NOVARTIS

Clinical Development

Bimagrumab (BYM338)

Clinical Trial Protocol CBYM338D2201 / NCT02152761

A 24-week double blind treatment and 24-week follow up, randomized, multi-center, placebo-controlled, phase IIa/IIb study to evaluate the safety and efficacy of i.v. bimagrumab on total lean body mass and physical performance in patients after surgical treatment of hip fracture

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[redacted]

List of abbreviations

ActRIIA/B	activin receptor type II A or type B
AFNH	avascular necrosis of the femoral head
AE	adverse event
AESI	adverse event of special interest
ADL	activities of daily living
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
BMI	body mass index
bpm	beats per minute
CPO	Country Pharma Organization
CT	Computerized tomography
DHEA	dehydroepiandrosterone
eCRF	electronic Case Report/Record Form
DMC	Data Monitoring Committee
DSM	Drug supply management
DXA	Dual Energy X-ray Absorptiometry
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
EoS	End of study
EoT	End of treatment
FAS	Full Analysis Set
GFR	glomerular filtration rate
GGT/ γGT	gamma-glutamyltransferase
GnRH	Gonadotropin-releasing hormone
GS	gait speed
GTL	Global trial leader
GWA	genome-wide association
HBs Ag	Hepatitis B surface antigen
HCV	Hepatitis C virus

[redacted]

HCV Ab	Hepatitis C virus antibody
HCV RNA PCR	Hepatitis C virus ribonucleic acid polymerase chain reaction
[redacted]	[redacted]
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International normalized ratio
IU	international units
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
LBM	Lean body mass
LLOQ	Lower Limit of Quantification
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Affairs
MHRA	Medicines and Healthcare products Regulatory Agency
MMSE	Mini Mental State Examination
MNAR	missing not at random
MRI	Magnetic Resonance Imaging
OA	osteoarthritis
PD	Pharmacodynamic
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
PP	Per-protocol
[redacted]	
PT	prothrombin
RAP	report and analysis plan
ROI	region of interest

[redacted]

ROM	range of motion
SAE	serious adverse event
SAF	Safety analysis set
SD	standard deviation
sIBM	Sporadic Inclusion Body Myositis
SPPB	short physical performance battery
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TGF-β	transforming growth factor–beta
TMV	thigh muscle volume
TNF-alpha	Tumor necrosis factor-alpha
ULN	upper limit of normal
VEGF	Vascular endothelial growth factor

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
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.
Premature patient discontinuation	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient discontinuation
Subject 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]

Amendment 4

Amendment rationale

The purpose of this amendment is to add a new safety monitoring guidance for patients with an increase of lipase and/or amylase and to modify the statistical analysis section to be consistent with the statistical analysis plan.

[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.

[redacted]

The wording of various sub-sections have been amended to reflect the rationale given above.

Additionally, this protocol amendment includes editorial changes for increased clarity of the text. Consequently, changes were implemented throughout the protocol.

Protocol Synopsis

- Incidence of falls added as a secondary objective

Section 1.2 Purpose

- Editorial changes

Section 2.1 Primary objective

- Editorial changes

Section 2.2 Secondary objectives

- Incidence of falls added as a secondary objective

[redacted]

Section 3.5 Purpose and timing of interim analyses/design adaptations and Section 9.6 Interim analysis

- Amended to clarify interim analysis planned for Jun2018

Section 3.6 Risk and benefits

- Patient exposure to bimagrumab updated
- Risk related to elevated lipase and amylase observations added.

Section 5.4 Treatment blinding and Section 9 Data analysis

- Independent Novartis team member will be unblinded to review and understand the primary analysis results.

Section 7.4 Lipase and amylase elevations

- Section added to provide guidance to the investigator for monitoring elevations of amylase and lipase throughout the trial.

Section 9.4.2 Statistical model, hypothesis, and method of analysis

- The within subject correlation structure for the mixed model has been updated.

Section 9.5.1.1 Gait speed and Short Physical Performance Battery (SPPB)

The testing strategy for the secondary endpoints has been updated from a step-down to a fixed sequence approach. **Section 9.5.1.3 Falls**

- Negative binomial regression added for event rates.
- Responder endpoint details added.

Section 9.5.2.4 Laboratory data

- Summary of pancreatic enzyme abnormalities included.

[redacted]

Section 9.7 Sample size and power calculation

- Removed references to previous testing strategy.
- Added power calculations for falls.

Section 13 Appendix 1: Clinically notable laboratory values

- Amylase and lipase ≥ 3x ULN added as clinically notable values that will be flagged at the central laboratory.

