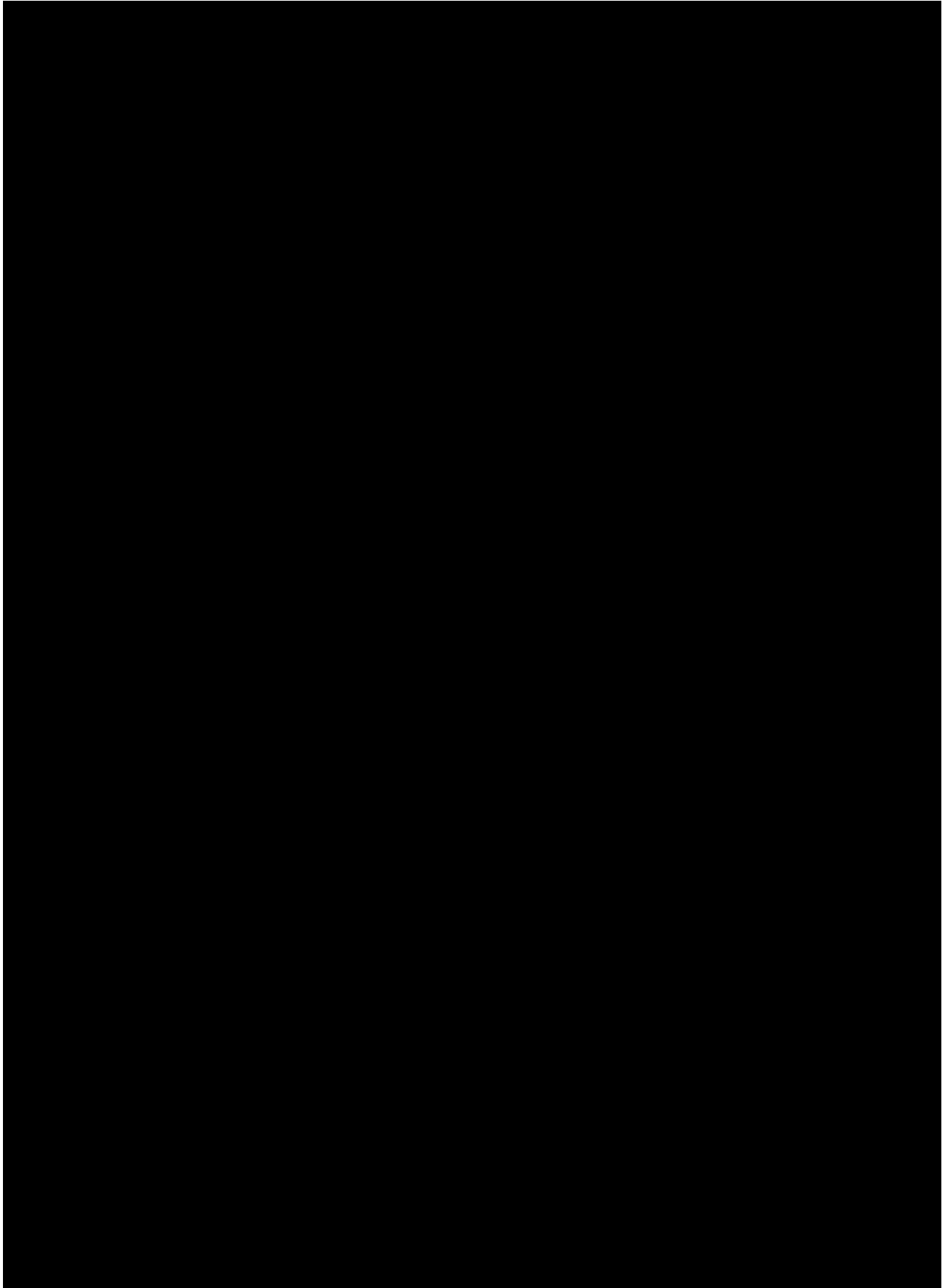
Further information is described in [Section 9.8](#).

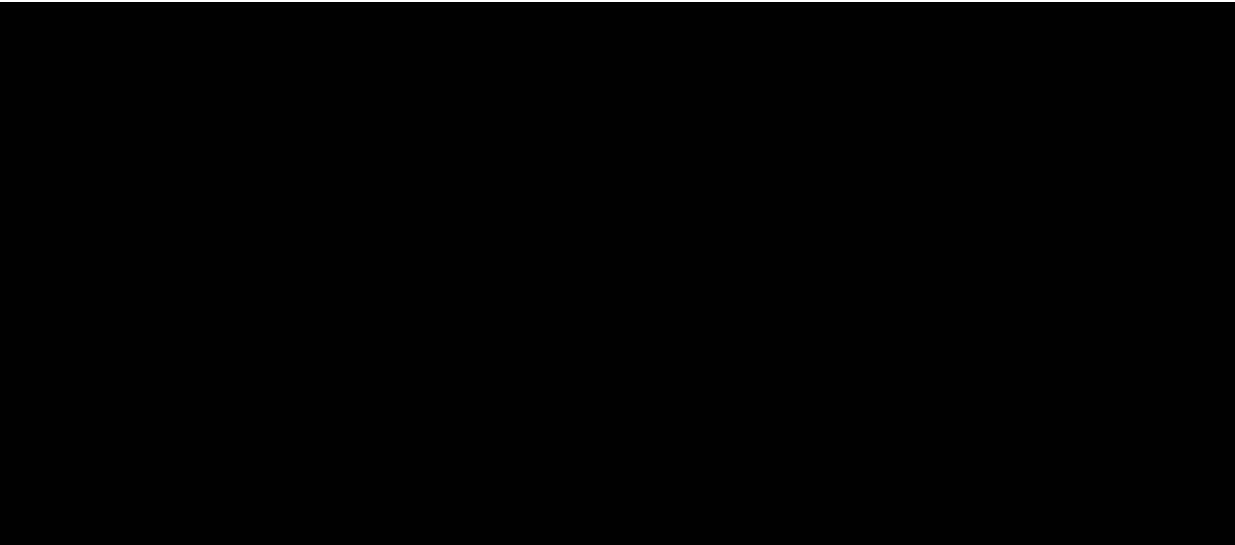
3.6 Risks and benefits

Target related risks and selection of participants

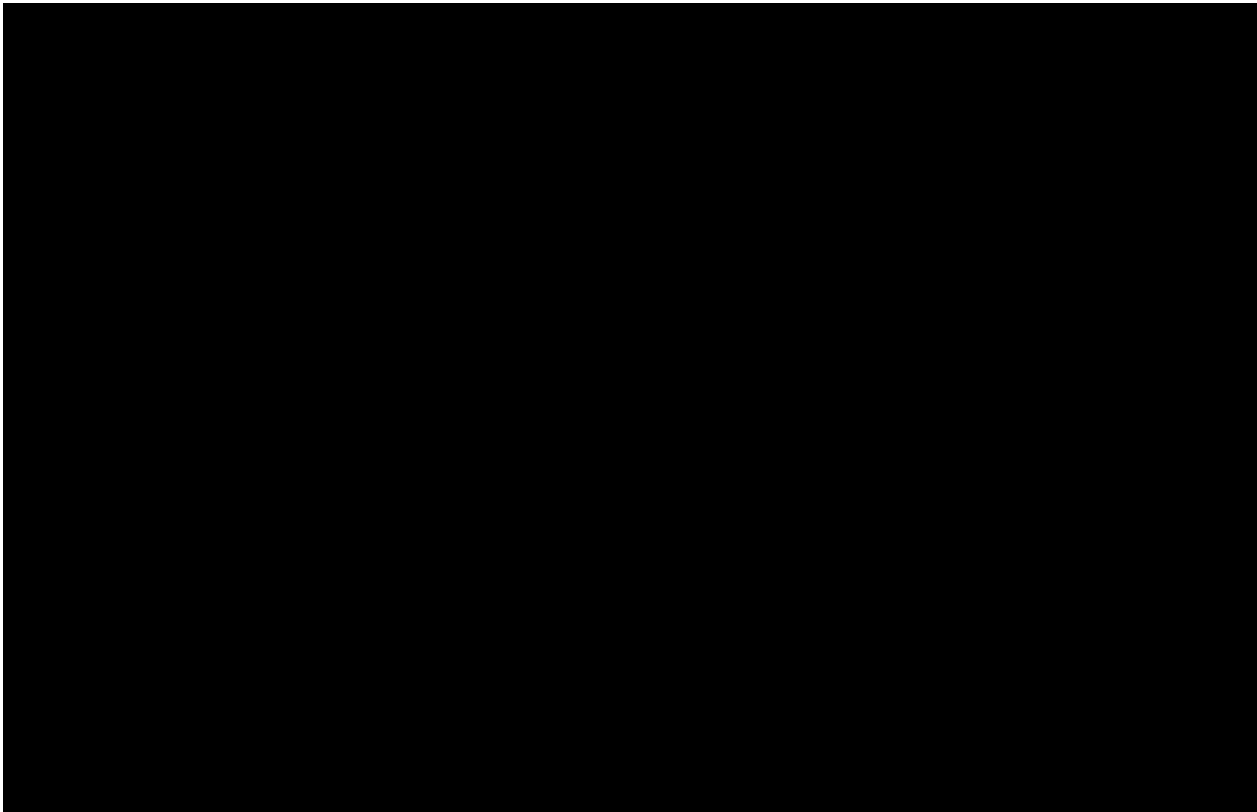
A paucity of human data limits the ability to predict the short and long-term risk of reducing the activity of myostatin and other ActRII ligands in older adults. However, the risk to patients in this trial will be minimized by adherence to the inclusion/exclusion criteria and close clinical monitoring.

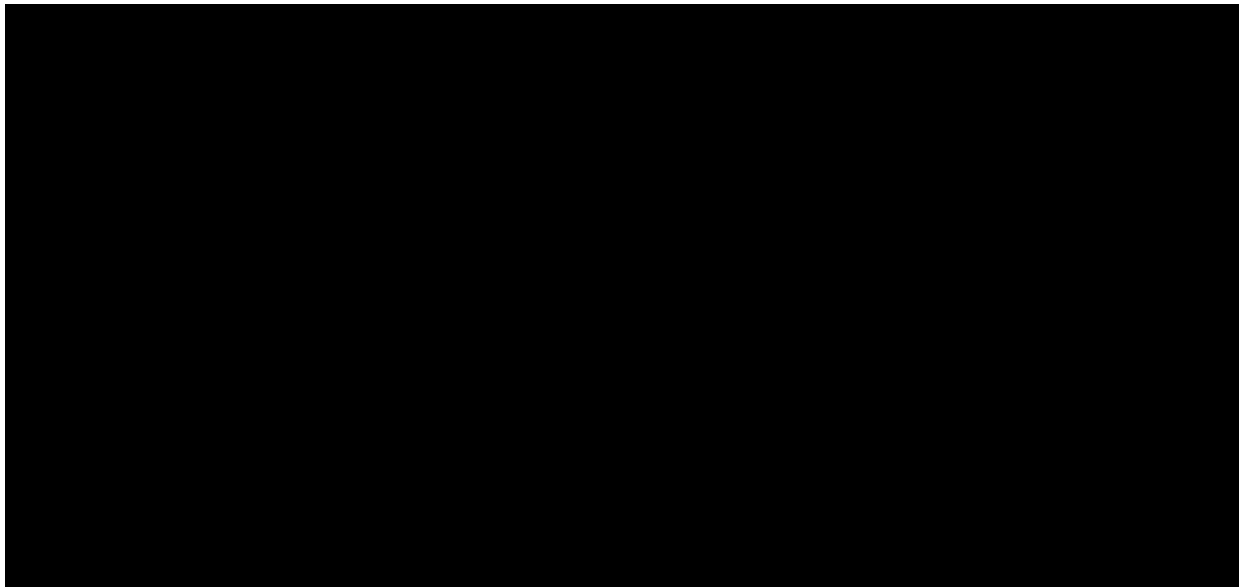
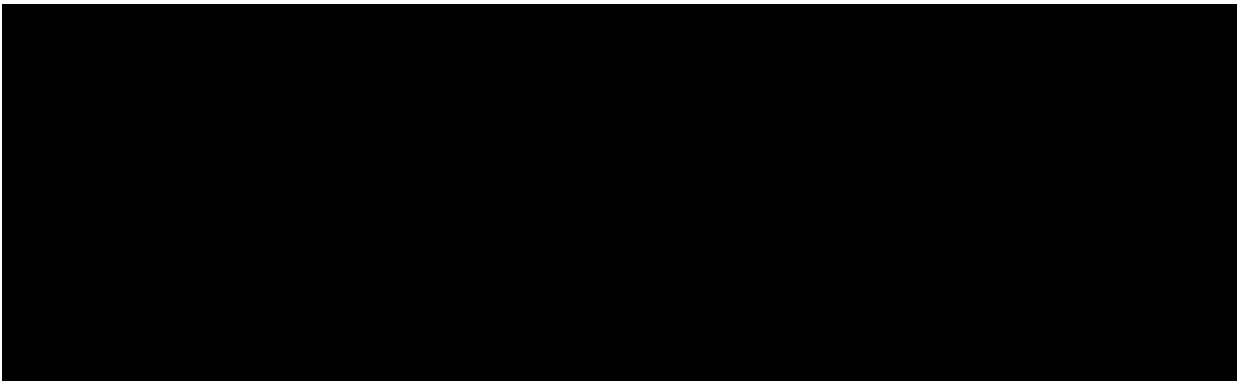






An external Data Monitoring Committee (DMC) will monitor safety data from the study and currently monitors the entire bimagrumab program for potential safety concerns (see [Section 8.4](#)).





3.6.2 Trial-related risks

Infusion risks

Infusion related reactions can occur with monoclonal antibodies. Hypersensitivity reactions can manifest as fever, chills, urticaria, dyspnea, headaches, myalgia and/or hypotension. A serious infusion reaction that results in anaphylaxis is a rare event in monoclonal antibody therapy. If a severe hypersensitivity reaction occurs, administration of bimagrumab should be discontinued and appropriate therapy initiated. Although not expected, an acute allergic reaction should be treated as needed using conventional counter measure therapies as indicated (including but not limited to epinephrine, antihistamine, corticosteroid, intravenous supplies, crystalloid, an oral airway, bag and mask, and supplemental oxygen). In the case of a serious adverse event in which decreasing the systemic concentration of bimagrumab may be of clinical benefit, the investigator should consider plasmapheresis. Study sites should not feel constrained in any way from providing necessary medical intervention.

Blood draw risks

During the collection of blood samples, subjects may experience pain and/or bruising at the insertion site of the needle/catheter. Although rare, localized clot formation, infections and

nerve injury may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw. Patients will be observed following all blood draws and discharged only when the Investigator observes stable health status. In addition, liquids by mouth in the form of water, fruit juice or a similar product will be provided following the blood draw to replenish the blood volume removed.

