NOVARTIS

Global Clinical Development - General Medicine

BYM338/bimagrumab
Clinical Trial Protocol CBYM338E2202E1 / NCT02468674
A 24 week off drug extension, parallel group, study assessing durability of effect on skeletal muscle strength and function following a 6-month double-blind, placebo controlled study evaluating bimagrumab in older adults with sarcopenia (InvestiGAIT extension)

Document type:	Clinical Trial Protocol
EUDRACT number:	2015-000471-27
Version number:	v01 (clean)
Development phase:	II
Release date:	26-Apr-2017

[redacted]

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[redacted]

List of abbreviations

ActRII	Activin Type II receptor
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ASMI	Appendicular skeletal muscle index
AST	Aspartate aminotransferase
BDR	Bioanalytical Data Report
BUN	Blood urea nitrogen
b.i.d.	Twice a day
BMI	Body mass index
BYM	Bimagrumab
CFR	US Code of Federal Regulations
CK	Creatine kinase
CK-MB	Creatine kinase (heart muscle)
CK-MM	Creatine kinase (skeletal muscle)
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Co-efficient of variation
DMC	Data Monitoring Committee
DXA	Dual energy X-ray absorptiometry
eCCG	eCRF Completion Guidelines
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of study
EOT	End of treatment
[redacted]	[redacted]
EU	European Union
EWGSOP	European Working Group on Sarcopenia in Older Persons
FAS	Full analysis set
FDA	US Food and Drug Administration

[redacted]

GCP	Good Clinical Practice
GS	Gait Speed
HgbA1C	Glycated hemoglobin
IB	Investigators Brochure
ICF	Inform Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	[redacted]
IN	Investigator Notifications
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
i.v.	Intravenous
LBM	Lean body mass
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
[redacted]	[redacted]
LLOQ	Lower Limit of Quantification
MedDRA	Medical dictionary for regulatory activities
mSv	Milisieverts per hour (background radiation measurement)
OC/RDC	Oracle Clinical/Remote Data Capture
QA	Quality Assurance
QTcF	Fridericia QT correction formula
[redacted]	[redacted]
PBO	Placebo
PD	Pharmacodynamics
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PP	Per-protocol
[redacted]	[redacted]
RBC	Red cell count
SAE	Serious adverse event
SAF	Safety set
SD	Standard deviation

[redacted]

[redacted]	[redacted]
sIBM	sporadic inclusion body myositis
SPPB	Short Physical Performance Battery
µSv	Microsieverts per hour (ionizing radiation measurement)
WBC	White cell count
WHO	World Health Organization
γ-GT	γ-Glutamyltransferase
6MWT	6 Minute Walk Test

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The 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	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
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.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Patient Number	A number assigned to each 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

[redacted]

Protocol summary

Protocol number	CBYM338E2202E1
Title	A 24-week off drug extension parallel group study assessing the durability of effect on skeletal muscle strength and function following a 6-month double blind placebo controlled study evaluating bimagrumab in older adults with sarcopenia
Brief title	A 24-week off drug extension study assessing the durability of effect of bimagrumab in older adults with sarcopenia previously participating in the 6-month core study
Sponsor and Clinical Phase	Novartis Phase IIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this extension study is to evaluate the durability of effect on skeletal muscle mass, strength and physical function upon discontinuation of treatment received in the core study
Primary Objective(s)	• The primary objective is to assess the durability of effect of bimagrumab (BYM338) as measured by the short physical performance battery (SPPB) total score at week 49.
Secondary Objectives	• To evaluate the safety and tolerability of bimagrumab following treatment withdrawal as assessed by measures such as vital signs, clinical laboratory variables, electrocardiogram (ECG), and adverse events (AE). • To evaluate the durability of effect of bimagrumab at week 49 as measured by: o 6 minute walk test (6MWT) o mobility as measured in gait speed (GS) over 4 meters o total lean body mass (LBM) and appendicular skeletal muscle index (ASMI) measured by dual energy X-ray absorptiometry (DXA)
Study design	This Phase IIb extension study is a 24 weeks off drug study following 24 weeks of treatment in the core study (CBYM338E2202) in older patients with sarcopenia.
Population	The study population will be community-dwelling men and women ages 70 years and older completing the full study treatment period (24 weeks) of the core study (CBYM338E2202) and willing to enter CBYM338E2202E1.
Inclusion criteria	• Men and postmenopausal women aged 70 years or older that have participated in, and have completed the full study treatment period per protocol (24 weeks) in the preceding core study (CBYM338E2202) • Written informed consent must be obtained before any assessment of the extension study is performed (can be obtained at the End of Treatment (EOT) visit of the core study).
Exclusion criteria	Any condition which should have led to treatment discontinuation per protocol in the core study.

[redacted]

Investigational and reference therapy	none
Efficacy assessments	• 6MWT to assess functional improvement • SPPB to assess physical functional improvement • Usual GS to assess physical functional improvement • LBM and ASMI assessed by DXA to measure total and regional lean body mass. [redacted]
Safety assessments	• Physical examination • Vital signs • Weight • Laboratory evaluations • ECG
Data analysis	Summary statistics by treatment arm will be provided for the primary endpoint and continuous secondary endpoints. A 95% confidence interval for the difference between each continued bimagrumab dose arm vs. corresponding placebo switched from the same bimagrumab dose will be calculated at each visit.
Key words	Durability of effect, safety of bimagrumab in patients with sarcopenia.

[redacted]

Amendment 1 (26-Apr-2017)

Amendment rationale

The purpose of this amendment is to revise the extension study design to align it with changes recently implemented in the core study CBYM338E2202 while maintaining and further focusing the primary purpose of the extension study to evaluate the durability of effect of 24 weeks of bimagrumab therapy upon treatment discontinuation.

The original study was designed to evaluate several questions i.e. how long the potential effect of 24 weeks of bimagrumab treatment would be maintained following treatment discontinuation and if a 48 weeks continuous treatment would provide additional benefit over a 24 weeks treatment period. The randomized withdrawal feature of the design reduced the sample size of each treatment arm with the risk of not being able to address the questions. Novartis with this amendment is removing this withdrawal randomization feature and is refocusing the study on one main question: how long the potentially observed effects after 24 weeks of treatment with bimagrumab will last once the treatment is discontinued? Therefore, all newly enrolled patients in this extension study will be followed off drug for a period of 24 weeks. As a consequence, the size of each treatment arm will remain as per study entry and not reduced as the withdrawal randomization would otherwise do. Questions no longer addressed by this study may be addressed at later stage of the bimagrumab clinical development program if they are still relevant.

Patient visits over the 24 weeks are reduced from seven to three since there is no need for on-site infusion every 4 weeks. This should substantially reduce patient burden and facilitate study acceptance. However in order to promote patients' engagement and adherence to the study, there is a required exercise program [redacted] and, monthly phone calls will be made to patients.

Patients active in the study upon implementation of this protocol amendment will remain on the original protocol visit schedule which reflects the randomized withdrawal design. This way all patients enrolled in this study prior to this protocol amendment will have a similar journey and even if the sample is small (estimated to approx. 45 patients) this sub-group of patients will provide valuable information on the effect of prolonged treatment for 49 weeks. At the time of this protocol amendment's implementation it is anticipated that 10 to 15 patients will be on going and will continue being dosed while newly enrolled patients will be followed off drug under a revised visit schedule.

The end of part A in the core study will trigger an interim analysis of the extension study data available at that time. Data from this extension study will be combined with the core study data and will enable decision making on the rest of the program. In addition, following this interim analysis, the global study team will be unblinded to the individual treatment codes from those patients included in this analysis. However, Novartis associates in the countries and site personnel will remain blinded to the treatment codes until the final study data base lock.

The rational for the changes implemented in the core study such as the change of primary endpoint, the reduction of the cardiac safety monitoring, [redacted] are described in the core protocol amendment #2 (CBYM338E2202).

At the time of this amendment, approximately 45 patients have been enrolled in the study.

[redacted]

Changes to the protocol

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.

The informed consent of the study will be amended. A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Health Authorities.