[redacted]

Amendment 3

Amendment rationale

The purpose of this amendment is to update the study design with progress made in the clinical development of bimagrumab program since the protocol was last submitted. It integrates new safety data from several recently completed bimagrumab studies (summarized in Section 3.6), further increases the inclusiveness of the trial, reduces patient and site burden, where possible [redacted] by Novartis specifically for this population.

[redacted]

[redacted]

[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 (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The main changes are the following:

[redacted]

[redacted]

Protocol Synopsis

Amended to reflect changes throughout the protocol

Section 2.2 – Secondary objectives

Amended to highlight that echocardiography is collected only on patients enrolled before Amendment #3

[redacted]

Section 3: Investigational plan

The description of the screening epoch has been amended to clarify the repeatability of assessments within the screening window and the last day when all eligibility criteria must be confirmed before randomization.

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

Further details to the rationale for early treatment initiation were added, which now better highlights the potential complications that may be prevented.

Section 3.6: Risk and benefits

The section has undergone extensive update triggered by the new Investigator Brochure version 9 incorporating new safety information from clinical trials completed in 2016.

In the radiation exposure section, a sentence comparing the magnitude of exposure to background radiation in normal daily life has been removed as this information may vary from country to country.

Section 4.1: Inclusion criteria

Amended to clarify the scope of inclusion criterion #3, namely fractures of the proximal femur (AO Classification 31A-C)

Section 4.2: Exclusion criteria

- Exclusion criterion #1: amended to better explain that a previous fracture or a major surgery on the lower extremity is exclusionary only if it caused a persisting functional sequelae, which directly impacts gait and is unlikely to recover during the study period.
- Exclusion criterion #3: amended to clarify that this exclusion criterion refers to isolated high-energy subtrochanteric fracture.

[redacted]

- Exclusion criterion #4: amended to allow patients with pancreatic insufficiency, if the condition is well controlled by medication/enzyme supplements.
- Exclusion criterion #8 (vitamin D): omitted. Instead of using 25-OH vitamin D measurements for eligibility assessment, the results will guide post-randomization patient care including a loading dose of vitamin D3 in case the patients is vitamin D deficient (i.e. 25-OH vitamin D < 30 nmol/L).
- Exclusion criterion #15: amended to raise the threshold of QTcF for both genders (500 msec). In addition, the amended criterion gives exempt to those patients with a QTcF prolongation (>500 msec) who has this ECG finding due to a ventricular pacemaker or presence of a bundle branch block (right or left).
- Exclusion criterion #21: amended to better explain that preventive treatments such as tamoxifene treatment after elective breast cancer surgery are not exclusionary. The amended version also gives extra emphasis to the fact that no patients with active cancer are allowed to enroll in the trial regardless of anatomic location or type of malignancy. Patients with non-melanoma skin cancers or with in situ cancers with excellent prognosis (e.g. carcinoma in situ of the uterine cervix) are allowed to enter the study, if they are considered completely cured by the time the patient entered the study (e.g. excised or resolved otherwise).
- Exclusion criterion #22: amended to increase the threshold of pre-surgical HgbA1c for exclusion (from 8.0% to 8.5%) based on recently communicated guidelines for the management of type 2 diabetes in older adults (Dunning et al 2014).
- Exclusion criterion #25: amended to better explain that the second sentence refers to patients who have already been diagnosed with latent tuberculosis and currently taking chemoprophylactic treatment.
- Exclusion criterion 26: amended to better explain the list of additional factors that the investigator needs to take into account when considering enrollment of a patient
- Exclusion criterion #27: amended to clarify that intravitreal administration of VEGF inhibitors is permitted. Systemic VEGF was added to the list of prohibited medications.
- Exclusion criterion #30: amended to indicate that ongoing corticosteroid treatment refers to systemic administration only.

[redacted]

[redacted]

Section 5.4: Treatment Blinding

Amended to indicate that following new guidelines to DMC activities, committee members are reviewing unblinded (not semi-unblinded) data.

Section is now highlighting DXA measures (lean and fat body mass), FSH and activin A as parameters that can reveal [redacted] effects of the treatment and therefore are not shared by central image reader / central laboratory, respectively.

Section 5.5.4: Instructions for prescribing and taking investigational treatment This section was amended to highlight which parameters are to be recorded on the eCRF form.

Section 5.5.8: Prohibited medications

Heading to the table now highlights potential effects on muscle strength (not just on muscle volume) as part of the rationale for prohibition.

Table itself has been amended to add systemic VEGF inhibitors as prohibited during study duration. Previously these were only mentioned in the list of in- and exclusion criteria.