Imaging risks

This clinical study involves exposure to radiation from a DXA total body scan. The radiation exposure by DXA is not necessary for medical care but is intended for research purposes only. The total amount of radiation exposure per subject from DXA will be about 25 μSv . This amount of radiation is equivalent to approximately 3.6 days of background exposure (approx. 0.3 μSv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired (Stabin 2009). DXA measures are also described as having no observable or biological effect and are similar to natural background levels of radiation in most countries. Therefore, DXA scans within the study period need not be limited from a safety perspective.

Exercise-related injuries

From the beginning of the run-in period to EOS, the patients will be required to perform a prescribed set of exercises two to three times each week. [REDACTED]

Some people participating in an exercise program may experience transient muscle soreness due to an increase in the volume and intensity of associated muscle contractions beyond their usual daily level. This risk of temporary muscle soreness is most commonly observed in individuals who are inexperienced with exercise and who are sedentary in their daily lives at the time of enrollment. [REDACTED]

4 Population

The study population will be community-dwelling men and women ages 70 years and older meeting the criteria for sarcopenia as defined by the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al 2010). A modification in the criterion for appendicular lean mass will be made for patients from countries in Asia to account for the population difference in normal levels of lean body mass (Chen et al 2014). This study population should reflect the general heterogeneity of older adults with sarcopenia with regard to co-morbidities, physical functional status, physiological reserve, polypharmacy, and physical activity patterns. [REDACTED]

■ The investigator must ensure that all patients being considered for the study meet the eligibility criteria prior to randomization. No additional exclusions should be applied by the investigator. Patient selection is to be established by checking through all inclusion/exclusion criteria at screening and baseline as stated in the protocol. A relevant record (e.g. checklist) must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria at screening. In addition, several of the criteria must be confirmed at baseline, as documented below:

1. Written informed consent must be obtained before any assessment is performed;
2. Men and postmenopausal women aged 70 years or older at screening, with self-reported mobility limitations such as difficulty standing up from a chair, walking for longer than 10 minutes on a flat surface or climbing a flight of stairs;
 - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
3. Gait speed over 4 meters of <0.8 m/s but ≥ 0.3 m/s at screening and baseline;
4. Appendicular skeletal muscle index (skeletal muscle of arms and legs in kg/ height in m^2) by DXA based on central reading:
 - ≤ 7.26 kg/m^2 for men and ≤ 5.5 kg/m^2 for women to be assessed during screening.
 - **ASIAN COUNTRIES:** ≤ 7.0 kg/m^2 for men and ≤ 5.4 kg/m^2 for women to be assessed during screening ([Chen et al 2014](#));
5. Total SPPB score of ≤ 9 at screening and baseline;
6. Weigh at least 35.0 kg and have a body mass index (BMI) within the range of 15.0 – 32.0 kg/m^2 ;
7. Usual dietary intake ≥ 20 kcal/kg body weight and ≥ 0.8 g protein/kg per day over the 4 weeks prior to baseline estimated by an established method of diet assessment (i.e. 24 hour recalls, food records or similar);
8. Be able to communicate well with the investigator and to understand and comply with the exercise program, oral nutritional supplements (ONS), visit schedule and other requirements of the study.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study.

Central laboratory assessments or ECG interpretations which fall outside of the **protocol-specified range** at screening can be repeated once at an unscheduled visit during the screening period to confirm patient eligibility prior to run-in.

Medical conditions limiting performance of physical assessments

1. History of a lower limb fracture (e.g. femur, tibia) within the past 6 months with persistent negative impact on lower extremity function or any significant impairment or disease adversely impacting gait (e.g. intermittent claudication in advanced peripheral vascular disease, spinal stenosis, or severe osteoarthritis of the knee or hip with joint pain not controlled with medication/injections that adversely impacts mobility);
2. Confirmed diagnosis of significant psychiatric disease (e.g. dementia/Alzheimer's disease, schizophrenia, depression or bipolar disorder). Individuals with adequately treated depression are eligible for enrollment;
3. A Patient Health Questionnaire – 9 (PHQ-9) score ≥ 10 at screening;
4. Neurological injury/disorder with significant persistent functional deficit (e.g. stroke with hemiparesis, spinal cord injury, muscular dystrophy, polymyositis, dermatomyositis, myopathy/myositides, myasthenia gravis, Parkinson's disease, peripheral polyneuropathy);
5. Intraocular surgery or intraocular laser procedures for refractive corrections within 6 months prior to screening;
6. Vitamin D deficiency defined as 25-OH-vitamin D levels < 12.0 ng/mL (30 nmol/L) at baseline:
 - In patients with 25-OH vitamin D level of < 12.0 ng/mL at screening and with no symptoms of osteomalacia or low serum calcium, administration of a loading dose of oral vitamin D (recommended minimum 50 000 IU of vitamin D3, but according to local guidance) will be allowed. (Different formulations of vitamin D3 are allowed based on the approved therapy in the patient's country. Vitamin D2 is permitted where D3 is not available);
7. Hemoglobin concentration below 11.0 g/dL (110 g/L) for men or below 10.0 g/dL (100 g/L) for women at screening.

Medical conditions associated with muscle loss

8. Chronic kidney disease [estimated glomerular filtration rate (GFR) < 30 mL/min];
9. History of confirmed chronic obstructive pulmonary disease with a severity grade > 2 on the Medical Research Council Dyspnea Scale;
10. Confirmed rheumatoid arthritis or other systemic autoimmune disease requiring immunosuppressive therapy or corticosteroids > 10 mg/d prednisone equivalent, acquired immunodeficiency syndrome (AIDS), or type 1 diabetes mellitus;
11. History of or ongoing gastrointestinal diseases known to cause malabsorption of protein or energy, such as inflammatory bowel disease, celiac disease, short bowel syndrome, pancreatic insufficiency. Individuals in which the disease is well controlled with medication/enzyme supplements (e.g., pancreatic insufficiency) or dietary modification (e.g., celiac disease) are eligible for enrollment;

Liver [REDACTED] related conditions

12. Abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin (except Gilbert's Disease), [REDACTED]. The investigator should be guided by the following criteria:

- Any single transaminase may not exceed 3x the upper limit of normal (ULN). A single parameter elevated up to and including 3x ULN should be re-checked as soon as possible, and always prior to enrollment/randomization, to rule out any lab error.
- If the total bilirubin concentration is increased above the ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 μ mol/L).

- 

13. Known history or presence of severe active acute or chronic liver disease (e.g., cirrhosis) or conditions with hepatotoxic potential (e.g. known gallbladder or bile duct disease, acute or chronic pancreatitis);

Cardiovascular conditions

14. Confirmed diagnosis of heart failure classified as New York Heart Association Class III and IV (e.g. dilated cardiomyopathy);
15. Myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention (e.g. angioplasty or stent placement), or deep vein thrombosis/pulmonary embolism within 12 weeks of screening. Patients with current/active unstable angina are excluded;
16. Severe cardiac valve disorders or defects (e.g. aortic or mitral stenosis);
17. Severe pulmonary hypertension uncontrolled with medication;
18. Clinically significant cardiac arrhythmia requiring medical intervention in the past 3 months (e.g. SVT, atrial fibrillation with RVR, AICD with discharge);

Other medical or living conditions

19. History of hypersensitivity to therapeutically administered antibodies.
20. Chest pain, severe shortness of breath, or occurrence of other safety concerns during the screening or baseline assessments.
21. Lack of peripheral venous access
22. Active cancer (i.e., under current treatment), or cancer requiring treatment in the last 5 years excluding nonmelanoma skin cancers or cancers with excellent prognosis (e.g., early stage prostate or breast cancer, carcinoma in situ of the uterine cervix);
23. Significant coagulopathy, platelet count less than 75,000/mm³;
24. Active systemic infection requiring hospitalization or treatment with i.v. anti-infectives or antibiotics within 4 weeks of screening;
25. Any chronic active infection (e.g., HIV, hepatitis B or C, tuberculosis, etc), to be confirmed prior to randomization. Patients receiving chemoprophylaxis for latent tuberculosis infection are eligible for the study;
26. Active alcohol/drug abuse, or alcohol/drug treatment < 12 months prior to screening; subjects having successfully completed an alcohol/drug treatment program >12 months prior to screening with sustained abstinence are eligible;

27. Patient has any medical condition or laboratory finding during screening (e.g. an unexplained or clinically significant lab result), which, in the opinion of the investigator may interfere with participation in the study, might confound the results of the study, or pose an additional safety risk in administering bimagrumab;
28. Patient plans to move out of the study area within 12 months or be out of study area for > 4 weeks continuously;
29. Individuals who require routine and regular (e.g., daily) assistance from another person to complete one or more basic activities of daily living (basic ADL bathing, dressing, toileting, feeding, grooming) regardless of where they reside. Assistance with instrumental ADL (i.e., shopping, meal preparation, housework) is permitted;
30. Patients with a Mini Mental State Examination score < 21 at screening;

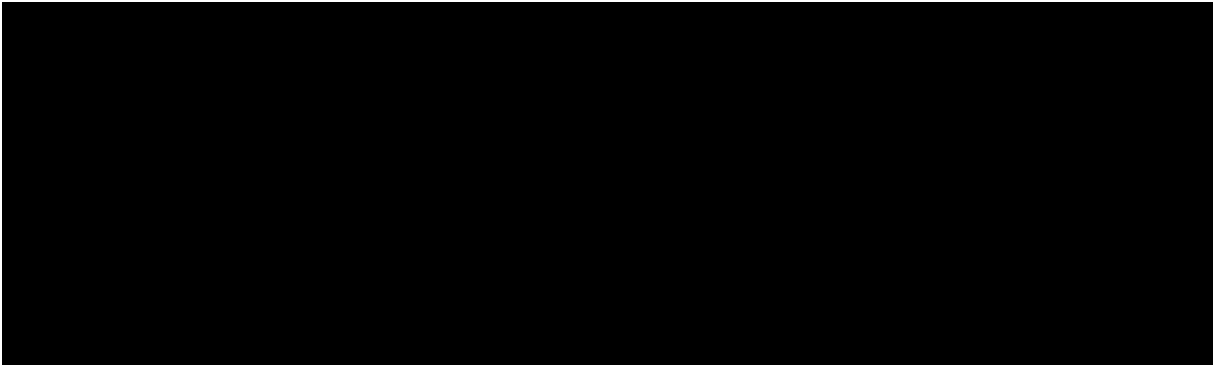
[REDACTED]

[REDACTED]

[REDACTED]

Prohibited medication

[REDACTED]



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.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment



Placebo will be a Dextrose 5% in water (D5W) infusion supplied by the site.

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored and appropriate temperature logs maintained as source data. Appropriate documentation of the subject specific dispensing process must be maintained. Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the patient.

*Note: To maintain the blind, the investigational treatments will be prepared by an unblinded pharmacist/designee, [redacted] and the investigational treatment will **only be administered by study personnel blinded to patient treatment allocation.***

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply. Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction.

5.1.2 Additional study treatment

Dietary counseling will be performed to support daily intake levels of at least 0.8 g protein/kg and 20 kcals/kg of body weight and to ensure daily supplementation with Vitamin D throughout the study and ONS during the run-in period [REDACTED]

[REDACTED] If it is determined to be necessary from one of the planned diet assessments, patients will be instructed to consume ONS as needed to ensure adequate protein intake (see [Section 5.5.3.2](#) and [Section 6.2](#)).

5.2 Treatment arms

In part A, patients will be assigned in a ratio of [REDACTED] (700mg bimagrumab: placebo).

In Part B, patients will be assigned in a ratio of [REDACTED] (210mg bimagrumab:70mg bimagrumab: placebo:700 mg bimagrumab).

By the end of the study, patients will have been assigned to one of the following 4 treatment arms to receive i.v. doses of the following:

1. Bimagrumab 70 mg 6 doses
2. Bimagrumab 210 mg 6 doses
3. Bimagrumab 700 mg 6 doses
4. Placebo 6 doses

5.3 Treatment assignment

Treatment / randomization numbers will be assigned in ascending, sequential order to eligible subjects (see [Section 5.5.1](#) for details).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will then assign a randomization number to the patient, which will be used to link the patient to a treatment arm. The randomization number is for internal use only and will not be communicated to the caller.

5.4 Treatment blinding

Randomized patients will remain blinded to treatment allocation from the time of randomization until database lock. Investigator staff, persons administering the assessments, and the Novartis clinical team will also remain blinded to treatment allocations throughout the study.

The following methods will be used to maintain the blind: (1) Randomization data are kept strictly confidential until the time of un-blinding and will not be accessible by anyone else involved in the study except for the un-blinded pharmacist [REDACTED] (see specifications provided in [Appendix 4](#)). (2) [REDACTED]

[REDACTED] (3) To the best extent possible the order of assessments will match the one used at each dosing visit, thus normalizing the process to all patients, (4) Any potentially unblinding parameters will not be available to the patient, site or study team, e.g. DXA results, FSH or Activin A. Randomization data are strictly confidential and will be accessible only to authorized personnel until unblinding of the trial after database lock (see [Appendix 4](#) for details). [REDACTED]

[REDACTED] Both the unblinded pharmacist and [REDACTED] will keep treatment allocation information confidential until clinical database lock. Un-blinding will only occur in the case of patient emergencies (see [Section 5.5.13](#)) and at the conclusion of the study.

IMPORTANT: Due to the difference in preparation methods between the active and placebo treatments, an unblinded pharmacist or other qualified trained personnel who is independent of the study team will be required. This unblinded pharmacist will receive the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the study team remains blinded throughout the course of dose administrations and the remainder of the study.

5.5 Treating the Patient

5.5.1 Patient numbering

Patient number

Each patient screened is assigned a unique patient number. The screening number is a combination of a four digit center number, which is provided by Novartis, and a three digit sequential number allocated by the investigator, starting with 001. Therefore, if the center number is 1001, the patient numbers will be assigned such as 1001001, 1001002, etc. in ascending order. If the center number is 1002, the patient numbers will be assigned such as 1002001, 1002002, etc.

The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT.

Patients can be re-screened and should be assigned a new patient number.

Randomization number

If the patient is deemed eligible for the study following Baseline and will commence the dosing, a randomization number will be assigned using an interactive response technology (IRT) system. Once assigned to a patient, a randomization number will not be reused.

5.5.1.1 Randomization scheme before protocol amendment v02:

All eligible patients were randomized [REDACTED] (bimagrumab 700mg : bimagrumab 210mg : bimagrumab 70mg : Placebo) ratio in 4 treatment arms. [REDACTED]

5.5.1.2 Randomization scheme for Part A:

Following protocol amendment 02, for Part A, patients will be randomized into bimagrumab 700 mg and placebo using a [REDACTED] scheme. [REDACTED]

[REDACTED] No randomization into lower dose groups (bimagrumab 70mg and bimagrumab 210 mg) will occur in Part A.

5.5.2 Dispensing the study treatment

The packaging of the investigational treatment will be open-label. Once prepared, bimagrumab will not be identical in appearance to placebo.

Refer to the Pharmacist Instruction Manual for details on dispensing, preparing and administering study treatment.