The main changes are the following:

- Re-focus of the study on assessing the durability of effect of bimagrumab over a 24 week period *off* drug. As a result the withdrawal randomization design feature is removed and all newly enrolled patients are followed off drug, while patients previously enrolled will complete the study more or less as per the original visit schedule
- Study is reduced to 24 weeks with site visits every 12 weeks instead of every 4 weeks and phone calls have been added in between visits to promote adherence and to record [redacted] other associated feedback from study participants.
- Addition of a planned interim analysis
- The need for unblinding of core treatment code for newly enrolled patients will follow the core study protocol procedure.
- All IMP related sections are only applicable to those patients enrolled under the original protocol version
- Inclusion/exclusion criteria were simplified as only patients willing and having fully completed the 24 weeks of core study treatment are eligible
- As part of the alignment between the core and the extension studies, the following key changes are implemented in this extension study:
  - The SPPB replaced the 6MWT as primary endpoint, the 6MWT changed to a secondary endpoint
  - The 400 meter walk test was removed
  - Echocardiography was eliminated and overall cardiac monitoring was reduced from a level of intense monitoring to one reflecting standard of care following the results of the dedicated profiling cardiac safety study
  - Additional safety monitoring guidance for patients with change in body weight since the core study baseline of +/- 5%
  - Removal of certain central laboratory assessments (i.e. urinalysis, coagulation measurement)
  - e-devices diaries [redacted] are replaced by paper diaries which are easier to use for this patient population
  - [redacted]
- The frequency of the DXA assessment was reduced to a final one at the EOS only

[redacted]

1 Introduction

1.1 Background

CBYM338E2202E1 is a 24-week post-treatment follow-up study of the Phase IIb sarcopenia study CBYM338E2202. This core study is a multi-centered, parallel group dose ranging finding study to assess the effect of 6 monthly doses of bimagrumab on skeletal muscle mass, strength and function in older patients with sarcopenia.

Sarcopenia, the age-associated loss of skeletal muscle mass and physical function (Cruz-Jentoft et al 2010; Fielding et al 2011), is a common geriatric syndrome with approximately 2-13% of individuals over 65 years and up to 30% of adults over 80 years affected (Dam 2014, Volpato 2013). While there is no single set of diagnostic criteria for sarcopenia, multiple consensus statements all agree that reductions of muscle mass and gait speed (GS) are the key patient characteristics of sarcopenia with only subtle differences with respect to the recommended cutpoints for each of these measures. More recently, in the first data-driven analysis of older adult subjects, cutpoints were recommended for both of these measures as well as grip strength (Studenski 2014). The most well accepted sarcopenia criteria at this time are those from the European Working Group on Sarcopenia in Older Persons (EWGSOP) and the Asian Working Group for Sarcopenia, and subjects enrolled in the Phase IIb study in sarcopenia (E2202) must meet the universal thresholds for gait speed and geographic specific thresholds for muscle mass for entry into the study (Cruz-Jentoft 2010).

Sarcopenia is associated with a myriad of complications, including mobility limitations, an increased risk of falls, fractures and hospitalizations, as well as additional healthcare costs, and increased mortality (Cruz-Jentoft 2010, Janssen 2004, Visser 2011). In addition, sarcopenic patients frequently require assistance with basic and instrumental activities of daily living (e.g., bathing, shopping) and lose independence. The societal cost of sarcopenia was calculated at over 18 billion US dollars in 2000 (Janssen 2004).

Currently, there is no pharmacological treatment for sarcopenia and recommended treatment for sarcopenia includes strength training and nutritional optimization (e.g., protein and Vitamin D).

As a potent inhibitor of the Activin Type II receptor (ActRII), bimagrumab blocks the effects of negative regulators of muscle growth including myostatin, activin A, and GDF11 working through this receptor. An accelerated loss of muscle mass, strength and physical function in the large and rapidly growing global aging population represents a substantial, unmet medical need and a novel opportunity for a pharmacotherapeutic that can promote skeletal muscle hypertrophy and improve patient function.

The efficacy and safety of bimagrumab in sarcopenia is currently being evaluated in the CBYM338E2202 core study. The core study protocol and the study design were substantially amended in September 2016, including changes to the primary and some of secondary endpoints.

To maintain consistency with the core study (CBYM338E2202), the Short Physical Performance Battery (SPPB) has become the primary endpoint for this extension trial and several other pertinent functional measures (e.g., 6 minute walk test (6MWT), gait speed (GS), spontaneous physical activity) will be collected as [redacted] secondary [redacted] endpoints.

[redacted]

1.2 Purpose

The purpose of this extension study (CBYM338E2202E1) is to evaluate the durability of effect on skeletal muscle mass, strength and physical function following 24 weeks of treatment with bimagrumab, in older patients with sarcopenia upon discontinuation of treatment.

The results of this extension study will support the design of a phase III study of bimagrumab treatment for sarcopenia.

2 Study objectives

2.1 Primary objective(s)

- The primary objective is to assess the durability of effect of bimagrumab (BYM338) on physical function as measured by the SPPB total score at week 49.

2.2 Secondary objectives

- To evaluate the long term safety effect of bimagrumab following treatment withdrawal as assessed by measures such as vital signs, clinical laboratory variables, electrocardiogram (ECG), and adverse events (AE)
- To evaluate the durability of effect of BYM at week 49 as measured by:
  - 6MWT
  - usual gait speed over 4 meters
  - total lean body mass (LBM) and appendicular skeletal muscle index (ASMI) measured by dual energy X-ray absorptiometry (DXA)

[redacted]

[redacted]

[redacted]

3 Investigational plan

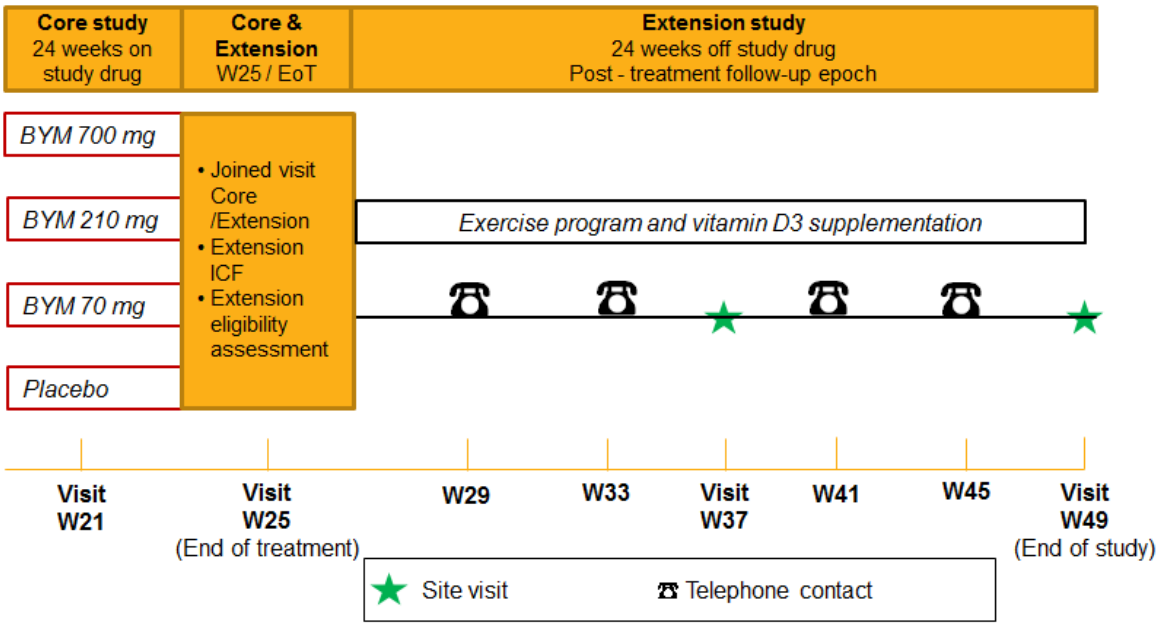
3.1 Study design

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

After completing 24 weeks of treatment in the core study (CBYM338E2202 End of Treatment (EOT) visit), newly consenting patients in the extension study CBYM338E2202E1 will continue with the same uniquely identified patient number that was assigned in the core study and will be followed for an additional 24 weeks off drug (see Figure 3-1). They will complete the end of study (EOS) at week 49.

Patients enrolled prior to this amendment #1, will follow the original study design described below Figure 3-2 and will continue to be treated as per the regimen assigned at entry of the extension study. It is anticipated that approximately a total 45 patients will be followed under this design and 10 to 15 of them will still be in the study at the time of implementing this amendment #1.