The unblinded pharmacist/designee will NOT administer the study drug to the subject.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance representative. Storage conditions must be adequately monitored and appropriate temperature logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the unblinded Monitor during site visits and/or at the completion of the trial.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any used, partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study (e.g. the unblinded monitor), the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate (appropriate local SOP must be in place).

5.5.3.2 Handling of other study treatments

Patients with vitamin D deficiency (< 12.0 ng/mL) at baseline are ineligible for this study, but may be rescreened following successful replenishment treatment. To ensure sufficient Vitamin D levels during the study, all patients will receive vitamin D supplementation from the start of the run-in period to the EOS. The vitamin D supplements should be locally sourced.

- daily administration of 800 IU to 4000 IU vitamin D3 (or D2 if D3 is not available) (dose and form of vitamin D should be chosen by the site based on patient need and country standard); or,
- equivalent weekly or monthly formulation if deemed to be of advantage for the individual patient's compliance.

Similarly the minimum baseline nutritional intake for participating in this study is an average of at least 20 kcal/kg body weight/day and 0.8 g protein per kg of body weight per day as estimated by an established method of dietary assessment such as 24-hour recall or food records.

For more details refer to [Section 6.2](#).

5.5.4 Instructions for prescribing and taking study treatment

Infusions will occur every 4 weeks, after all pre-dose assessments have been performed. Six doses will be administered during the course of the study (see [Section 3.1](#)).

Only the materials (infusion bag, administration set and filter) specified in the pharmacy manual should be used for administration of the study medication.

All dosages prescribed and dispensed to the patient during the study must be recorded on the Dosage Administration Record eCRF page.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments are not permitted.

Dose interruptions should be avoided for the duration of treatment. However, for patients who are unable to tolerate the protocol-specified dosing scheme, dose interruptions of investigational treatment are permitted in order to keep the patient on study drug.

[REDACTED]

5.5.6 Recommended treatment of adverse events

[REDACTED]

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

Although not expected, any acute allergic reactions should be treated as needed using conventional counter measure therapies as indicated (including but not limited to epinephrine, antihistamine, corticosteroid, intravenous supplies, crystalloid, an oral airway, bag and mask, and supplemental oxygen). In the case of a serious adverse event in which decreasing the systemic concentration of bimagrumab may be of clinical benefit, the investigator should consider plasmapheresis. Study sites should not feel constrained in any way from providing necessary medical intervention.

[REDACTED]

5.5.7 Rescue medication

Not applicable, as there are no approved pharmacotherapies for sarcopenia.

5.5.8 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study. All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications eCRF or Surgical and Medical procedures eCRF.

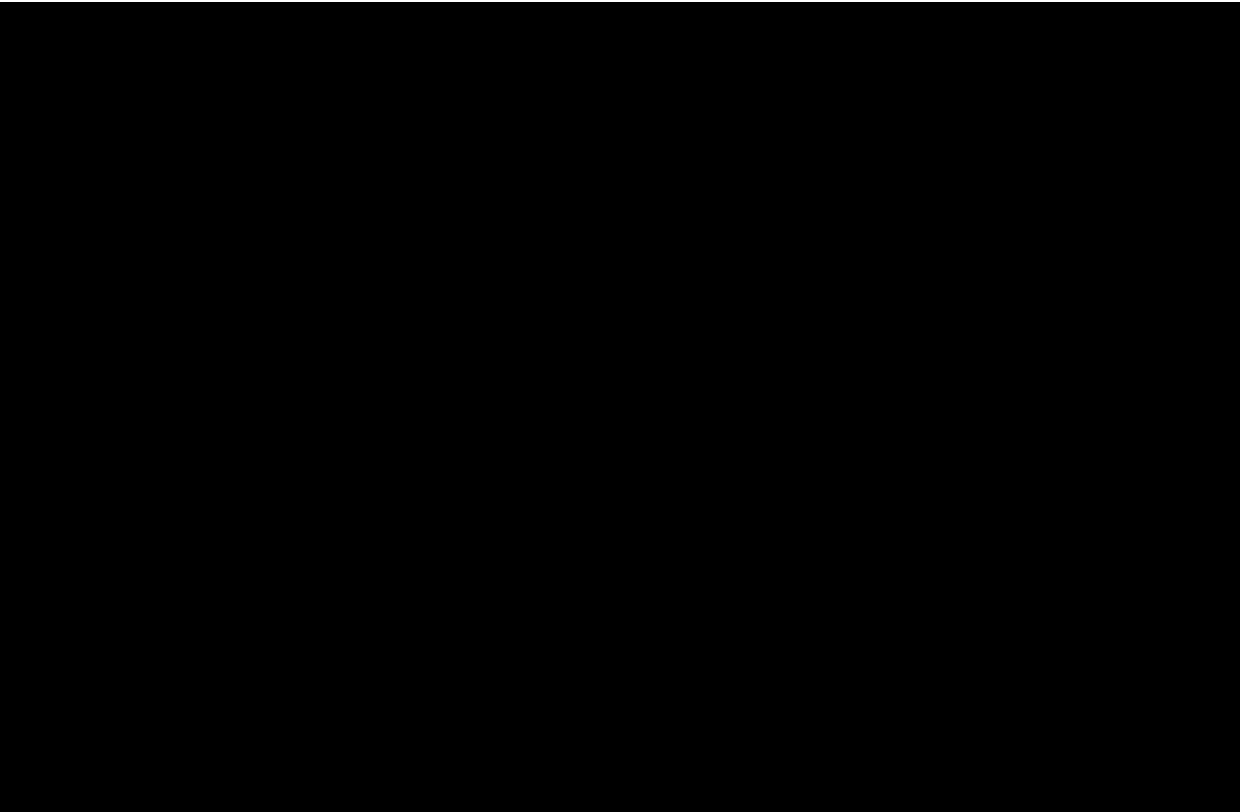
[REDACTED] Each concomitant drug must be individually

assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

5.5.9 Prohibited treatment

Any investigational treatment on a different protocol is forbidden at the time of enrollment or within 5 half-lives of the investigational treatment prior to enrollment.



5.5.10 Discontinuation of study treatment

Study “Stopping rules”

An external Data Monitoring Committee (DMC) will monitor unblinded safety data from a bimagrumab program perspective, including this study, for potential safety concerns (see [Section 8.4](#)). If the Committee views the benefit-risk to change adversely at any time, a decision could be made to stop and re-evaluate the protocol or continue the study. In addition,

if any of the following situations occur, the study may be placed on hold and, upon review of study data by the clinical trial team and the safety team and discussion with the investigators, may be terminated or a dose level re-evaluated:

- The investigators and Novartis consider that the number and/or severity of adverse events justify discontinuation of the study
- The sponsor unilaterally requests it.

The study may be terminated at any time for any reason by Novartis. Should this be necessary the Investigator will be informed of the procedures to be followed to assure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing their IEC / IRB of the early termination of the trial.

Individual subject withdrawal

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the person's well-being.

Investigational treatment *must* be discontinued under the following circumstances:

- Use of prohibited treatment as per [Table 5-1](#).
- Any other protocol deviation that results in a significant risk to the patient's safety
- Breaking of the blind (inadvertently or for emergency reasons)
- Severe hypersensitivity reaction occurs
- Liver event definition met as per [Appendix 1](#) or [Appendix 2](#)
- Death
- Withdrawal of consent
- Sponsor decision to terminate (part of) the study

Investigational treatment *may* be discontinued under the following circumstances:

- [REDACTED]
- Emergence of one or more adverse events that in the judgment of the investigator, taking into account the patient's overall status, prevent the patient from safely continuing in the study
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from safely continuing in the study

Patients who discontinue study treatment should **NOT** be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 5.5.11](#)). They should return approximately 4 weeks after their last dose for the EoT visit. The EoS visit should be scheduled 4 weeks after EoT. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in [Section 5.5.12](#).

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit, including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

5.5.11 Withdrawal of consent

Patients may voluntarily withdraw consent and cease to participate in the study for any reason at any time.

Withdrawal of consent occurs only when (1) a subject does not want to participate in the study anymore and (2) does not want to participate in any further visits or assessments and (3) does not want any further study related contacts and (4) does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information in the eCRF. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used and must be destroyed. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.12 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

Patients who are discontinued from the study for any reason will not be replaced.

5.5.13 Emergency breaking of assigned treatment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT system. When the investigator contacts the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Leader that the code has been broken.

The unblinded treatment code should not be recorded on the eCRF.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. If appropriate, the investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken or for any non-emergency reason (see [Section 5.5.10](#)).

5.5.14 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety. The study will complete when the last patient completes his/her Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or when the last patient has completed his/her End of Treatment visit and has transferred to the extension study.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.15 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely discontinued subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

6 Visit assessments

The full [Assessment schedule](#) is presented before [Section 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, and should also ensure that consecutive infusions are performed at least 14 days apart:

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

Visits 2 and 3 (early run-in visits) and Visits 5 and 101 (Final baseline and Day 1 dosing) may be combined [REDACTED]

[REDACTED] and where it is deemed safe by the investigator.

[REDACTED]

Assessments for a particular visit may be split over more than one day (as long as within the required visit window), however the order of assessments should be preserved.

Below are guidelines for organizing and performing the study assessments.

- Assessments should be performed sequentially in the morning as follows: ECG collection, vital signs, blood sampling.
- After blood sampling, patients may be offered breakfast.
- [REDACTED]
- Physical performance measures should be performed in the order outlined in the Outcomes Manual. Please refer to this manual for more information.
- After assessment of the physical performance measures and any other protocol-specified pre-dose assessment, patients can be dosed.
- [REDACTED]

Patients who discontinue study treatment should **NOT** be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 5.5.11](#)). They should return for the assessments indicated by an asterisk (*) in the Assessment Table. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in [Section 5.5.12](#).

At a minimum, patients will be contacted for reporting and follow-up of serious adverse events during the 30 days following the last study visit, including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

6.1 Dietary, fluid and other restrictions

At any visit where required, patients will fast (i.e. no food and liquid except water) for at least 8 hours prior to the blood draws. Breakfast will be offered after the blood draws and prior to performing the performance measures.

6.2 Dietary Requirement

6.2.1 Dietary assessment

It is important that patients eat a sufficient amount of calories and protein to allow a muscle anabolic therapy to be effective. The minimum nutritional intake for participating in this study is an average over the past four weeks of at least 20 kcal/kg body weight/day and 0.8 g protein per kg of body weight/day as estimated by an established method of dietary assessment (see [Section 4.1](#)). This assessment must be administered through a face to face meeting with a dietician or comparably trained professional using an established method of dietary assessment, (e.g., three serial 24-hour recalls, 3-day dietary record, or similar). Patients not meeting the minimum requirement at baseline can be offered dietary counseling and can be re-screened after 4-5 weeks.

At visits after randomization, the nutritional status of patients may be evaluated using an interview format diet assessment if the investigator deems it necessary based on a review of the patient's status. In particular, if a weight increase or decrease of 5% or more compared to

baseline is seen, a comprehensive diet assessment using repeated 24-hour recalls or food records should be conducted by the dietitian.

Patients should be encouraged at each clinic visit to consume adequate dietary calories and protein. Patients who report low protein intake at screening (less than 0.8 g/kg/day) or at any time during the study should be provided nutritional counseling on ways to increase dietary protein and other nutrient intake through food or supplementation

Similarly, potential patients who are noted to have vitamin D deficiency at the screening visit (less than 12.0 ng/dl) should be advised to discuss this deficiency with their primary physician, and if appropriate, recommended Vitamin D supplementation (as per [Section 6.2.2](#)). If the investigator feels that an individual is a good study candidate, the person may be re-screened at least four weeks later to ensure that corrective measures have been taken and the patient's protein and/or vitamin D deficiency has been adequately addressed in order to fulfill the inclusion criteria.

Nutritional status and subsequent actions taken (e.g. dietary counseling) will be entered into the Nutritional Status eCRF.

6.2.2 Nutritional supplement

An oral Vitamin D supplement will be provided to all study patients throughout the study.

- In patients with 25-OH vitamin D level of ≥ 12.0 ng/mL at screening:
 - daily administration of vitamin D (800 IU to 4000 IU, D3 preferable but D2 also acceptable per local availability); or,
 - equivalent weekly or monthly formulation if deemed to be of advantage for the individual patient's compliance.
- In patients with 25-OH vitamin D level of < 12.0 ng/mL at screening and with no symptoms of osteomalacia or low serum calcium:
 - administration of loading dose of oral vitamin D (recommended minimum 50 000 IU of vitamin D3, but according to local guidance) will be allowed.
(Different formulations of vitamin D3 are allowed based on the approved therapy in the patient's country. Vitamin D2 is permitted where D3 is not available) Per the exclusion criteria, patients must have a 25-OH-vitamin D level ≥ 12.0 ng/mL at baseline.

[Redacted]

[Redacted]

6.3 Patient demographics/other baseline characteristics

6.3.1 Demographic Information

Patient demographic and baseline characteristic data to be collected on all subjects include: date of birth, age, sex, race, predominant ethnicity.

6.3.2 Medical History

All relevant medical history and current medical conditions occurring prior to the date of informed consent will be captured in the Medical History eCRF. Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature. The aim is to capture the diagnoses rather than symptoms.

Fall History will be reported separately on the Falls History eCRF page.

6.3.3 Cardiovascular and metabolic co-morbidities

Information on cardiovascular co-morbidities will be collected. Following conditions will be recorded in the eCRF if met by the study subject:

- Cardiomyopathy
- Hyperthyroidism
- Valvular Heart Disease
- Diabetes (with and without complications)
- Hypertension
- Dyslipidemia/Hyperlipidemia
- Myocardial infarction
- Peripheral arterial disease
- Prior stroke (hemorrhagic, ischemic, or unspecified)
- Prior transient ischemic attack
- Atrial fibrillation

The cardiovascular and metabolic history will be recorded in the Cardiovascular History eCRF, before randomization.

6.4 Treatment exposure and compliance

Patients will receive all study medication at the Investigator site. Study medication will be administered by site personnel, compliance will be ensured by appropriate training of site personnel. The date and time of administration of study drug will be recorded in the dosage administration record section of the eCRF.

Every effort will be made to follow each patient; [REDACTED] should be made wherever possible on non-visit weeks to assess for the presence of AEs, [REDACTED] and to keep patients engaged in the study.

[REDACTED]

Throughout the study, patients will be required to participate in an exercise program with defined minimum requirements (see [Section 3.1](#)). [REDACTED]

[REDACTED]

6.5 Efficacy / Pharmacodynamic assessments

Pharmacodynamic assessments are detailed below.

Efficacy measurements in the study will include:

- Short physical performance battery (SPPB) to assess physical function
- Gait Speed (GS is a component of SPPB) to assess physical function
- 6 minute walk test (6MWT) to assess physical function
- [REDACTED]
- Total lean body mass (LBM) and appendicular skeletal mass index (ASMI) assessed by DXA to measure lean body mass and skeletal muscle mass of the arms and legs, respectively.
- [REDACTED]

6.5.1 Short physical performance battery

[REDACTED]

The Short Physical Performance Battery (SPPB) has been shown to be highly predictive of subsequent disability, hospitalization, institutionalization, and mortality in community-dwelling elders in epidemiological studies and outpatient clinics ([Guralnik et al 2000](#); [Studenski et al 2003](#)). The disability remains even after adjustment for level and severity of comorbidity and self-report functional status. Collectively, SPPB is considered to be a nonspecific but highly sensitive indicator of global health status reflecting several underlying physiological impairments.