Figure 3-1 Study design for patients enrolled after the protocol amendment #1



[redacted]

Exercise program

All patients will be requested to continue their home exercise program (2-3 times each week) as it was prescribed and performed in the core study, CBYM338E2202. At the patient's request, the study staff will be able to provide a new set of exercise instructions in order to encourage study participation and adherence.

The exercise program contains activities for muscle strength, endurance, balance and flexibility, as well as warm-up (i.e. walking) and cool-down periods to improve comfort, prepare the body for increased effort, and reduce the risk of training injuries. The exercise program is described in detail in the CBYM338E2202E1 Outcomes Manual.

[redacted]

Week 25/EOT – Joined Core and Extension visit

All EOT assessments of the core study will be performed 4 weeks after the last dose of study drug as outlined in core study CBYM338E2202. Consenting, eligible patients will start in this extension study on the same day (i.e., EOT visit of CBYM338E2202).

The ability and willingness of the patient to continue performing the home-based exercise program should be re-assessed by the investigator or a team member during this visit.

For a complete list of assessments, please refer to Section 6 Table 6-1.

Subsequent Visits – Weeks 29-45

Between the extension study entry visit (week 25) and the EOS (week 49), newly enrolled patients will only visit the site once for the week 37 visit. In between the visits, the patients will be contacted monthly by phone by the site personnel to enquire on the patient's health status and to check compliance with the [redacted] diaries.

For a complete and detailed list of assessments, please refer to Section 6 and Table 6-1.

End of study (EOS)/Week 49

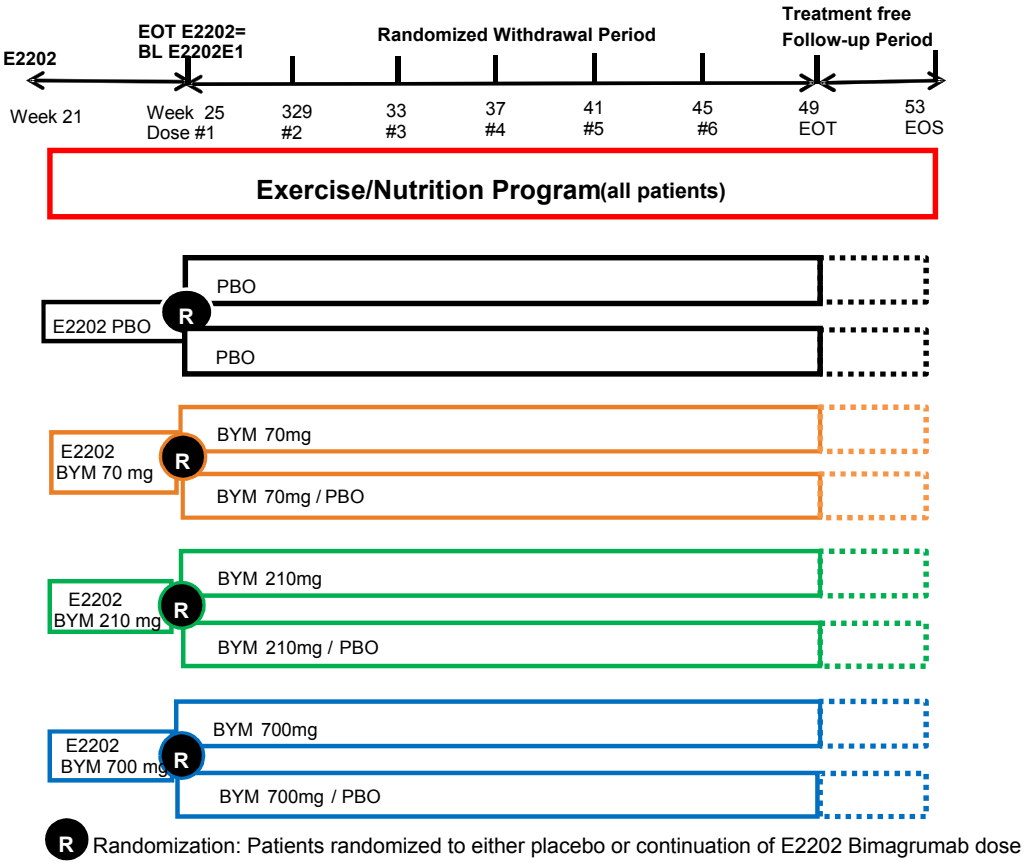
This is the last planned visit in the study. It will take place at week 49 or earlier in case of premature study discontinuation.

Following the EOS visit, the patient will be followed by his/her treating physician according to the local standard of care and the patient's situation.

For a complete and detailed list of assessments, please refer to Section 6 Table 6-1.

[redacted]

Figure 3-2 Study design for patients enrolled prior to protocol amendment #1



Management of patients enrolled prior to the protocol amendment #1

Patients enrolled prior to the study amendment #1 will continue to be dosed every 4 weeks until week 49 (EOT) and will then have a 4 weeks follow-up period until week 53 (EOS).

These patients will also continue the exercise program described above.

Please refer to Section 6 and the specific Table 6-2 for a complete and detailed list of assessments for these patients.

3.2 Rationale of study design

The aim of developing bimagrumab therapy in elderly adults with sarcopenia is to enable them to increase their physical function to a certain level that they could afterwards maintain without any support other than regular exercise and potentially vitamin D supplementation. This extension study is the natural follow-up of the patients treated for 24 weeks in the core study; it will evaluate the changes in physical function of this patient population over 24 week off-treatment period as well as assess the overall long-term safety of bimagrumab.

The study population will be comprised of men and women aged 70 years or older with sarcopenia who participated in the core study CBYM338E2202. Only patients who complete the 24 weeks of treatment in the core study will be eligible for this study given the purpose to evaluate the durability of 24-week therapy. Of the 293 patients expected to enroll in the core

study, it is expected that approximately 200 patients will be eligible and will agree to participate in this extension study.

Although patients enrolled under this amendment will not receive any investigational drug as part of this extension, they will have a standardized exercise program. The schedule of two to three exercise sessions per week will be maintained throughout the studies (core and extension) and will serve as a standard of care together with the vitamin D supplementation.

The code of the treatment received in the core study will remain blinded to sites and patients for the entire study duration including this extension study. This will avoid a potential reporting bias that patients and site staff may otherwise have when assessing physical function, mobility or reporting safety.

In line with the primary endpoint used in the core study, the extension will use the SPPB total score as the primary endpoint. The SPPB score and 4-meter gait speed have emerged as the predominant measures that characterize impaired lower extremity function in older adults in general and in those with sarcopenia and frailty (Studenski et al 2014).

As the natural follow-up of the core study population, a number of efficacy (e.g. SPPB, [redacted]) or safety (vital signs, laboratory measurements, cardiac adjudication) assessments are being carried over in the extension study in order to fully evaluate the patient journey over approximately a 1 year period. Given the absence of required monthly drug infusion, the frequency of the visits is reduced in comparison to the core study in order to limit patients' burden. However, in order to maintain patient's compliance and avoid under-reporting of events such as [redacted] monthly phone calls to the patients will be performed.

As patients enrolled prior to the protocol amendment #1 will differ (e.g. placebo effect) from patients newly enrolled in the extension, it was decided to keep them on their 4-weekly dosing regimen as originally designed, to maximize the understanding of these regimen. They will therefore follow a different visit schedule.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

This extension study will assess the durability of the observed effect of bimagrumab upon treatment discontinuation. There is therefore no study drug administration as part of this study for patients enrolled following protocol amendment #1.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis will be triggered by the analysis of the core study Part A at the completion of Part A. This interim analysis will analyze key efficacy data. The results from the interim analysis, together with core study Part A and any additional data on the rest of the program, will be used for the next step decision making.

3.6 Risks and benefits

All patients in this study will participate in a structured, monitored, mildly intense exercise program designed to improve physical and emotional status in older adults with impaired physical function. In addition, results from the bimagrumab proof of concept study in

[redacted]

sarcopenic patients suggest that patients receiving active drug are likely to experience an increase in lean body mass and improvement in mobility performance. Given the half-life of bimagrumab, the effect is still expected to be present for an additional few weeks in the extension study after the last infusion.

Risks with bimagrumab

The risks of bimagrumab are not fully understood, but in healthy young, middle aged, and older adults and in patients with sporadic inclusion body myositis (sIBM) up through 78 years of age and in sarcopenic patients up to age 86, the drug was well tolerated and the AE profile was consistent across populations. Based on prior human studies there is a risk to participants of experiencing certain tolerability-related adverse events. The most common AEs include a transient skin condition (acne) and involuntary muscle contractions (i.e., twitches/spasms) as well as transient diarrhea. Transient increases in AST and ALT have been observed, sometimes in association with CK elevation (suggesting a muscle source) and sometimes not. Other observed adverse events (AEs) include arthralgia, muscle strain erythema and rash. [redacted] there have been no adverse cardiac findings in humans with current dose levels and regimens.

Refer to the Investigator's Brochure for a thorough evaluation of expected adverse events observed in clinical studies to date as well as data from in vivo pharmacology, animal toxicology, animal and human pharmacokinetic (PK), immunogenicity studies.

Blood draw risks

During the collection of blood samples, patients 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 patient from DXA will be about 25 µSv. 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 (Njeh 1999). 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

During the study, the patients will be required to perform a prescribed set of exercises 2-3 times each week. The exercise program will involve warm-up (i.e., walking) and cool-down periods to improve comfort, prepare the body for increased effort, and reduce the risk of injury.

[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. The risk of temporary muscle soreness will be reduced in these extension study participants as they will have already been participating in the exercise program for the full 8 month duration of the core study. In addition, the exercise programs will be tailored to each individual's level of fitness and interest during the evaluation and mid-study visit with the site staff.

4 Population

The study population will be community-dwelling men and women ages 70 years and older completing 24 weeks of treatment of the core study (CBYM338E2202 EOT visit) and willing to enter CBYM338E2202E1; these patients will be eligible providing they meet all inclusion and exclusion criteria of the extension protocol. No additional exclusions should be applied by the investigator. A relevant record (e.g., checklist) must be stored with the source documentation at the study site. Failure to meet any entry criterion excludes a patient from entering the post-treatment follow-up epoch.

It is expected that approximately 200 patients will participate in the extension study and that approximately 140 will complete it assuming a 30% drop out rate.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Men and postmenopausal women aged 70 years or older that have participated in, and have completed the full study treatment period per protocol (24 weeks/EOT visit) in the preceding core study (CBYM338E2202)
2. Written informed consent must be obtained before any assessment of the extension study is performed (can be obtained at the EOT visit of the core study).

4.2 Exclusion criteria

This is an extension study and has the same exclusions as the core study. Because only participants who complete the core study are eligible for inclusion in this study, patients who no longer qualify or should be discontinued from the core study are excluded from participating in this study. Patients fulfilling the following criterion are not eligible for inclusion in this study:

1. Any condition which should have led to treatment discontinuation per protocol in the core study

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

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Patients newly enrolled after protocol amendment #1 will not receive any investigational treatment as part of this protocol.

[redacted]

For patients enrolled prior to protocol amendment #1 the investigational treatment is as follow:

- Bimagrumab [redacted] prepared by Novartis and supplied to the Investigator site as open labeled bulk medication.
- Placebo will be a Dextrose 5% in water infusion supplied by the site

Study drug preparation will be detailed in a separate pharmacy manual.

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 throughout the study. If it is determined to be necessary from one of the planned diet assessments, patients will be instructed to consume a nutritional supplement to ensure adequate protein intake.

Even though patients enrolled based on protocol amendment #1 will not be exposed to bimagrumab or placebo, during this extension study, all enrolled patients in this study will receive specific study treatments as part of this protocol:

- Vitamin D supplementation
- Exercise program

The vitamin D3 (or D2 if D3 is not available) supplements will be locally sourced with a recommended dosage:

- daily administration of 800 IU to 4000 IU vitamin D3 (dose chosen by 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.

Exercise program is presented in more details in Section 3.1.

5.2 Treatment arms

Patients enrolled following protocol amendment #1 will not receive investigational treatment.

Patients enrolled prior to the protocol amendment #1 have been assigned to one of the following 2 treatment arms in a ratio of 1:1 to receive i.v. doses of the following and will continue with this treatment until their EOT:

1. Patients on BYM338 70 mg in core study were randomized 1:1 to receive either BYM338 70 mg or placebo (BYM 70/PBO) for 6 doses in the extension study

2. Patients on BYM338 210 mg in core study were randomized 1:1 to receive either BYM338 210 mg or placebo (BYM 210/PBO) for 6 doses in the extension study

3. Patients on BYM338 700 mg in core study were randomized 1:1 to receive either BYM338 700 mg or placebo (BYM 700/PBO) for 6 doses in the extension study

4. Patients on BYM338 0 mg (placebo) in core study were randomized 1:1 to receive BYM338 0 mg (placebo) in both arms for 6 doses in the extension study

5.3 Treatment assignment, randomization

Not applicable.

[redacted]

5.4 Treatment blinding

Patients as well as the site staff will remain blinded to core treatment allocation as well as the extension randomization code for patients enrolled prior to the extension protocol amendment #1 from the time of randomization in the core study CBYM338E2202 until the final database lock of the extension study CBYM338E2202E1. The Novartis core clinical study team will have access to the treatment codes after the interim analysis. Other Novartis team members in the countries will remain blinded until the final study data base lock.

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 and the [redacted] bioanalyst. (2) Any potential visible difference in treatments will be concealed by the use of an opaque sleeve (applicable only for patients enrolled prior to amendment#1. (3) Any potentially unblinding parameters (e.g. DXA results) will not be available to the patient, site or study team, Randomization data are strictly confidential and will be accessible only to authorized personnel until un-blinding as described above. The study bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the samples. Both the un-blinded pharmacist and bioanalyst will keep treatment allocation information confidential. Un-blinding will only occur in the case of patient emergencies (see Section 5.5.13) and as described above.

IMPORTANT for sites with patients enrolled prior to protocol amendment #1: Due to the difference in preparation methods between the active and placebo treatments, an un-blinded pharmacist who is independent of the study team will be required. This un-blinded pharmacist will receive the appropriate treatment allocation. Appropriate measures must be taken by the un-blinded pharmacist to ensure that the study team remains blinded throughout the course of dose administrations and the remainder of the study even in the follow-up epoch.

5.5 Treating the patient

5.5.1 Patient numbering

Patients in the extension study CBYM338E2202E1 will continue with the same uniquely identified patient number that was assigned in the core study.

As in the core study, the patient 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.

Patients will be given the informed consent form (ICF) during one of the scheduled visits (e.g., Week 25 or at earlier visit) in study CBYM338E2202 to read and understand for their participation in this extension study. Patients will NOT be signing the ICF before completing the Week 25 (EOT) assessments of the core study.

Patients who are eligible based on the inclusion/exclusion criteria will be asked to sign the ICF. If the patient fails for any reason, he/she should not enter the extension and should complete the EoS visit of the core study as per the core study protocol.

5.5.2 Dispensing the investigational treatment

Section only applicable to patients enrolled prior to the protocol amendment#1.

[redacted]

The investigational drug, bimagrumab [redacted] will be prepared by Novartis and supplied to the Investigator's site as open labeled bulk medication.

Appropriate documentation of the patient 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.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

For patients enrolled prior to protocol amendment#1 only

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 un-blinded 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 un-blinded 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).

For ALL patients enrolled in the study

As in the core study, to avoid Vitamin D deficiency during the extension study, all patients will continue to receive vitamin D3 supplementation (or D2 if D3 is not possible) (800 IU-4000 IU per day) from the start of the study to the EOS visit. The vitamin D supplements will be locally sourced.

For more details refer to Section 5.1.2.

5.5.4 Instructions for prescribing and taking study treatment

Section only applicable to patients enrolled prior to the protocol amendment#1.

[redacted] End of infusion

[redacted]

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).

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 electronic case report form (eCRF) page.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Section only applicable to patients enrolled prior to the protocol amendment#1.

Study drug dose adjustments are not permitted.

Study drug interruptions or dosing delays should be avoided wherever possible and should occur within the given window as detailed in the Section 6 and Table 6-2.

If a patient misses two doses the patient must be discontinued from investigational treatment (refer to Section 5.5.10)

5.5.6 Recommended treatment of adverse events

Acne may be treated with a face wash containing 4-10% benzoyl peroxide wash and over the counter topical treatments. On occasion, a prescription topical treatment (i.e., antibiotics) or oral antibiotic (i.e., minocycline 100 mg b.i.d.) may be recommended at the Investigator's discretion. Early intervention is recommended when acne presents.