The SPPB evaluates lower extremity status by measuring three domains of physical function: maintenance of standing balance, usual gait speed and lower extremity strength and power. The corresponding tasks include three static positions with decreasing base of support to challenge balance, walking at usual speed over 4-meters and, the ability to rise from a chair without the use of the arms once and then five times consecutively. The final score is a composite of the three groups of tasks and uses a standardized scale of 0-12, with the higher score reflecting a higher level of function. A change of 1.0 on the SPPB score is considered clinically relevant ([Perera et al 2006](#), [Pahor et al 2014](#)). Complete details of test administration, equipment and recording into the eCRF are described in the CBYM338E2202 Outcomes Manual.

6.5.2 Gait speed

Gait speed in this study will be assessed as part of the SPPB, over a 4 meter distance of a 6 meter course. This test 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 down a hallway).

Usual gait speed represents one of the most clinically relevant physical performance measures to evaluate older persons. Gait speed is associated with physical activity levels, changes in strength of lower extremity muscles, frailty and falls ([Newman et al 2003](#), [Chandler et al 1998](#), [Cesari et al 2005](#)).

Gait speed is a well-established measure of physical function, it has shown to predict future disability in diverse community-dwelling elderly populations and is sensitive to changes in physical status in response to an intervention (e.g. physical activity and rehabilitation) ([Barthuly et al 2012](#)). Poor functional performance as measured by slow or declining gait speed is related to an increased risk of mobility disability, hospitalization and mortality ([Studenski et al 2011](#)), whereas improvements in gait speed are related to reductions in mortality risk ([Hardy et al 2007](#)). For these reasons, gait speed has been suggested as a key indicator of overall health in the geriatric population.

Complete details of test administration, equipment and recording into the eCRF are described as part of the SPPB protocol listed in the CBYM338E2202 Outcomes Manual.

6.5.3 6 minute walk test

The 6 minute walk test (6MWT) is a simple test that measures how many meters a person can walk in 6 minutes. Repeated measurement of the 6MWT over time has been used in studying numerous musculoskeletal, pulmonary, and cardiovascular conditions and is a validated outcome in investigational drug trials.



Complete details of course set-up, test administration, equipment and recording into the eCRF are described in the CBYM338E2202 Outcomes Manual.



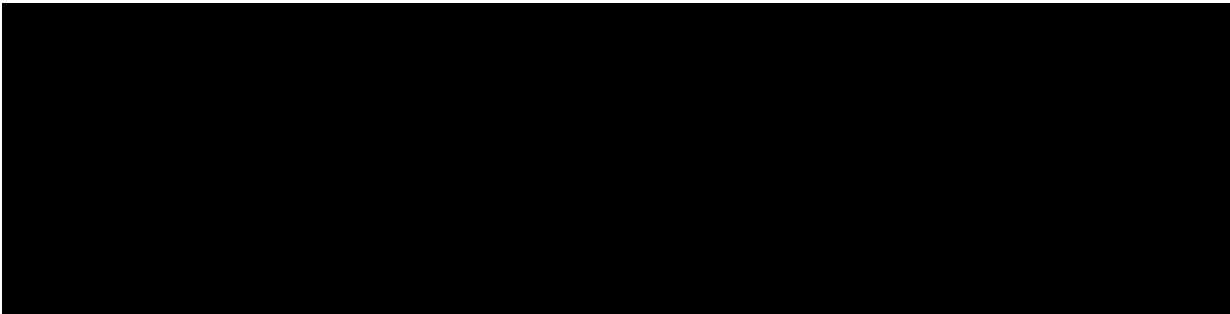
6.5.5 Total lean body mass and appendicular skeletal mass index (ASMI) assessed by DXA

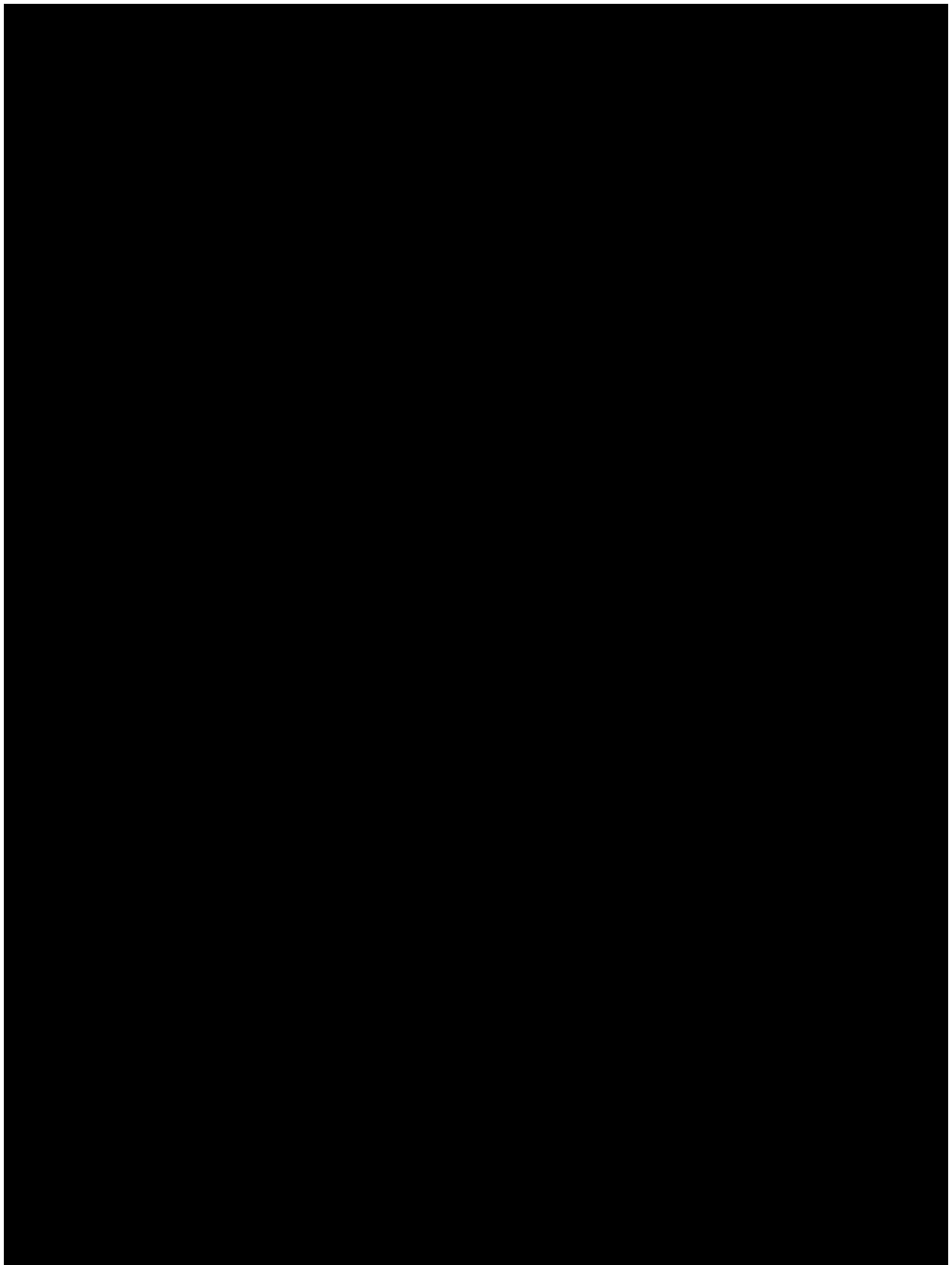
Dual energy X-ray absorptiometry (DXA) will be used to assess changes in total lean body mass (LBM) and appendicular skeletal mass index (ASMI). DXA instruments use an x-ray source that generates and is split into two energies to measure bone mineral mass and soft tissue from which fat and fat-free mass (or lean body mass) are estimated. The exam is quick (~5-6 min), precise (0.5-1%) and non-invasive. DXA scanners have the precision required to detect changes in muscle mass as small as 5%.

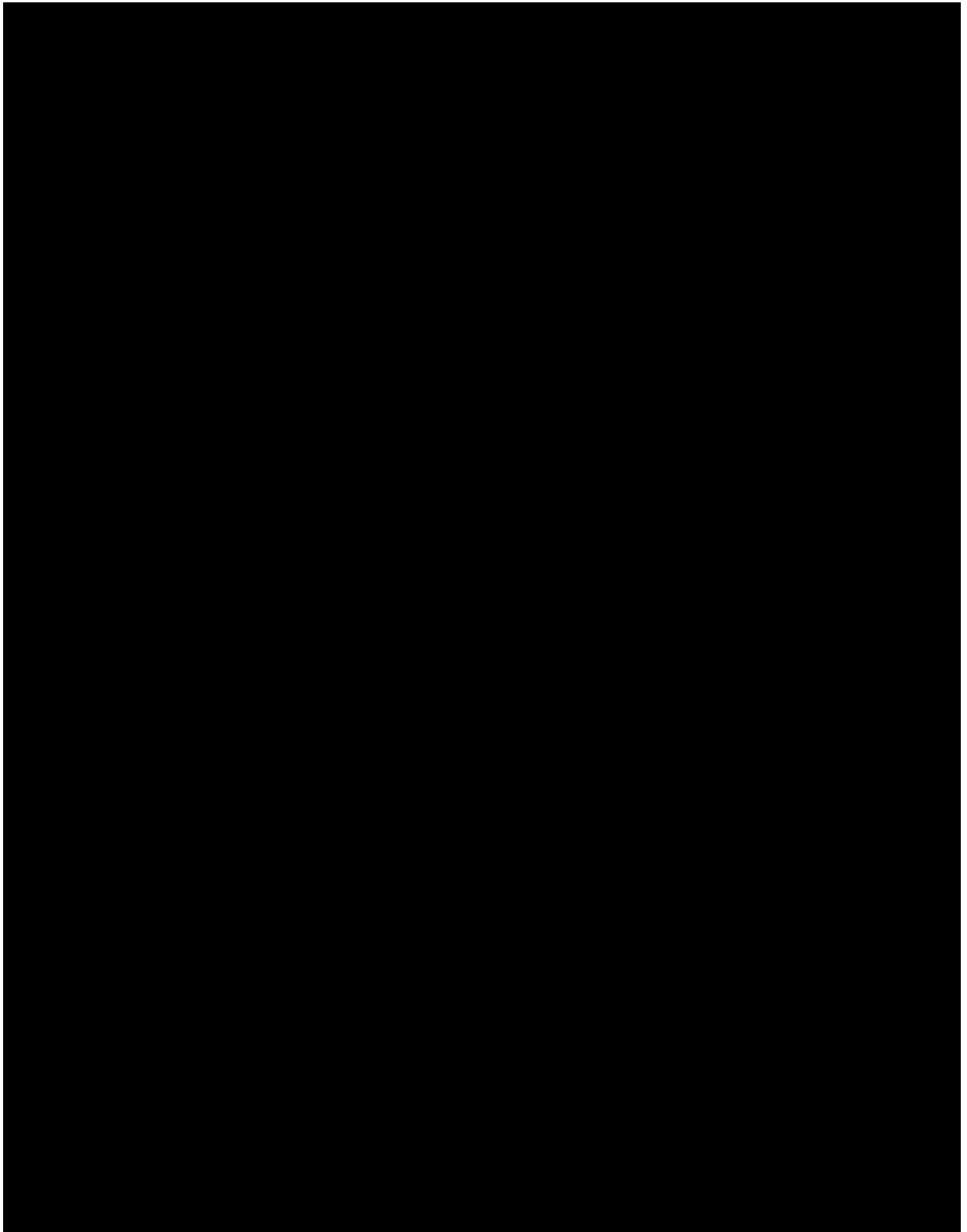
Radiation exposure from DXA scans is minimal. The National Council of Radiation Protection and Measurements (NCRP) has recommended the annual effective dose limit for infrequent exposure of the general population is 5,000 μSv and that an annual effective dose of 10 μSv be considered a Negligible Individual Dose. The effective dose of a DXA whole body scan on an adult is 5 μSv . The total amount of radiation exposure per subject from DXA in this study will be about 25 μSv . This amount of radiation is equivalent to approximately 3.6 days of background exposure (approx. 0.3 μSv per hour at sea level).

Studies have shown that quality assurance is an important issue in the use of DXA scans to determine body composition. DXA instrument manufacturer and model should remain consistent and their calibration should be monitored throughout the study. Use of a standardized scan acquisition protocol and appropriate and unchanging scan acquisition and analysis software is essential to achieve consistent results. Likewise, because of variability in interpretation of the scans, it is important to utilize centralized scan analysis by experienced staff.

The images will be transmitted to a central reading vendor for independent review. Sites will receive appropriate training for data transfer as well as a DXA manual that will include detailed instructions and data transfer procedures.







6.6 Safety

6.6.1 Physical examination

A complete physical examination will include the examination of general appearance, skin (including special attention to telangectasias of the skin or nail-folds and acne), neck (including thyroid gland, and oral mucosa for evidence of bleeding, hypertrophy, ulceration, or other changes from baseline), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological parameters. Only if indicated based on medical history and/or symptoms, should rectal, external genitalia, breast, and/or pelvic exams be performed.

Skin-related issues will be assessed by the investigator or assigned clinician at each physical exam time point.

If possible, assessments for an individual patient should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the eCRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History eCRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF.

6.6.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the patient has been resting for 3 minutes in a seated position, systolic and diastolic BP will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a manual sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are out-of-range, the Investigator may obtain two additional readings, so that a total of up to three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within range at screening and baseline in order for the subject to qualify. All readings should be recorded on the eCRF.

Whenever possible, at each visit, vital signs should be measured using the same arm.

6.6.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

Body mass index (BMI) will be calculated using the following formula:

- $BMI = \text{Body weight (kg)} / [\text{Height (m)}]^2$

6.6.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening or at baseline and there is a reason to believe the result is an anomaly, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and may be discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

6.6.4.1 Hematology

The following tests will be measured centrally: Hemoglobin, hematocrit, white cell count (WBC) with differential as percentage or absolute value (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes), red cell count (RBC), reticulocyte count and platelet count will be measured.

6.6.4.2 Clinical chemistry

The following tests will be measured centrally: Albumin, aldolase, alkaline phosphatase, bicarbonate, total bilirubin (*note*: if the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated), calcium, chloride, cholesterol, C-reactive protein (CRP), creatinine, γ -GT, glucose (fasting), HgbA1c, phosphate, lipase, amylase, potassium, total protein, AST, ALT, sodium, magnesium, triglycerides, urea/BUN, uric acid, and vitamin D.

25-OH Vitamin D is part of the clinical chemistry panel, but listed separately in the [Assessment schedule](#) because of its importance for eligibility.

6.6.4.3 Cardiac Biomarker Panel

The following tests will be measured centrally: creatine kinase (CK), CK-MB and CK-MM, and troponin T.

6.6.4.4 Hormone panel

The following hormones will be measured centrally at screening only: testosterone and thyroid stimulating hormone (TSH). If TSH is abnormal, free thyroxine (free T4 - not total T4) should be reported.

Hormones are listed per assessment frequency in the [Assessment schedule](#).

6.6.4.5 Urinalysis

The following tests will be measured centrally at screening only: A midstream urine sample (approx 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

This analysis will comprise of specific gravity, pH, semi-quantitative “dipstick” evaluation of glucose, protein, nitrites, bilirubin, ketones, leukocytes and blood. A microscopic examination including RBC, WBC, bacteria and casts will be performed only when dipstick evaluation is positive for WBC, or proteins, or blood.

6.6.5 Electrocardiogram (ECG)

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

A standard local 12 lead ECG will be performed supine. Interpretation of the tracing must be made by a qualified physician locally and documented on the ECG / in the ECG section of the eCRF. Each ECG tracing should be labeled with the

- study number
- subject initials
- subject number
- date and time

ECG tracings will be dated and signed by the person who makes the interpretation and kept in the source documents at the study site. The clock on the ECG machine should be synchronized with the central clock on a daily basis. For any ECGs with patient safety concerns, two additional ECGs should be performed to confirm the safety finding.

Clinically significant abnormalities should be recorded on the relevant medical history/Current medical conditions eCRF page prior to informed consent signature and on the Adverse Events page thereafter (see [Section 7.1](#) and [Section 7.2](#)). Clinically significant findings must be discussed with the sponsor.

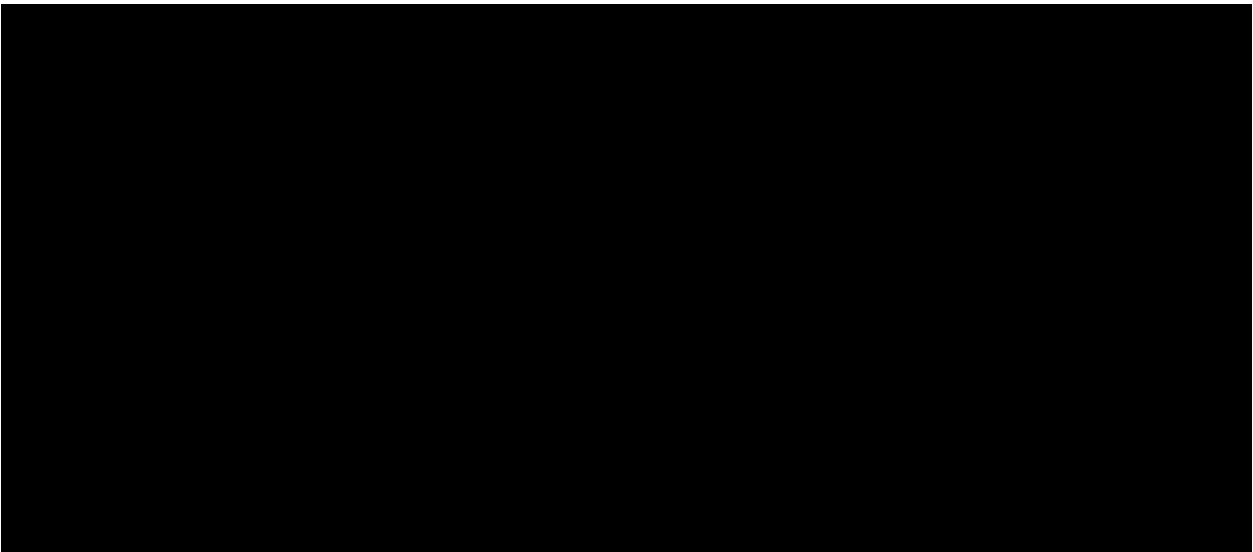
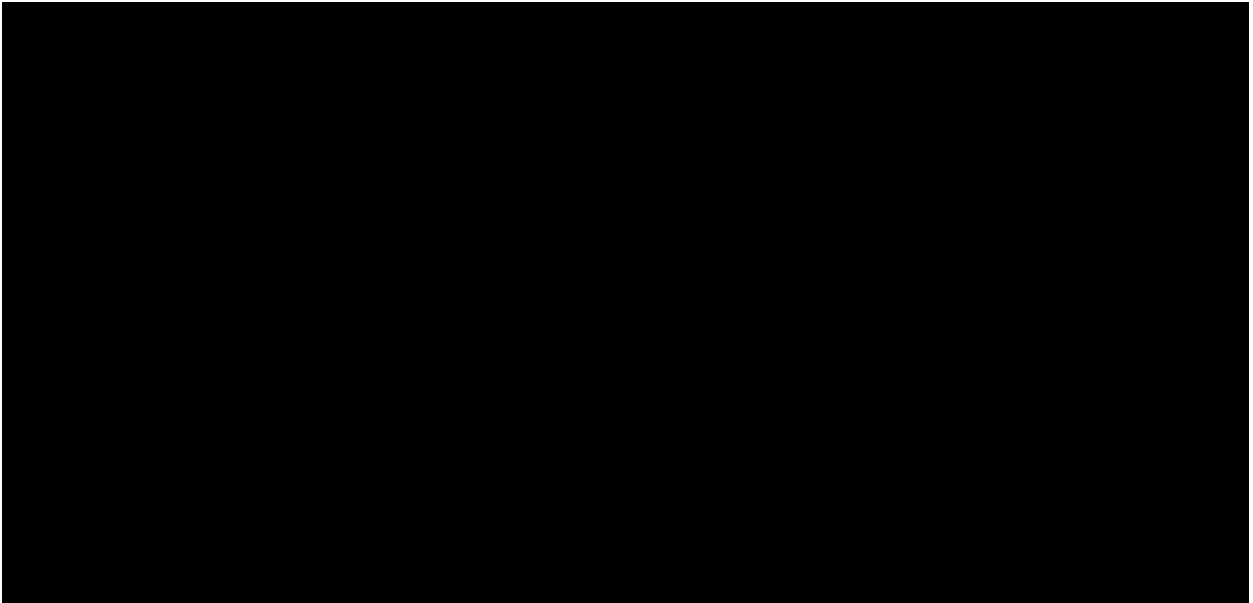
The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT interval uncorrected
- QTcF
- QRS duration

Original ECG tracings, appropriately signed, will be archived at study site.

6.6.6 Pregnancy

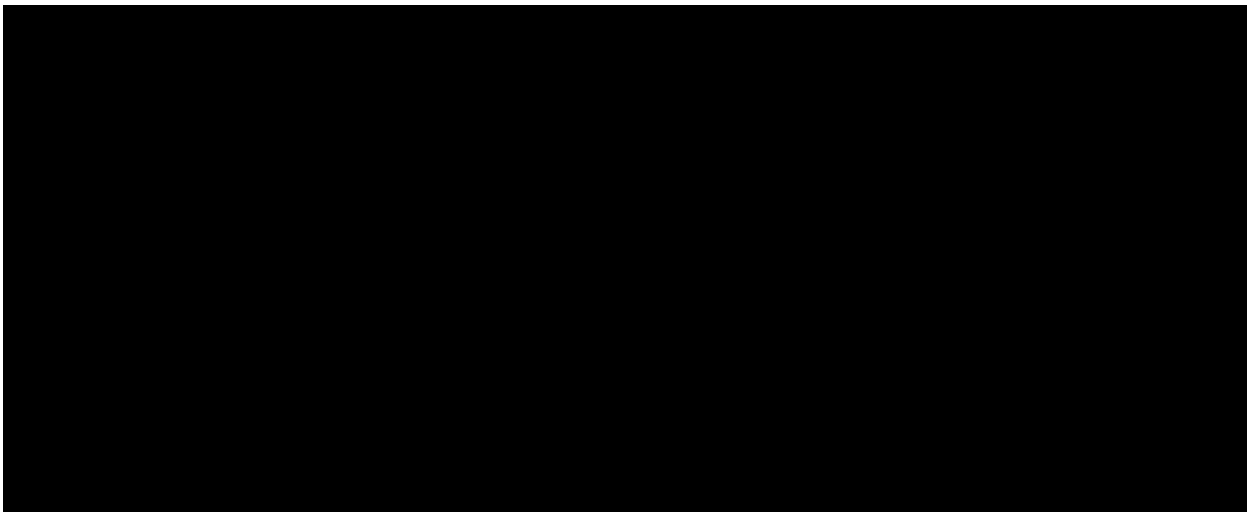
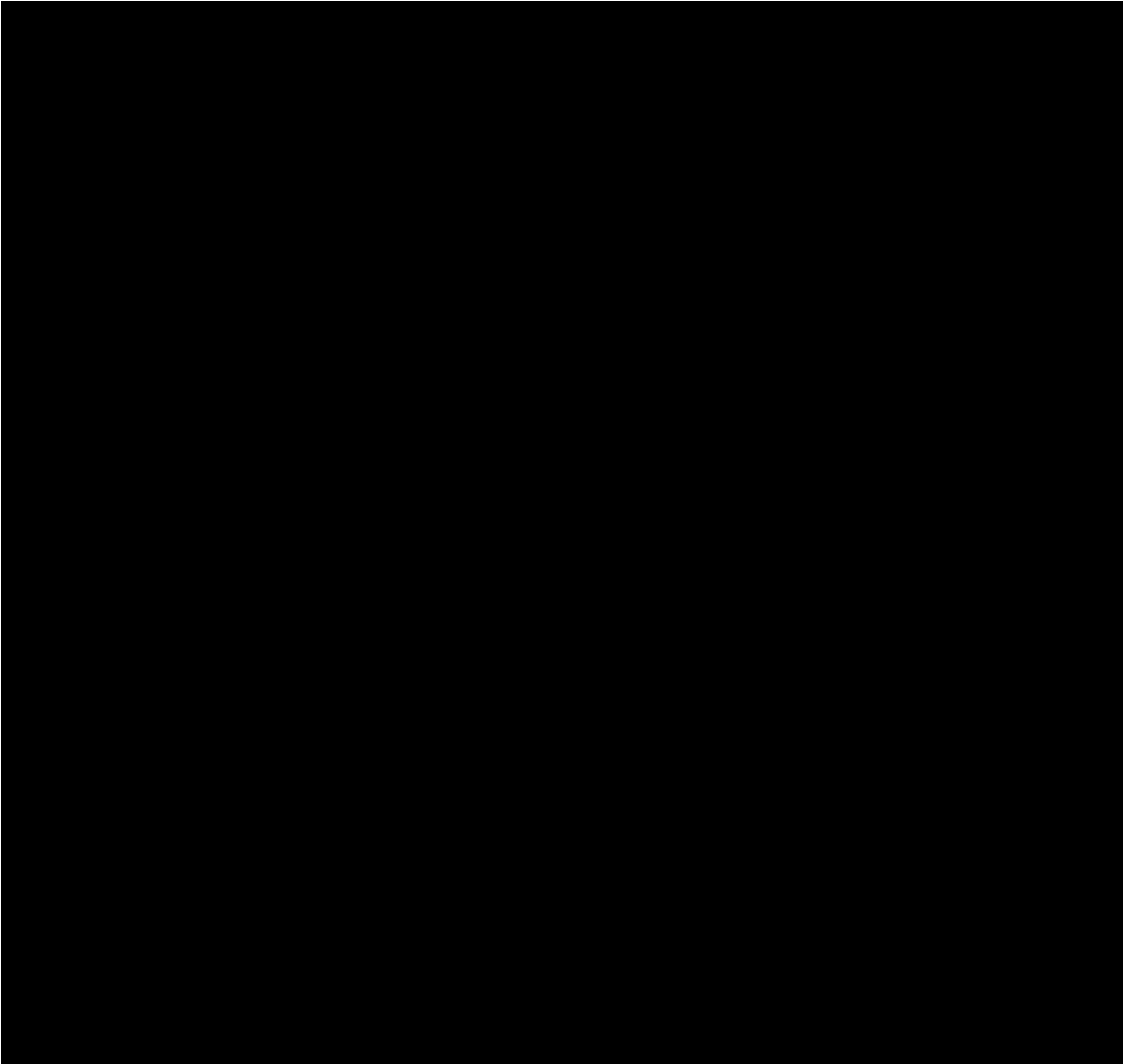
Only postmenopausal women aged 70 or older are included in this study. No pregnancy testing will be performed as pregnancy is a very low risk in this study.

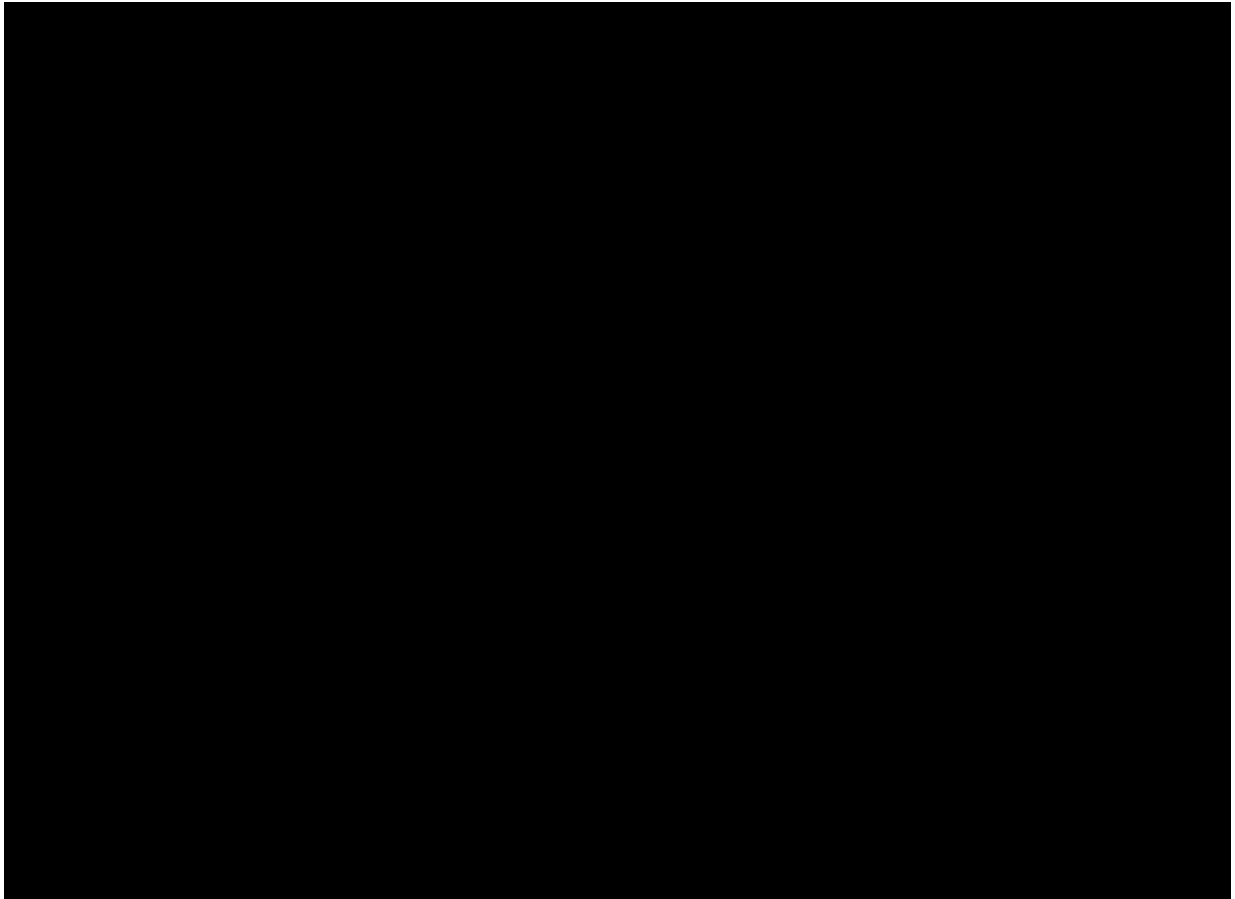


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7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

All patients who have signed informed consent and are entered into the study will have all adverse events occurring after informed consent is signed recorded on the Adverse Event eCRF.