Muscle symptoms can be addressed with light self-massage of the involved area concentrating on improving circulation and relaxing muscle tissue. If excessive or prolonged soreness presents, then acetaminophen may be used as needed.

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.

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 prior and concomitant medications or on the surgical and medical procedures eCRF pages.

[redacted]

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.

Use of the treatments displayed in the table below are NOT allowed throughout the extension study). The following treatments are not allowed because of their biological effect on muscle anabolism or catabolism, which would potentially confound the assessment of efficacy.

[redacted]

5.5.10 Discontinuation of study treatment or from study

For patients enrolled prior to the protocol amendment#1.

Individual subject discontinuation

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the subject'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

[redacted]

- Liver event definition met as per Appendix 1
- Total of two (2) doses were missed in the entire study
- Death
- Withdrawal of consent
- Sponsor decision to terminate (part of) the study

Investigational treatment may be discontinued under the following circumstances:

- 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 as close to 28 days since the last dose received and complete the EOT visit and enter the Post-treatment follow up. The EOS visit should be scheduled 4 weeks after EOT. If they fail to return for these visits 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. Investigators or site personnel must contact the IRT to register the patient's discontinuation from treatment.

For patients enrolled after the protocol amendment#1.

Patients have to be discontinued from the study if they receive any of the prohibited medication listed in Section 5.5.9.

Patient can be discontinued if in the judgment of the investigator, taking into account the patient's overall status prevents the patient from safely continuing in the study.

Patients should then return to the site to perform the EOS visit as soon as possible and not later than 4 weeks after the decision being taken.

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. No further assessments must be 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.

NOTE: The investigator must also notify Novartis of the premature withdrawal.

[redacted]

5.5.12 Lost 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 reasons will not be replaced.

5.5.13 Emergency breaking of assigned treatment

Emergency un-blinding 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.

For patients enrolled prior to protocol amendment #1

Emergency code breaks are performed using the IRT system. When the investigator contacts the system to un-blind a patient, he/she must provide the requested patient identifying information and confirm the necessity to un-blind 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 Global Trial Leader that the code has been broken.

The un-blinded 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 un-blinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency un-blinding. 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).

For patients enrolled after protocol amendment #1, in case an emergency un-blinding of the core study treatment code is required, the investigator will have to follow the procedure described in the core study protocol CBYM338E2202.

5.5.14 Study completion and post-study treatment

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.

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.

[redacted]

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 schedule and assessments

For patients enrolled after the protocol amendment #1, the full assessment schedule is presented in Table 6-1 below. Patients enrolled prior to the protocol amendment #1 will be followed according to the visit scheduled presented in Table 6-2.

In order to allow sufficient reflection time for the informed consent process, the extension study may be presented and discussed early enough in the core study in order to allow the ICF signature process to be done at the Week 25/core EOT visit. The ICF must not be signed before the core EOT visit to avoid complications in the safety reporting requirements.

Patients following Table 6-1 should be seen for all visits on the designated day within a recommended 'visit window' of +/- 14 days. Day 1 must be the same day as the EOT visit of the core (i.e. the visit date is the date of the EOT visit of the core).

Patients should arrive to the visit fasted when blood samples for laboratory assessments will be taken at that visit.

Assessments for a particular visit may be split over several days. These may not be consecutive days but should respect the visit window period.

Below are some recommendations for organizing and performing the study assessments at visits with blood sampling.

- Assessments should be performed sequentially in the morning as follows: ECG collection, vital signs, blood sampling.
- After blood sampling, patients should be offered breakfast.
- [redacted]

For patients enrolled prior to the protocol amendment #1, the visits window to be applied is +/- 3 days. When scheduling the assessments of a visit, the same principle as stated above should apply. In addition, study treatment administration should be the last procedure.

Patients who discontinue the study should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 5.5.11). They should return and complete the EOS visit. If they fail to return for these visits for unknown reasons, every effort should be made to contact them as specified in Section 5.5.12.

Patients enrolled prior to the protocol amendment #1, who prematurely discontinue study treatment, should return as close to 28 days following the last dose received and complete the EOT visit. Their EOS visit should be scheduled 4 weeks after their EOT.

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.

[redacted]

Table 6-1 Assessment schedule for patients enrolled after the protocol amendment #1

Epoch	Screening epoch	Post-treatment follow-up epoch						
Timepoint	1	1	2	3	4	5	6	7
Site Visit	1(EOT)	1 (EOT)			2			3 (EOS)[5]
Phone contact			X	X		X	X	
Month	7	7	8	9	10	11	12	13
Week	25	25	29	33	37	41	45	49
Day	1	1	29	57	85	113	141	169
Obtain Informed consent	x							
Inclusion/Exclusion criteria	x							
Relevant medical history		x[2]						
Demography	x							
Physical examination		*			s			s
Body weight		*[1]			x			x
Body height		*[1]						
Blood pressure/pulse rate (sitting)		*[1]			x			x
Electrocardiogram		*[1]			x			x
Laboratory samples (hematology, biochemistry, vitamin D)		*			x			x
Vitamin D3 supplementation		Equivalent to daily administration of 800 IU to 4000 IU						
Supervised exercise		*[1]			x			
Home based exercise		2-3 times per week						
6 minute walk test		*[1]			x			x
Short physical performance		*[1]			x			x

[redacted]

Epoch	Screening epoch	Post-treatment follow-up epoch						
battery								
Exercise diary		Daily by the patient to report level of home based exercise						
[redacted]								
DXA		*						x
Diet assessment/ nutritional status		*[1]			x			x
[redacted]								
AE[3]/SAE[4]		x[2]	Any time as per AE/SAE reporting requirement					
Concomitant therapies		x[2]	Any time as per Concomitant therapies reporting requirement					
Comments	Any time as per investigator judgement							
Epoch disposition	x							x

S : mark procedure documented in the patient's source file only and not in the CRF

* Assessment performed at EOT visit of the core study. 3rd party data will be automatically transferred.

[1] Site must re-enter the data from EOT of core study onto the corresponding eCRF page of the extension study

[2] Ongoing events/conditions (i.e. SAEs/AEs, concomitant medications, cardiovascular and other relevant medical history) at EOT of the core study must be recorded on the appropriate eCRF of the extension study

[3] From the time of signing informed consent until EOS

[4] From the time of signing informed consent until 30 days after a patient stopped study participation

[5] Patients who discontinue study should return for EOS visit within the next 4 weeks unless they withdraw their consent

[redacted]

Table 6-2 Assessment schedule for patients enrolled prior to the protocol amendment #1

Epoch	Screening Epoch	Treatment Epoch												Post-treatment Follow-up Epoch
Visit	1	1		2		3		4		5		6		7 (EOT)[4]	8(EOS)[4]
Month	7	7		8		9		10		11		12		13	14
Week	25	25		29		33		37		41		45		49	53
Day	1	1		29		57		85		113		141		169	197
Hours	Pre-dose	Pre-dose/ *EOT of core	0	Pre-dose	0	Pre-dose	0	Pre-dose	0	Pre-dose	0	Pre-dose	0		
Obtain informed consent	x														
Inclusion / Exclusion criteria	x														
Relevant med. hist. / Current med. cond./Cardiovascular medical his.		X[7]													
Concomitant Meds / Therapies		X[7]	Any time as per concomitant therapies reporting requirement												
Demography	X[8]														
Physical examination[9]		*[8]		s				s				s		s	s
Body weight		*[8]		x				x				x		x	x
Body height		*[8]												x	
Blood pressure / Pulse rate (sitting)		*[8]		x				x				x		x [4]	x
Electrocardiogram (ECG)		*[8]		x				x				x		x	x

[redacted]

Epoch	Screening Epoch	Treatment Epoch												Post-treatment Follow-up Epoch
Visit	1	1		2		3		4		5		6		7 (EOT)[4]	8(EOS)[4]
Month	7	7		8		9		10		11		12		13	14
Week	25	25		29		33		37		41		45		49	53
Day	1	1		29		57		85		113		141		169	197
Hours	Pre-dose	Pre-dose/ *EOT of core	0	Pre-dose	0	Pre-dose	0	Pre-dose	0	Pre-dose	0	Pre-dose	0		
Echocardiography		*												x[10]	
Hematology		*		x				x						x	
Clinical Chemistry		*		x				x						x	
Cardiac Panel		*													
Vitamin D quantification		*						x						x	
Vitamin D3 supplementation		Equivalent to daily administration of 800 IU to 4000 IU													
Supervised exercise		*[8]				x				x				x [4]	
Home-based exercise				2-3 times per week											
6 minute walk test		*[8]				x				x				x	
Short physical performance battery		*[8]				x				x				x	
Exercise diary		Daily by the patient to report level of home based exercise													
[redacted]															
Lean Body Mass and Appendicular skeletal mass index by DXA		*						x						x [4]	
Randomization		x													