Pre-existing medical conditions/diseases (i.e. Medical History) are considered AEs if they worsen after providing written informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in [Appendix 2](#).

Adverse events must be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade (mild, moderate, severe)
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
2. its relationship to the study treatment (no/yes), or investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its outcome, or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE)
5. action taken regarding study treatment
6. its relationship to study treatment
7. its duration (e.g. start and end date)
8. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)

9. the classification of the AE (general, heart failure, implant related events, cardiomyopathy, ischemic heart disease cardiac rhythm disturbances, spontaneous muscle contraction, bone related event, soft tissue related event, diarrhea)

An SAE is defined as any AE which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

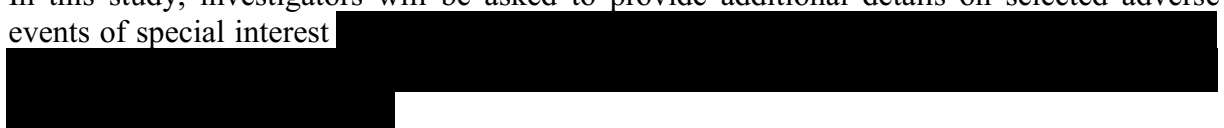
Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the subject during the study as needed.

In this study, investigators will be asked to provide additional details on selected adverse events of special interest



7.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form. Study site personnel must also inform the Novartis Medical Expert and/or Clinical Trial Leader (according to [page 2](#) of this protocol). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and also a copy to the Novartis Medical Expert and/or Clinical Trial Leader (according to [page 2](#)). The telephone and fax numbers of the contact persons in the local Drug Safety and Epidemiology department, specific to the site, are listed on page 2 of this protocol and/or in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 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.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of elevated transaminases and/or bilirubin (elevated liver function tests (LFTs)).
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

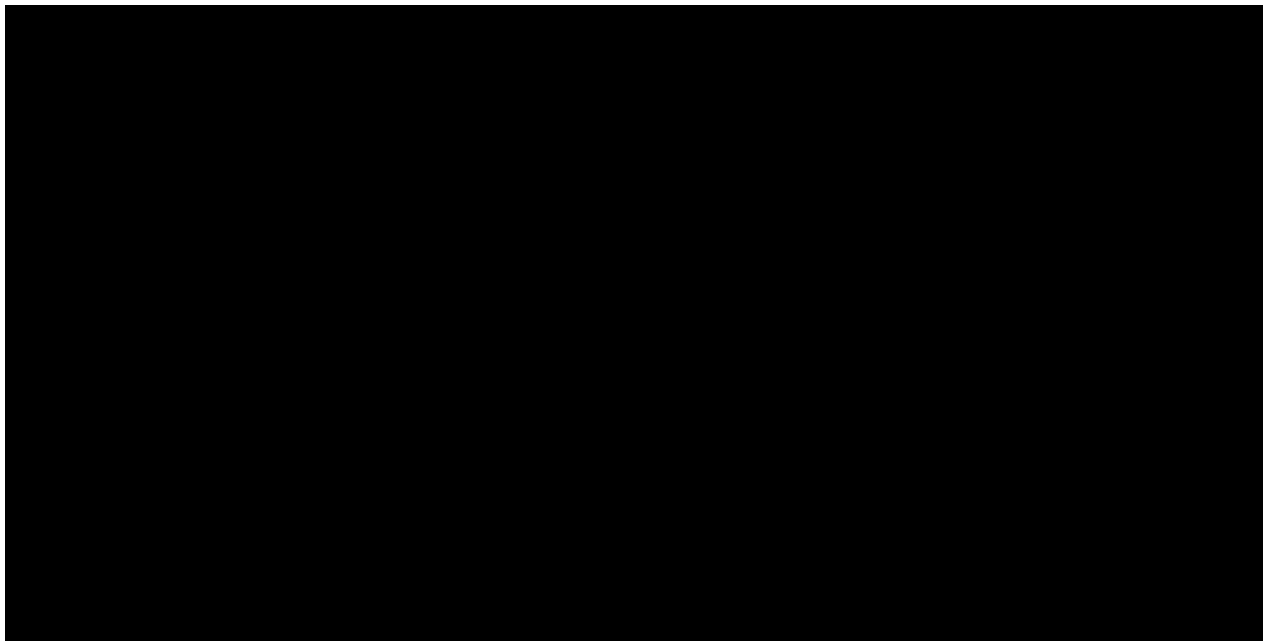
Please refer to [Table 14-1-Appendix 2](#) for complete definitions of liver events.

Any liver event which meets the criteria for a “**medically significant**” event should follow the **standard procedures for SAE reporting** as described in [Section 7.2](#).

Every liver event as defined in [Table 14-1-Appendix 2](#) should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in [Table 14-2-Appendix 2](#).

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist’s consultancy, based on investigator’s discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF.



7.5 Pregnancy reporting

Based on the inclusion of only postmenopausal women and the age range of patients, pregnancy is a very low risk in this study.

In the unexpected event of a pregnancy occurring while the patient is on study treatment, Novartis must be notified within 24 hours of learning of the pregnancy. All activities associated with the pregnancy will be reviewed with the site as needed.

7.6 Safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis or the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic), the eCRF is not considered as source.

8.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The imaging CRO will collect all imaging data (DXA and echocardiography) from sites and send for quantitative analysis to a blinded expert reader. The analysis results are then collected by the imaging CRO and then transformed into a format according to a Novartis data transfer specification. The transformed output will then be sent to Novartis data management for incorporation into the CSR. The imaging CRO will be responsible for all image data clarification forms and missing data at all sites.

Subject questionnaires will be entered into an electronic device by the subject. The system will be supplied by a vendor who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Randomization codes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

8.4 Data Monitoring Committee

An independent, program-wide DMC is instituted for bimagrumab with focus on safety.

The DMC will periodically review the safety information throughout the study to monitor the trial's progress for unexpectedly large differences of toxicity between treatment groups.

The DMC for the study will be composed of individuals with experience and expertise in the management of patients with muscle wasting diseases, and in the monitoring of randomized clinical trials as well as a DMC statistician. None of the DMC members will be involved in the operational conduct of the study or any other bimagrumab clinical or pre-clinical study, except as a member of the DMC.

The mission of the DMC is to independently review and evaluate the unblinded safety data generated during the study as defined in this protocol. The DMC ensures that study participants are not exposed to unnecessary or unreasonable risks and that the study is conducted with high scientific and ethical standards. As needed, the DMC makes recommendations to the Sponsor on actions to be taken regarding the study, which may include the following:

- Discontinuation of the study.
- Suggested modifications to the study protocol and/or the informed consent document.
- Continuation of the study according to the protocol and the relevant amendments.

The DMC is accountable to the Sponsor for appropriate monitoring of the study data.

Although the DMC may make recommendations to the Sponsor about changes in the conduct of the study, final decisions will be made by Novartis. In the case of early termination, consultation with Health Authorities may be required.

Members of the DMC will not share any unblinded or semi-blinded information with anyone outside of the DMC. Particularly, the Sponsor will remain fully blinded to any results throughout the study unless the DMC recommends changes in the conduct of the study (for example, early termination due to negative safety findings).

An independent statistical reporting team not involved in the conduct of the studies will prepare the information for the DMC according to the specifications from the DMC statistician. The main tasks may include:

- Generation of unblinded outputs for the DMC (Treatment A or Treatment B), including tables, figures, and listings, as required.
- Preparation of any other reports requested by the DMC during the closed session.
- Review of the semi-blinded reports before sending to the DMC.

The frequency of the DMC meetings will be determined by the members and ratified in the DMC Charter.

8.5 Adjudication committee

Independent adjudication committees will be used to monitor specific safety events.

Events will be blindly reviewed as they occur during the trial to confirm that they have been evaluated appropriately and diagnosed correctly. Details regarding the adjudication process will be available in the relevant bimagrumab Adjudication Committee charter. The committee members will remain blinded to treatment assignment and may provide expert reports at the end of the study.

The clinical database will be searched by Data Management for targeted adverse events including but potentially not limited to the following categories:

- Cardiac safety events

When an adverse event in this category is identified, a follow-up form will be sent to the clinical site to document the adverse event in detail and to request the submission of any applicable supplemental data which may be available, including copies of source documents. Source documents include, but are not limited to, relevant clinical notes, imaging studies (e.g., radiographs), ECGs, operative and pathology reports, hospital discharge summaries. In addition, an interview with the patient may be needed (in person or via telephone) to fully clarify the circumstances of the event.

The outcome of the adjudication or the expert review will be captured in the clinical data base.

9 Data analysis

9.1 Analysis sets

The Full Analysis Set (FAS) used for all efficacy analyses will consist of all randomized patients who received at least one dose of investigational treatment after randomization and had at least one post-dose efficacy assessment. Patients who are randomized due to erroneous use of the IRT system will be excluded. Patients will be analyzed according to the treatment they were assigned to at randomization.

The safety (SAF) Analysis Set will consist of all patients who received at least one dose of study medication. Patients will be analyzed according to the treatment received.

Per-protocol (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 population will be identified and finalized based on blinded review of the data, prior to the final database lock.

9.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Analyses in this section will use the safety analysis set.

9.3.1 Study medication

The number and percentage of patients who prematurely discontinued study medication will be summarized by reason for discontinuation.

Duration (days) of study medication administration will be summarized. For each patient, the number of days of drug exposure will be taken to be the number of calendar days between the first and last infusion date plus 28 days.

9.3.2 Concomitant medications

The number and percentage of patients using prior or concomitant medications will be summarized by Anatomical Therapeutic Classification (ATC) codes and treatment group, and grouped by anatomical main group (the 1st level of the ATC codes).

Prior medications are defined as drugs taken and stopped prior to first dose of investigational treatment. Any medication given at least once between the day of first dose of investigational treatment and the date of the last study visit will be defined as a concomitant medication. This includes those that were first administered pre-baseline and continued into the treatment period. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of reported administration. If it cannot be established with certainty that the use of a prior medication has ended prior to the first dose of investigational treatment, then it will be considered concomitant.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

The primary variable is Short Physical Performance Battery (SPPB) test score.

9.4.2 Statistical model, hypothesis and method of analysis

This study is planned to be conducted in two parts.

9.4.2.1 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]

[REDACTED]

[REDACTED]

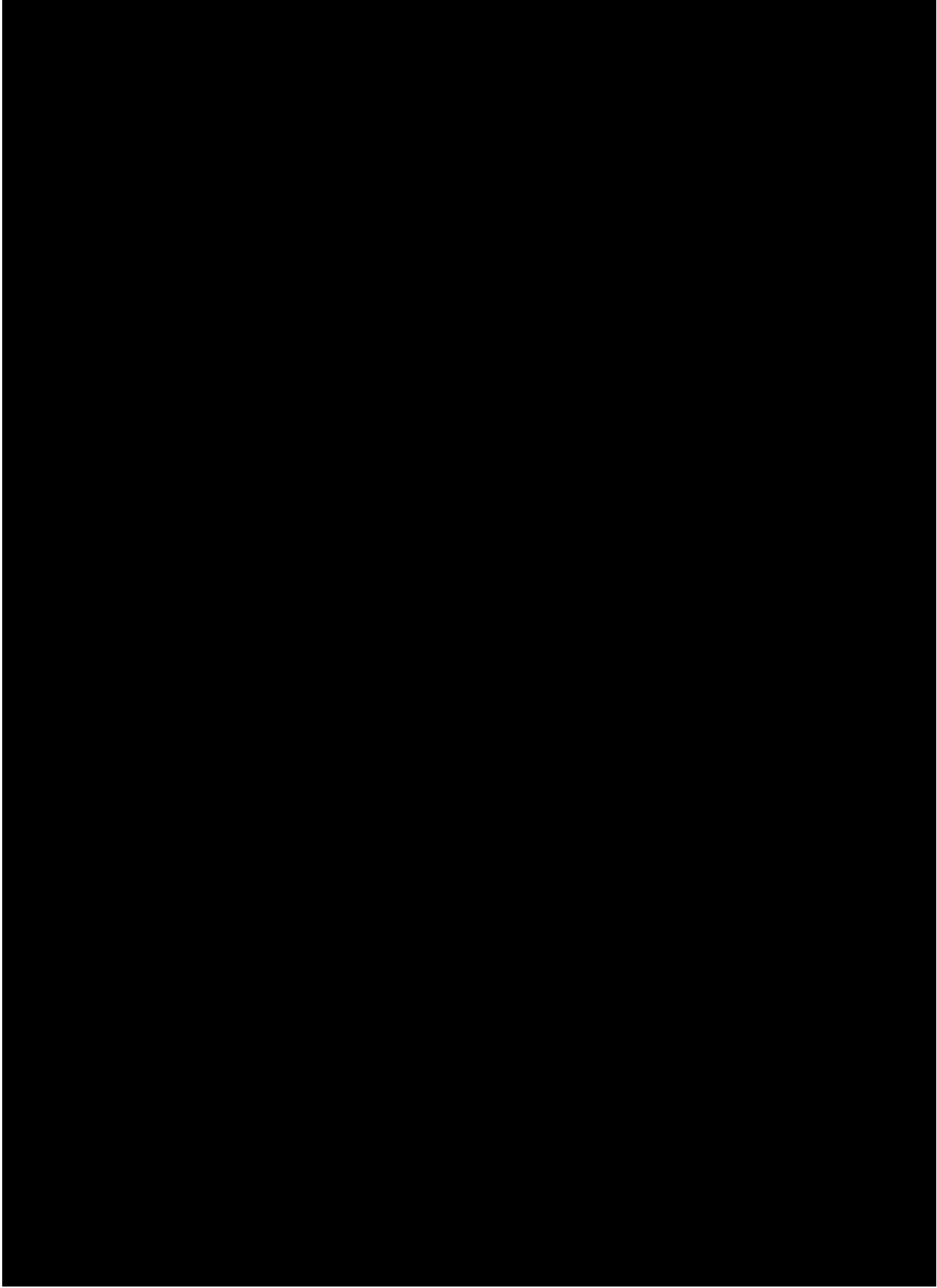
[REDACTED]

[REDACTED]

[REDACTED]

In addition to the primary objective, 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.