[redacted]

Epoch	Screening Epoch	Treatment Epoch												Post-treatment Follow-up Epoch
Visit	1	1		2		3		4		5		6		7 (EOT)[4]	8(EOS)[4]
Month	7	7		8		9		10		11		12		13	14
Week	25	25		29		33		37		41		45		49	53
Day	1	1		29		57		85		113		141		169	197
Hours	Pre-dose	Pre-dose/ *EOT of core	0	Pre-dose	0	Pre-dose	0	Pre-dose	0	Pre-dose	0	Pre-dose	0		
Drug administration			x		x		x		x		x		x		
Diet assessment / nutritional status		x				x				x				x [4]	
[redacted]															
AEs[2, 7]		As required per AE reporting requirement													
SAEs [3, 7]		As required per SAE reporting requirement													
Comments		Any time as per investigator judgement													
Epoch disposition[6]	x													x [4]	x [4]

* Assessment performed at EOT visit of the core study. 3rd party data will be automatically transferred.

S : mark evaluation documented in the patient source file only and not in the CRF

[redacted]

2 For randomized patients, from the time of signing informed consent until EOS

3 For all patients, from the time of signing informed consent until 30 days after a patient stopped study participation

[redacted]

4 Patients who discontinue study treatment should return for EOT visit 28 days after last dose received and continue into the Post-Treatment Epoch with EOS visit 4 weeks after EOT unless they withdraw their consent

5 Screening epoch to obtain informed consent, demography and confirm I/E criteria for extension study is captured at visit 1 prior to dosing.

6 Disposition captured at completion of each epoch: Screening; Treatment; and Post-Treatment Follow-up

7 Ongoing SAEs/AEs at EOT of core must be recorded as AEs/SAEs on the appropriate eCRF of the extension study. Ongoing concomitant medications and ongoing cardiovascular/relevant medical history/current medical conditions must be recorded on the appropriate eCRF pages of the extension study.

8 Site must re-enter the data from EOT of core onto the corresponding eCRF page of the extension study.

9 Physical examinations are performed at scheduled visits. Details of the exams are recorded in the source documents. Medical history of the core study which is ongoing at EOT of core is included in the Relevant and Medical History eCRF of the extension study. Significant findings observed after informed consent signature of the extension study which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF of the extension study

10. Echocardiography at EOT will only be performed for patients with new abnormal finding on the echocardiography reading of the core Week 25/EOT visit.

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6.1 Patient demographics/other characteristics at study entry

6.1.1 Subject demographics

Subject demographic data to be collected on all patients include: date and /or year of birth, sex, race, predominant ethnicity. The demographic data of the extension study will be the same as the demographic data of the core study. Instructions for completing the extension study eCRF will be provided in the eCRF completion guidelines (eCCGs).

6.1.2 Other characteristics at study entry

At the core study week 25 EOT visit before a patient enters the extension study, the investigator must review the following baseline data of the core study (CBYM338E2202): Cardiovascular History eCRF, Medical History eCRF. Any cardiovascular or medical history that is still ongoing at week 25 EOT of the core study must be recorded on the Cardiovascular History eCRF or Medical History eCRF of the extension study.

Similarly, any concomitant medications ongoing at week 25 EOT of the core study must be recorded on the Prior and Concomitant Medications eCRF of the extension study.

In addition, any ongoing AEs at week 25 EOT of the core study must be recorded as AEs in the extension study eCRF.

Instructions for completing the extension study eCRF will be provided in the eCCGs.

6.2 Treatment exposure and compliance

Throughout the study, patients will be required to participate in an exercise program with defined minimum requirements (see Section 3.1). Patients will record their training sessions on an exercise diary to track program adherence. The content of the paper diary will be recorded in the Exercise diary eCRF.

In addition patients will have vitamin D supplementation (see Section 5.1.2) recorded in the prior and concomitant eCRF.

For patients enrolled prior to the protocol amendment #1 only:

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.

[redacted]

6.3 Efficacy

Physical function efficacy assessments will be done at all sites by trained site personnel to ensure standard results. Training of the assessment protocols will be provided to each study site team by Novartis.

Efficacy measurements in the study will include:

[redacted]

- 6MWT to assess physical function
- SPPB to assess physical function
- Usual Gait Speed to assess physical function
- Total LBM and ASMI assessed by DXA to measure lean body mass and skeletal muscle mass of the arms and legs, respectively.

6.3.1 6 minute walk test

The 6 minute walk test (6MWT) is a simple, economical and reproducible test that measures how many meters a person can walk in 6 minutes. 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.

Patients will be instructed by the test administrator using a script and established testing protocol. The testing should be conducted on an individual basis (patient and testers) with no additional audience or support other than that of the trained personnel conducting the test. If a walking aid is required, patients will be asked to use the least assistive walking aid that in their opinion will enable them to complete the 6MWT test safely. Patients should be encouraged to use the same walking aid when performing all tests throughout the study. A change in walking aid to perform the test is permitted if required for safety reasons (e.g., deterioration of balance). The testing should occur at approximately the same time of the day throughout the study to prevent any possible diurnal variations. The same test administrator should perform all repeat tests on a patient whenever possible to reduce technician-related differences in test performance.

Complete details of course set-up, test administration, equipment and recording into the eCRF are described in the CBYM338E2202E1 Outcomes Manual.

6.3.2 Short physical performance battery

The 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 at al 2003). The disability remains even after adjustment for level and severity of comorbidity and self-report functional status. Collectively, SPPB might be considered to be a nonspecific but highly sensitive indicator of global health status reflecting several underlying physiological impairments.

The SPPB evaluates lower extremity function 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. Complete details of test administration, equipment and recording into the eCRF are described in the CBYM338E2202E1 Outcomes Manual.

[redacted]

6.3.3 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 from one store to another).

Usual gait speed represents one of the most suitable 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 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.

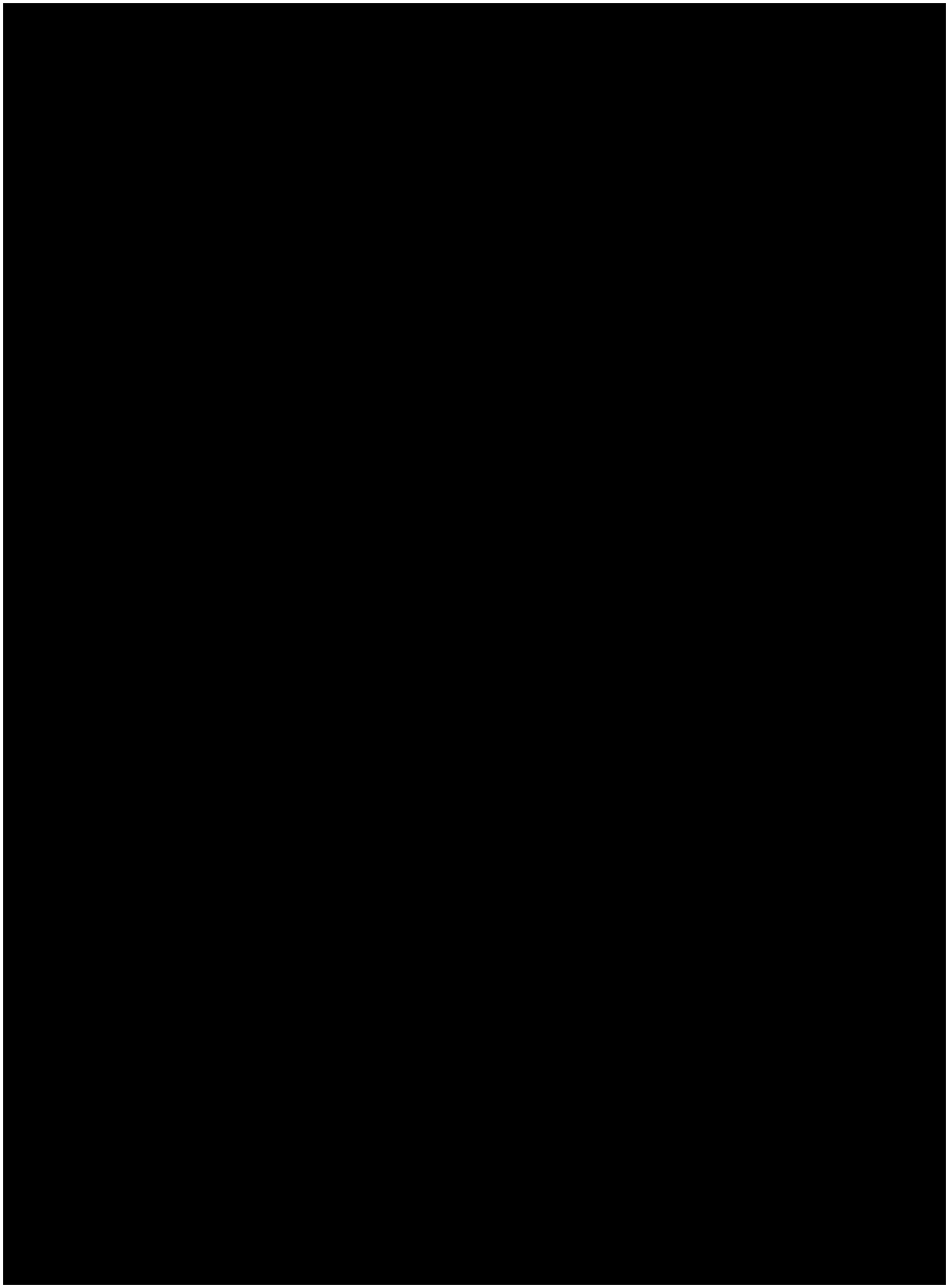
Complete details of test administration, equipment and recording into the eCRF are described as part of the SPPB protocol listed in the CBYM338E2202E1 Outcomes Manual.

6.3.4 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 LBM and 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%.

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.

Details of the test administration are provided in the CBYM338E2202E1 Imaging Manual.



6.4 Safety

6.4.1 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. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Skin-related issues will be assessed by the investigator or assigned clinician at each physical exam time point. Particular attention should be devoted to the assessment of acne due to the previously noted increased incidence of acne in people treated with bimagrumab.

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 on the eCRF. Medical history of the core study which is ongoing at EOT of core is included in the Relevant and Medical History eCRF of the extension study. Significant findings observed after informed consent signature of the extension study which

meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF of the extension study.

6.4.2 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 three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment. All readings should be recorded on the eCRF.

Vital signs will be collected at scheduled visits indicated in Table 6-1 and Table 6-2 as appropriate. Whenever possible, at each visit, vital signs should be collected using the same arm.

6.4.3 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 at scheduled visits indicated in Table 6-1 and Table 6-2 as appropriate.

If a weight decrease of 5% or more compared to the core baseline is seen, a comprehensive diet assessment should be conducted as per Section 5.1.2.

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

- BMI = Body weight (kg) / [Height (m)]^2

6.4.4 Laboratory evaluations

In the case where a laboratory result is outside the reference range for the laboratory parameter 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.

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 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 be contacted.

[redacted]

6.4.4.1 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.

6.4.4.2 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, creatinine, γ-GT, glucose (fasting), HgbA1c, phosphate, lipase, amylase, potassium, total protein, AST, ALT, sodium, magnesium, triglycerides, urea/BUN, uric acid, and vitamin D.

6.4.4.3 Cardiac Biomarker Panel

The following tests will be measured centrally: creatine kinase (CK), CK-MB and CK-MM, and troponin I and T only as part of the EOT/Week 25 joined visit with the core study as per Table 6-2.

6.4.5 Electrocardiogram (ECG)

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

A standard local 12 lead ECG will be performed supine at scheduled visits indicated in Tables 6-1 and 6-2 as appropriate.

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
- patient initials
- patient 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).

The eCRF will contain:

- date and time of ECG
- heart rate

[redacted]

- PR interval
- QT interval uncorrected
- QTcF
- QRS duration

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

6.4.6 Echocardiography

Section only applicable to patients enrolled prior to the protocol amendment#1.

Two dimensional echocardiography measurements will be assessed during the study as per the Table 6-2. The images will be transmitted to a central reading vendor for independent review. Sites will receive appropriate training for data transfer as well as an Echocardiography manual that will include detailed instructions and data transfer procedures.

6.4.7 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.

[redacted]

[redacted]

[redacted]

6.7 Telephone contact

Sites will contact patients by telephone on a monthly basis as per Table 6-1. At least 3 attempts on different days should be documented before considering the contact as missed.

During these telephone contacts, site staff should query the patient in a structured manner on adherence to the exercise program, occurrence of [redacted] any potential adverse event.

[redacted]

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 1.

[redacted]

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 duration (e.g. start and end date)
7. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)

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.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

[redacted]

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 as appropriate; 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 (IN). 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 such as but not limited to events of spontaneous muscle contraction with associated pain, diarrhea, or cardiac events that may require adjudication (see Section 8.5).

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 Global Trial Leader. 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. The telephone and fax numbers of the contact persons in the local Drug Safety and Epidemiology department, specific to the site 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.

[redacted]

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.

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 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 13-1-Appendix 1 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 13-1-Appendix 1 should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in Table 13-1-Appendix 1.

- 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.

[redacted]

7.4 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.

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.

[redacted]

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 that 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 a blinded expert reader will perform the quantitative analysis. The analysis results are 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.

[redacted]

Randomization codes assigned to patients enrolled before Amendment #1 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 un-blinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

8.4 Data Monitoring Committee (DMC)

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 will be to independently review and evaluate the unblinded safety data generated during the study as defined in this protocol. The DMC will also ensure that study participants are not exposed to unnecessary or unreasonable risks and that the study is conducted with high scientific and ethical standards. Finally, the DMC must make recommendations to the Sponsor on the actions to be taken on 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 un-blinded information with anyone outside of the DMC. Particularly, the Sponsor will remain fully blinded to any results until the interim analysis as described in Section 5.4 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, including tables, figures, and listings, as required.
- Preparation of any other reports requested by the DMC during the closed session.
- Review of the unblinded 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

An independent adjudication committee will be used for specific cardiac safety events (i.e. cardiomyopathy, heart failure, ischemic heart disease and cardiac rhythm disturbances).

[redacted]

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 report at the end of the study.

The clinical database will be searched by the clinical team for targeted cardiac adverse events mentioned above. When an adverse event is identified for adjudication, the clinical site will be notified and will be requested to document the adverse event in detail and submit any applicable supplemental data which may be available, including copies of source documents. Source documents include, but are not limited to, relevant clinical notes, ECGs, operative and pathology reports, hospital discharge summaries. In addition, an interview with the subject may be needed in person or via telephone.

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

9 Data analysis

9.1 Analysis sets

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

Safety set (SAF): The safety set comprises all subjects who received at least one dose of study drug from the core or extension study and enrolled in the extension study.

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

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

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

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

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

[redacted]

9.2 Patient demographics and other baseline characteristics

Descriptive statistics for demographics and baseline characteristics will be presented to describe the FAS. For Population I, all summaries will be presented by treatment group in the extension study and overall. For Population II, all summaries will be presented by treatment assigned in the Core study and overall.

Demographic variables taken at screening, including age, sex, child bearing potential of female subjects, height, weight, body mass index of baseline, race and ethnicity, will be summarized.

Baseline characteristics may include and are not limited to: nutritional status, exercise, tobacco/alcohol use, quadriceps strength, total and appendicular LBM, SPPB and 6MWT.

Descriptive statistics (mean, median, standard deviation, minimum and maximum, Q1 and Q3) will be presented for continuous variables for each treatment group and overall in the FAS. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and overall.

9.3 Treatments

For Population I, for each subject, cumulative exposure to study treatment will be calculated as the number of days of drug exposure = last infusion date – first infusion date + 56 days. The first infusion date refers to the first dose date following the last dose in the core study. The duration of exposure to study drug will be summarized by treatment group as a continuous variable.

For Population I, prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment epoch. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taking. If it cannot be established that the use of a prior medication has ended prior to the first dose of study treatment due to a missing end date, then it will be considered concomitant.

For Population II, no exposure will be presented, but concomitant medications will be presented.