[REDACTED]



9.4.4 Supportive analyses

[REDACTED]

The last measurement of SPPB obtained during the run-in phase, but prior to the double-blinded treatment will be included as covariate. Three two-sided significance tests for the treatment to placebo comparison (70 mg vs. placebo, 210 mg vs. placebo, 700 mg vs. placebo) at the 25 week time point will be computed. 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.

[REDACTED]

The primary and secondary analyses will be done for the PP population as well.

9.5 Analysis of secondary [REDACTED] variables

For Part B, gait speed over 4 meters and 6MWT will both be analyzed in the same way as mentioned in [Section 9.4.2](#). [REDACTED]

9.5.1 Efficacy / Pharmacodynamics

Not applicable

9.5.2 Safety

All safety analyses will be performed on the Safety Analysis Set.

9.5.2.1 Cardiac Toxicity Analysis

The relative risk (to placebo) of one or more confirmed cardiac toxicity event will be reported with 95% confidence intervals for each of the bimagrumab treated groups.

9.5.2.2 Adverse Events

Treatment emergent adverse events (events start after the first dose of investigational treatment or events present to the first dose of investigational treatment but increased in severity) will be summarized by primary system organ class, preferred term and treatment.

Separate summaries will be performed for study medication related events, death, serious adverse events, adverse events leading to discontinuation of study medication or dose adjustment, and other adverse events of interest.

9.5.2.3 Laboratory data

The summary of laboratory measurements by visit will be presented with descriptive statistics (mean, standard deviation, minimum, median, and maximum) for quantitative variables; and with frequency for categorical variables. In addition, change from baseline will be summarized and shift tables will be provided for all parameters to compare post-baseline measurements with corresponding baseline values.

Baseline values will be defined as last non-missing assessment prior to the first dose of study medication. Patients with abnormal laboratory values will be listed and selected parameters will be flagged during study conduct according to pre-defined clinically relevant values. Incidence of abnormalities based on clinically notable criteria will be tabulated.

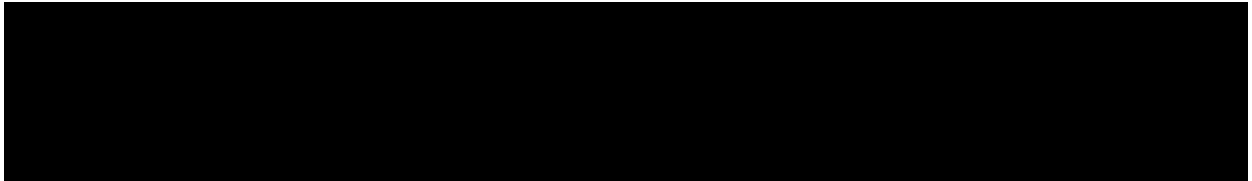
In addition, all laboratory data will be listed by treatment, patient, and visit and if ranges are available abnormalities will be flagged.

9.5.3 Vital signs

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

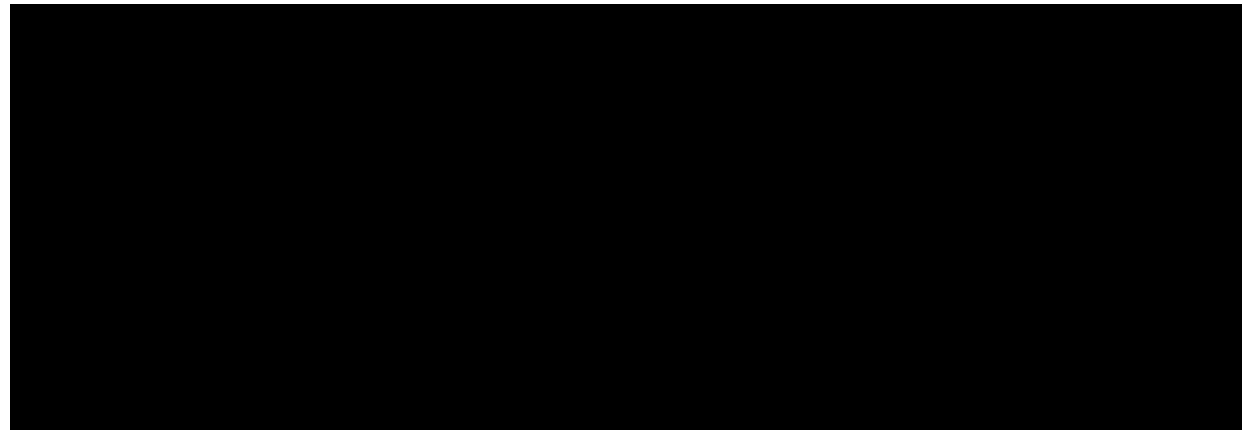
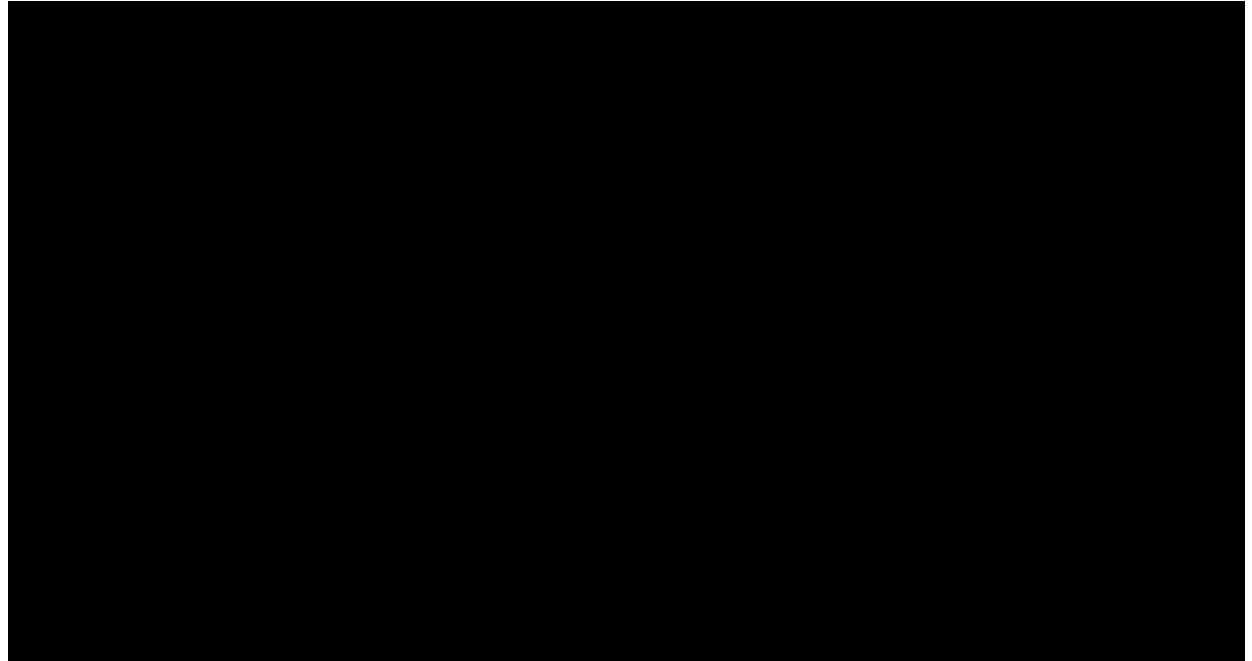
9.5.4 ECG evaluations

All ECG data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.



9.5.6 [REDACTED] / pharmacodynamic interactions

Not Applicable.



9.6 Sample size calculation

9.6.1 Sample size for primary objective:

Assumptions for part-A:

Decision criteria for part-A is based on the maximum BYM338 dose group (700 mg) and placebo. [REDACTED]

For SPPB, several relevant references are available for judging the standard deviation of SPPB between two time points.

Table 9-1 Standard Deviation of SPPB

Reference	Study description	SD
Perera et al (2006)	N=492 community dwelling adults	1.42
Kwon et al. (2009)	N=424 older sedentary adults	0.46
Papanicolau et al (2013)	N=120 sarcopenic elderly women	1.6

Based on these references, we consider an SD of 1.5 for the change in SPPB from baseline to 6 months to be a realistic estimate while 2.0 is a conservative estimate. [Table 9-2](#) evaluates the power of the comparison between the BYM338 700 mg and placebo groups [REDACTED]

Table 9-2 Power calculation for statistical significance in Part A

Standard Deviation (SPPB points)	Treatment Effect: BYM338 – Placebo (SPPB Points)	Power
1.50	1.1	0.98
	1.2	0.99
	1.3	1.00
	1.4	1.00
	1.5	1.00
1.75	1.1	0.94
	1.2	0.97
	1.3	0.99
	1.4	0.99
	1.5	1.00
2.00	1.1	0.87
	1.2	0.92
	1.3	0.95
	1.4	0.97
	1.5	0.99

Table 9-3 below shows the probability of passing both criteria; that is, achieving significance as well as a point estimate at or exceeding 1 SPPB point.

Table 9-3 Probability of passing dual criteria in Part A

Standard Deviation (SPPB points)	Treatment Effect: BYM338 – Placebo (SPPB Points)	Power
1.50	1.1	0.64
	1.2	0.77
	1.3	0.87
	1.4	0.93
	1.5	0.98
1.75	1.1	0.62
	1.2	0.73
	1.3	0.83
	1.4	0.90
	1.5	0.95
2.00	1.1	0.62
	1.2	0.72
	1.3	0.80
	1.4	0.87
	1.5	0.92

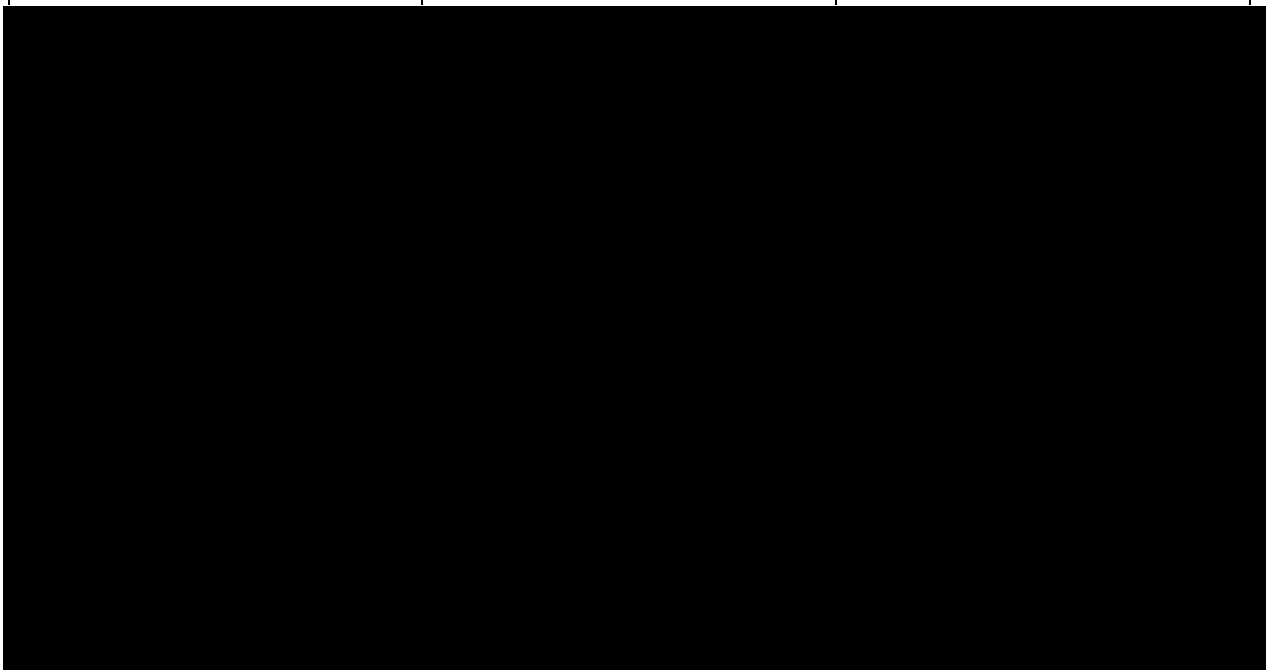


Table 9-4 Optimal contrasts used for the power calculation

Dose (mg)	Linear Model (C_1)	E _{max} Model (C_2)	Exponential Model (C_3)
0	-0.4168	-0.7009	-0.3308
70	-0.3155	-0.1622	-0.3043
210	-0.1128	0.1969	-0.2285
700	0.845	0.6661	0.8636

9.7 Power for analysis of key secondary variables

For secondary endpoints no power calculation is performed for part A. Therefore, the numbers in [Table 9-6](#) and [Table 9-8](#) are prediction of success rates for final analysis conducted at end of part-B.

As to Gait Speed, from references within-subject standard deviation in the range of, respectively, 0.15-0.16 m/Sec ([Perera et al 2006](#)) and 0.15-0.18 m/Sec ([Papanicolaou et al 2013](#)). A treatment effect in the range 0.10-0.20 m/Sec has been deemed to be a clinically meaningful difference. In addition, [Table 9-6](#) below shows the power to detect a dose-response by the MCP-MOD procedure.

Table 9-6 Power to detect a significant dose-response trend by MCP-MOD (using a monotonic increasing alternative at 2.5% level) for GS endpoint

Treatment Effect (m/sec)	Standard Deviation (m/sec)		
	0.15	0.2	0.25
0.2	1.00	1.00	1.00
0.15	1.00	0.99	0.94
0.12	1.00	0.94	0.81
0.1	0.98	0.84	0.65

The following information is available for judging the variability in 6MWT:

Table 9-7 Variability in 6MWT

	Remarks	Estimated standard deviation (m)
IA of PoC study CBYM338X2201	30 sarcopenic elderly subjects treated with one dose of bimagrumab 30 mg/kg. SD of change to 16 weeks.	69 (SD of baseline scores) 65 (by ancova analysis)
Perera et al. (2006)	100 elderly subjects with mild to moderate mobility limitations. SD of 3 month change in stable subjects	45-53 (SD of baseline scores)

A change in 6MWT distance of 50 m is considered a substantial clinically meaningful change ([Perera et al 2006](#)).

Table 9-8 Power to detect a significant dose-response trend by MCP-MOD (using a monotonic increasing alternative at 2.5% level) for 6MWT endpoint

Treatment Effect (m)	Standard Deviation (m)				
	50	60	70	80	90
30	0.94	0.84	0.71	0.59	0.49
40	1.00	0.98	0.92	0.84	0.74
50	1.00	1.00	0.99	0.96	0.91
60	1.00	1.00	1.00	0.99	0.98
70	1.00	1.00	1.00	1.00	1.00

The dose response shapes are essentially assumed to be same for 6MWT and GS as considered in for primary endpoint. However the minimum power from three candidate shapes is represented in [Table 9-6](#) and [Table 9-8](#).