9.4 Analysis of the primary variable(s)

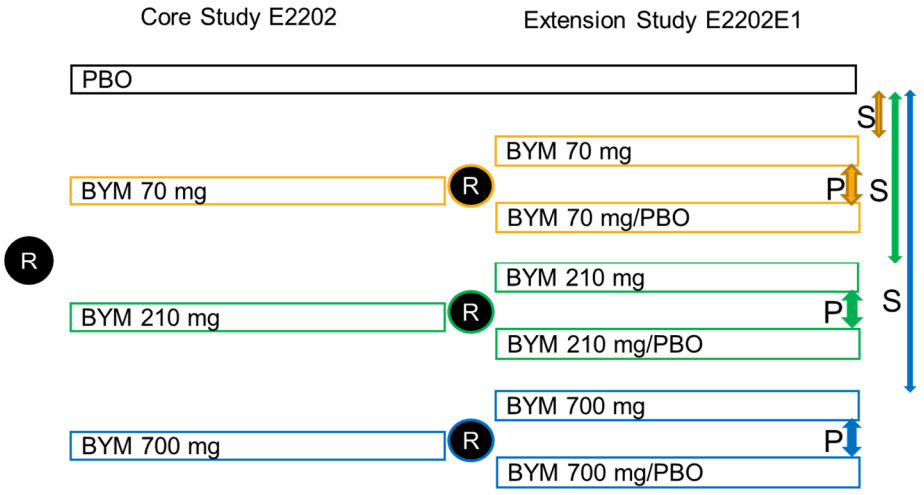
9.4.1 Variable(s)

The primary endpoint is SPPB at Week 49.

[redacted]

9.4.2 Statistical model, hypothesis, and method of analysis

Figure 9-1 Comparisons between Treatment Arms for Population I



No formal hypothesis testing will be performed in the study. All efficacy analyses will be based on FAS.

Summary statistics, i.e., mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval will be provided for the primary endpoint by treatment arm for each population.

For Population I, a 95% confidence interval for the difference in the primary endpoint between each continued bimagrumab dose arm vs. corresponding placebo switched from the same bimagrumab dose will be calculated, as shown as primary comparisons in Figure 9-1.

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

9.4.3 Handling of missing values/censoring/discontinuations

Summary statistics will be provided for observed data (no imputation).

9.4.4 Supportive analyses

The same analysis will be performed on PP set.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Secondary variables include:

- 6MWD at Week 49
- Gait speed at Week 49
- Total and appendicular lean body mass and ASMI as measured by DXA

[redacted]

[redacted]

Lean body mass will be logarithmically transformed for analysis.

For each continuous secondary variable, summary statistics (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) will be provided by treatment arm at each visit for each population.

For Population I 95% confidence interval will be provided for the difference between each continued bimagrumab dose arm vs. corresponding placebo (switched from the same bimagrumab dose arm) at each visit. 95% confidence interval will be provided for the difference between each continued bimagrumab dose arm and the placebo arm continued from the core study at each visit, as shown as the secondary comparisons in Figure 9-1.

[redacted]

9.5.2 Safety variables

All safety evaluations will be performed on the safety set (SAF) and analyzed for Population I and Population II separately. For Population I, all safety will be summarized by treatment group assigned in this extension study. Safety will be compared between the 3 continued bimagrumab dose arms against the placebo arm continued from the core study. For Population II, safety analysis will be presented by the treatment assigned in the Core study.

Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. Only primary paths within MedDRA will be considered for adverse event reporting.

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

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation of study treatment and adverse events leading to dose adjustment (including study treatment discontinuation).

Safety topics of interest such as cardiovascular events defined in the Safety Profiling Plan will be listed and analyzed separately.

[redacted]

Vital signs

Summary statistics in vital signs for each visit will be presented by vital sign and treatment group for Populations I and II separately.

All information collected will be listed by subject and abnormal values will be flagged.

Laboratory data

The summary of laboratory evaluations will be presented for the following groups of laboratory tests (see respective sections for details) for Populations I and II separately:

- Hematology
- Clinical chemistry

Descriptive summary statistics for each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group.

Subjects with abnormal laboratory values will be listed and selected parameters will be flagged during study conduct according to pre-defined clinically relevant values.

Newly occurring or worsening liver enzyme abnormalities will be summarized.

ECG

Summary statistics for Populations I and II separately will be presented for ECG variables by visit and treatment group.

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTcF).

QTcF will summarized by computing the number and percentage of subjects with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- PR > 250 msec

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

Echocardiography

For Population I summary statistics will be presented by visit and treatment group for the following measurements:

- Left ventricular wall (anterior and posterior) and septal thickness
- Left ventricular mass and mass index
- End-diastolic volume
- End-systolic volume
- Left ventricular ejection fraction
- Left ventricular diastolic and systolic diameter

[redacted]

- Left atrial size and volume
- Right ventricular wall thickness and function
- Interrogation of all valves for function, stenosis, regurgitation and morphology

[redacted]

9.5.4 PK/PD

Not Applicable

9.6 Interim analyses

An interim analysis will be triggered by the analysis of the core study Part A. Data from primary and key secondary efficacy parameters will be summarized. This interim analysis will provide a preliminary evaluation of endpoints over approximately 12 months; and together with core study Part A data will support next step decision making.

9.7 Sample size calculation

All the subjects from the core (CBYM338E2202), if eligible, can enter this extension study after they complete informed consent.

The standard deviation of SPPB can be found in the references in Table 9-1, which are also referred by the core study protocol.

Table 9-1 Standard deviation of SPPB

Reference	Study description	SD
Perera et al (2006)	N=492 community dwelling adults	2.7 (Baseline)
Kwon et al. (2009)	N=424 older sedentary adults	1.42 (Baseline)
Papanicolaou et al (2013)	N=120 sarcopenic elderly women	1.48 (Baseline)
		2.19 (After 6 months treatment)

[redacted]

	1.93 (After 6 months placebo)

With 40 to 50 patients per each bimagrumab dose arm,, assuming a standard deviation of SPPB of 1.5, 2.0, 2.5, and 3.0, the half-width of 95% confidence interval for SPPB is presented below in Table 9-2.

Table 9-2 Half-width of 95% confidence interval for SPPB

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

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed 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.

[redacted]

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 patients. 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 patients 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. If an 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 and health authorities, where required, 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 prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety monitoring should be followed.

[redacted]

12 References

Available upon request.

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.

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.

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.

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.

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.

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.

Njeh CF, Fuerst T, Hans D, et al (1999) Radiation exposure in bone mineral density assessment. App. Radiation and Isotopes; 50: 215-236.

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

[redacted]

(SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013; 17(6):533-43

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.

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.

Visser M, Schaap LA. Consequences of sarcopenia, Clin Geriatr Med. 2011Aug;27(3):387-99

Volpato Bianchi L, Cherubini A, Landi F, Maggio M, Savino E, Bandinelli S, Ceda GP, Guralnik JM, Zuliani G, Ferrucci L. Prevalence and clinical correlates of sarcopenia in community-dwelling older people: application of the EWGSOP definition and diagnostic algorithm. J Gerontol A Biol Sci Med Sci. 2014 Apr;69(4):438-46

[redacted]

13 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity *

Table 13-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert	• Repeat LFT within 48 hours • If elevation persists, discontinue	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator

[redacted]

Criteria	Actions required	Follow-up monitoring
syndrome)	the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*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

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

14 Appendix 2: Sample Log

Sample Log (all matrices): Time schedule for collection of blood for safety, [redacted] and pharmacodynamic (PD) assessments as per Table 6-1 and 6-2 as appropriate.

Sample volumes are the maximum size at any given visit.

For patients newly enrolled following protocol amendment#1

Study Epoch	Visit #	Day	Safety[1]
			size (ml)
SCR	1	1	
Post Treatment Follow-up	1	1	30*
	2	85	30
	3	169	30
[1] Includes when applicable: clinical chemistry (incl. vitamin D), hematology, * Sample collected at EOT visit of the core study E2202			

For patients enrolled prior to protocol amendment #1. All samples are to be collected pre-dose.

Study Epoch	Visit #	Day	Safety[1]	[redacted]
			size (ml)	
SCR	1	1		
Treatment	1	1		
	2	29	30	
	3	57		
	4	85	30	
	5	113		
	6	141		
	7	169	30	
Post Treatment Follow-up	8	197	30	

[redacted]

[1] Includes when applicable: clinical chemistry (incl. vitamin D), hematology,

[redacted]

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

[redacted]