9.8 Interim analyses

Interim analysis is planned at the end of Part A. An unblinded interim analysis will be performed [REDACTED]. This interim analysis will be conducted by an independent study team and the core study team will remain blinded to individual treatment data until final database lock. [REDACTED]

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.



In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the

instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. Novartis does not grant protocol deviations. Under no circumstances should the investigator contact Novartis or its agents to request approval of a protocol deviation. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the Health Authorities (where required) and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulation.

12 References

Available upon request.

ATS Statement: Guidelines for the six-minute walk test (2002) *AmJRespirCritCareMed*; 166: 111-117.

Barthuly AM, Bohannon RW, Gorack W (2012) Gait speed is a responsive measure of physical performance for patients undergoing short-term rehabilitation. *Gait Posture*; 36(1):61-4.

Baumgartner RN, Koehler KM, Gallagher D, et al (1998) Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147:755–63.

Biomarkers Definitions Working Group. (2001) Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics*; 69:89-95.

Brown TR and Simnad VI (2016) A randomized crossover trial of dalfampridine extended release for effect on ambulatory activity in people with multiple sclerosis. *Int J MS Care*; 18(4):170-6.

Cesari M, Kritchevsky SB, Penninx BW, et al (2005) Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc*; 53:1675-80.

Chandler JM, Duncan PW, Kochersberger G, et al (1998) Is lower extremity strength gain associated with improvement in physical performance and disability in frail, community-dwelling elders? *Arch Phys Med Rehabil*;79(1):24-30.

Chen L-K, Liu L-K, Woo J, et al (2014) Sarcopenia in Asia: Consensus report of the Aisan working group for sarcopenia. *JAMDA*; 15 95-101.

Corsonello A, Lattanzio F, Pedone C, et al (2011) Prognostic significance of the Short Physical Performance Battery in older patients discharged from acute care hospitals. *Rejuvenation Rej*; 15:41-8.

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al (2010) Sarcopenia: European consensus on definition and diagnosis Report of the European Working Group on Sarcopenia in Older People. *Age and Ageing*; 39: 412–423.

Dam T-T, Peters KW, Fragala M, et al (2014) An evidence-based comparison of operational criteria for the presence of sarcopenia. *J Gerontol Med Sci* 69: 584-590.

Dunning T, Sinclair A, Colagiuri S (2014) New IDF Guideline for managing type 2 diabetes in older people. *Diabetes Res Clin Pract*. Mar;103(3):538-40.

Fielding R, Vellas B, Evans W, et al (2011) Sarcopenia: An Undiagnosed Condition in Older Adults. Current Consensus Definition: Prevalence, Etiology, and Consequences. International Working Group on Sarcopenia. *J Am Med Dir Assoc*;12: 249–256.

Freire AN, Guerra RO, Alvarado B, et al (2012) Validity and reliability of the Short Physical Performance Battery in two diverse older adult populations in Quebec and Brazil *J Aging Health* 24:863-78.

- Gill TM. (2010) Assessment of function and disability in longitudinal studies; *Journal of the American Geriatrics Society*, 58:S308-12.
- Gottdiener JS, Bednarz J, Devereux R, et al (2004) American Society of Echocardiography Recommendations for Use of Echocardiography in Clinical Trials. *J Am Soc Echocardiogr*; 17:1086-1119.
- Guralnik JM, Simonsick EM, Ferrucci L, et al (1994) A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *Journal of Gerontology*, 49:M85-94.
- Guralnik JM, Ferrucci L, Simonsick EM, et al (1995). Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *The New England Journal of Medicine*, 332:556-62.
- Guralnik JM, Ferrucci L, Pieper CF, et al (2000) Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci*; 55(4):M221-31.
- Hardy SE, Perera S, Roumani YF, et al (2007) Improvement in usual gait speed predicts better survival in older adults. *J Am Geriatr Soc*; 55(11):1727-34.
- Janssen I, Shepard DS, Katzmarzyk PT, et al (2004) The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc*. Jan;52(1):80-5.
- Kwon S, Perera S, Pahor M, et al (2009) What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). *J Nutr Health Aging*. 2009 Jun;13(6):538-44.
- Latham NK, Mehta V, Nguyen AM, et al (2008) Performance-based or self-report measures of physical function: which should be used in clinical trials of hip fracture patients? *Arch Phys Med Rehabil*. 89:2146-55.
- Latham NK, Harris BA, Bean JF, et al (2014) Effect of a home-based exercise program on functional recovery following rehabilitation after hip fracture: a randomized clinical trial. *JAMA* 311:700-8.
- Lee SJ, Lee YS, Zimmers TA, et al (2010) Regulation of muscle mass by follistatin and activins. *Mol.Endocrinol.*; 24 (10):1998-2008.
- Lee SJ, Reed LA, Davies MV, et al (2005) Regulation of muscle growth by multiple ligands signaling through activin type II receptors. *Proc.Natl.Acad.Sci.U.S.A*; 102 (50):18117-18122.
- McAuley E, Wójcicki TR, Gothe NP, et al (2013) Effects of a DVD-delivered exercise intervention on physical function in older adults. *J Gerontol:Med Sci*; 68:1076-82.
- Morris DR, Rodriguez AJ, Moxon JV, et al (2014) Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 3(4):1-11.
- Muscaritoli M, Anker SD, Argilés J, et al (2010) Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr*. Apr;29(2):154-9. doi: 10.1016/j.clnu.2009.12.004.

Newman AB, Haggerty CL, Kritchevsky SB, et al; Health ABC Collaborative Research Group (2003). Walking performance and cardiovascular response: associations with age and morbidity--the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*; Aug; 58(8):715-20.

Ostir GV, Volpato S, Fried LP, et al (2002) Reliability and sensitivity to change assessed for a summary measure of lower body function: Results from the Women's Health and Aging Study *JClinical Epidemiology*; 55:916-921.

Papanicolaou DA, Ather SN, Zhu H, et al (2013) A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. *J Nutr Health Aging*. 2013;17(6):533-43

Pahor M, Blair SN, Espeland M, et al (2006) Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. *Journals of Gerontology: Medical Sciences*; 61:1157-65.

Pahor M, Guralnick JM, Ambrosius WT, et al (2014) Effect of structured physical activity on prevention of major mobility disability in older adults: the **LIFE study** randomized clinical trial. *JAMA*. 311(23):2387-96

Perera S, Studenski S, Chandler J, et al (2005) Magnitude and patterns of decline in health and function in 1 year affect subsequent 5--year survival. *JGerontology: Medical Sciences*; 60:894-900.

Perera, S, Moody SH, Woodman, RC, et al (2006) Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. May;54(5):743-9

Pinheiro JC, Bornkamp B. and Bretz F (2006) Design and analysis of dose finding studies combining multiple comparisons and modeling procedures, *Journal of Biopharmaceutical Statistics*, 16, 639–656

Prestmo A, Hagen G, Sletvold O, et al (2015) Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial; *Lancet* 385:1623-33.

Rosow I, Breslau N (1966) A Guttman health scale for the aged. *J Gerontology*. Oct; 21(4):556-9.

Simonsick EM, Gardner AW, and Poehlman ET (2000) Assessment of physical function and exercise tolerance in older adults: reproducibility and comparability of five measures. *Aging (Milano)*. Aug;12(4):274-80

Stabin MG (2009); *Nuclear Medicine Radiation Risks*. *J Nucl Med*. Feb 17.

Studenski, S. (2009) What are the outcomes of treatment among patients with sarcopenia? *Journal Nutrition, Health Aging*; 13(8), 733-36.

Studenski S, Perera S, Patel K, et al (2011) Gait speed and survival in older adults. *JAMA*; 305(1):50-8.

Studenski S, Perera S, Wallace D, et al (2003) Physical performance measures in the clinical setting. *J Am Geriatr Soc*; 51(3):314-22.

Studenski SA, Peters KW, Alley DE, et al (2014) The FNIH Sarcopenia Project: Rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci.*69(5):547-558.

Tomlinson B, Cruickshank JM, Hayes Y, et al (1990) Selective beta-adrenoceptor partial agonist effects of pindolol and xamoterol on skeletal muscle assessed by plasma creatinine kinase changes in healthy subjects. *Br J Pharmacol*; 30: 665-672.

Trendelenburg AU, Meyer A, Jacobi C, et al (2012) TAK-1/p38/nNFkB signaling inhibits myoblast differentiation by increasing levels of Activin A. *Skeletal Muscle*; 2(1):3.

Upton PD, Davies RJ, Trembath RC, et al (2009) Bone Morphogenetic Protein (BMP) and Activin Type II Receptors Balance BMP9 Signals Mediated by Activin Receptor-like Kinase-1 in Human Pulmonary Artery Endothelial Cells. *J Biol Chem.* 284(23): 15794-804.

13 Appendix 1: Sample log table – all matrices

Sample Log (all matrices): Time schedule for sampling for safety bloods and urine, [REDACTED], pharmacodynamic (PD), [REDACTED]

Study Phase	Visit Numbers	Month post-randomization	Week post-randomization	Day	Hours (post-dose)	Safety ¹	Urinalysis	
						Size (ml)	Size (ml)	
Screening	1	-	-	-50 to -30	-	26	5	
Run-In	2	-	-	-29 to -23	-			
	3			-22 to -16				
	4			-15 to -10		17		
	5			-5 to -1				
Treatment	101	1	1	1	pre-DOSE	21		
					0			
	1015	3	15	15	0.5		12	
	102	2	5	29	pre-DOSE	13		
						0		
	103	3	9	57	pre-DOSE	22		
						0		
	104	4	13	85	pre-DOSE	12		
						0		
105	5	17	113	pre-DOSE	17			
					0			
106	6	21	141	pre-DOSE	10			
					0			
EoT	107	7	25	169	0.5			
EOS	199	8	29	197		22		

¹ includes when applicable: virology, drug and alcohol screen, clinical chemistry (incl. vitamin D), hematology, and cardiac and hormonal panels.

Study Phase	Visit Numbers	Month post-randomization	Week post-randomization	Day	Hours		Blood Volume (mL)	Urine volume (mL)
Screening	1	-	-	-50 to -30	-		26	5
Run-In	2	-	-	-29 to -23	-			
	3			-22 to -16	-			
	4			-15 to -10	-			
	5			-5 to -1	-			
Treatment	101	1	1	1	pre-DOSE		56	15
					0			
	1015			3	15		3	
	102	2	5	29	pre-DOSE		12	
					0		13	
	103	3	9	57	pre-DOSE		22	
					0			
	104	4	13	85	pre-DOSE		41	15
					0			
	105	5	17	113	pre-DOSE		17	
				0				
106	6	21	141	pre-DOSE		16		
				0				
					0.5		3	
EoT	107	7	25	169			51	15
EOS	199	8	29	197			25	
Study Total:							302	50

¹ includes when applicable: virology, drug and alcohol screen, clinical chemistry (incl. vitamin D), hematology, and cardiac and hormonal panels.

14 Appendix 2: Liver event definitions and follow-up requirements

Table 14-1 Liver Event Definitions

	Definition/ threshold
Adverse event of special interest	
Laboratory values	ALT or AST > 3 x ULN ALP > 2 x ULN TBL > 1.5 x ULN
Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) TBL > 3 x ULN Potential Hy's Law cases (defined as ALT/AST > 3 x ULN <u>and</u> TBL > 2 x ULN [mainly conjugated fraction] <u>without</u> notable increase in ALP to > 2 x ULN)
Adverse events	Any clinical event of jaundice (or equivalent term) ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

Table 14-2 Liver Event Follow Up Requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case ^a OR ALT or AST >3xULN and INR >1.5	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)
ALT or AST > 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)

Criteria	Event type	Actions required	Follow-up monitoring
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for <i>more than 2 weeks</i> , discontinue the study drug Report to Novartis as an SAE Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms ^b	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	

Criteria	Event type	Actions required	Follow-up monitoring
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to \leq 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
\leq 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)
“Drug-related hepatic disorders - severe events only” SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality Complete liver CRF	Investigator discretion

^a Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

^b General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

^c Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

15 Appendix 3: Clinically notable laboratory values

The following criteria will be used as guidance for notable abnormalities of key laboratory tests and vital signs.

Clinically notable values will be forwarded to Novartis at the same time that they are sent to the investigators. Any action based on these laboratory values should be discussed with Novartis personnel.

Table 15-1 Clinically notable lab values

Laboratory Variable	Notable Criteria
██████	██████
██████	██████
Hemoglobin	<8.0 g/dL
Glycated hemoglobin (HbA1c)	≥7.5%
Average blood glucose	≥9.0 mmol/L
Platelet count	<75000 mm ³
Estimated GFR	<30 mL/min
Total bilirubin concentration	>1.5 x ULN
Total serum bilirubin	>1.6 mg/dL (27µmol/L)
AST	>3xULN
ALT	>3xULN

16 Appendix 4: Blinding and unblinding

Randomization data are kept strictly confidential. Prior to final clinical database lock, unblinding is allowed only for authorized personnel as described in the table below.

Table 16-1 Blinding levels

Role	1	Time or Event					
		2	3	4	5	6*	7
Drug Supply	UI	UI	UI	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI	UI	UI	UI
Data Monitoring Committee	B	UI	UI	UI	UI	UI	UI
Subject	B	B	B	B	UI	B	B
Treating Physician	B	B	B	B	UI	B	B
Primary Investigator	B	B	B	B	UI	B	B
Blinded Study Monitor	B	B	B	B	UI	B	B
Unblinded Study Monitor	B	UI	UI	UI	UI	B	UI
Clinical Trial Leader	B	B	B	B	UI	UG	UI
Data Manager	B	B	B	B	UI	B	B
██████████	B	UI	UI	UI	UI	UG	UI
██████████	B	B	B	B	UI	UG	UI
Statistician	B	B	B	B	UI	UG	UI
Translational Medicine Expert	B	B	B	B	UI	UG	UI
Independent Trial Leader	B	B	B	B	B	UI	UI
Independent Translational Medical Expert	B	B	B	B	B	UI	UI
Independent Statistician	B	B	B	B	B	UI	UI
Independent Data Manager	B	B	B	B	B	UI	UI
Independent Programmer	B	B	B	B	B	UI	UI
Modeler	B	B	B	B	UI	UI	UI
Programmer	B	B	B	B	UI	UI	UI

*In the event the study is terminated with the Interim Analysis, then all interim data will be treated as final database lock (event 7).

UG Allowed to be unblinded on treatment group level

UI Allowed to be unblinded on individual patient level

B Remains blinded

1 Generation of randomization list, QC and lock randomization list

2 Patient allocation to treatment

3 Single-blinded treatment administration

4 Double-blinded treatment administration

5 Safety emergency event (unblinding of a single subject)

- 6 Interim Analysis
- 7 Database lock