Section 6: Visit schedule

Amended to include some instructions regarding how to calculate visit window for future visits, if a visit was delayed or missed completely. Sites must always use the date of the Randomization/Baseline dose as reference to calculating visit window for the upcoming visit.

In addition, the section was updated to re-emphasize that assessments pertinent to a given visit – including the randomization visit – can be spread over several days.

Table 6-1: Amended to reflect changes in the schedule of assessments and provide further instructions in the Note column, where needed. The table also clarifies prior discrepancies with the rest of Section 6 and its sub-sections (e.g. pulse and blood pressure to be measure and collected at each visit).

Footnote to the table clarifies the different scenarios of premature treatment discontinuation, or premature study discontinuation and outlines the instructions to follow. It also reminds investigators to complete echocardiographic monitoring only for patients enrolled in the study prior to this amendment.

Section 6.1: Information to be collected on screening failures

Amended to clarify the possibility of re-screening, if the patient was declared as screen failure due to reasons that may improve in a second attempt (mobility, ECG, lab parameter, MMSE score, etc.).

Section 6.2.2: Medical history

Amended to explain that history of falls refers to the occurrence of any fall during the past 12 months prior to screening excluding the fall that led to the hip fracture under investigation.

Section 6.2.3: Eligibility assessments

Amended to explicitly highlight laboratory assessments essential for eligibility and to omit Echocardiography for new patients enrolling after Amendment #3. “Gait speed” was replaced by “Confirmed ability to complete a 4 meter gait speed test” to better explain the requirement for eligibility.

[redacted]

Section 6.2.4: Other pre-treatment characteristics

Amended to add Serology and 25-OH Vitamin D, which are no longer required for eligibility but rather as pre-treatment characteristics

Section 6.4.3: Gait speed

Amended to add information on the use of walking aids at screening and during the study starting from baseline (D1) with special emphasis on the use of wheeled walkers/rollators

Section 6.4.4: Falls

Amended to emphasize the use of a diary to be used as an "aide-memoire" for patients in order to support patient's interview on falls.

Section 6.5: Safety

Amended to highlight that Echocardiography as a safety monitoring will only be utilized for patients who enrolled before Amendment #3.

Section 6.5.3: Height and Weight

This section now explicitly states that body height is measured at baseline only, whereas body weight at each study visit.

Section 6.5.4: Laboratory evaluations

[redacted]

Table 6-3: Added haptoglobin to the table, as this was only indicated in Appendix 2.

Section 6.5.5: ECG

Amended to clarify the protocol for the collection of triplicate ECGs, correct thresholds of eligibility, and explain when a follow-up ECG is required at EOS.

The paragraph on the need of reassessing QT prolongation by local ECG reading has been removed to align with Exclusion criterion #15. Similarly, the ECG assessment at W48, which was implemented to follow-up on new clinically meaningful ECG changes several months after last dose, was omitted.

Section 6.5.6: Echocardiography

Amended to reflect that echocardiography will be no longer required for patients randomized after Amendment #3. Those enrolled prior to the amendment will still have to complete their echo monitoring, including assessment at Week 48, if the W24 assessment indicated clinically meaningful abnormality. Instruction as to when the patient is required to undergo an additional assessment at Week 48 has also been included.

The requirement of re-assessing QTcF by local ECG reading at baseline has been omitted; eligibility will only be assessed at screening utilizing central reading.

When referring to Left Ventricular Wall thickness measurement in the list of echocardiographic parameters in scope, the word 'anterior' was included by mistake and is now removed from the parenthesis.

Section 6.5.7: X-ray

[redacted]

This section has been updated to better explain how this imaging method is utilized for eligibility assessment (local image) and for monitoring of fracture healing and orthopedic complications. It also explains when the protocol requires the collection of follow up images at W36 and W48. Finally, the section was amended to better explain the principle by which radiographs will be assessed by the central reader (2 independent reader and a third standing by to break the tie in case of conflicting diagnostic).

Section 6.5.8: Dietary Assessment/[redacted]

Based on cumulative experience [redacted] in the CBYM338B2203 study and feedback from sites in this multicenter study, this questionnaire will no longer be collected to obtain information on the dietary habits of the patient population 12 weeks after surgery.

Based on DMC recommendations, a sentence has been added requesting referral to a nutritionist or other health care provider to exclude malnutrition and need for taking additional therapeutic measures in case of seeing weight loss from baseline exceeding 5%.

Section 6.5.12: Appropriateness of safety measurements

Amended to explain the rationale for the change in cardiac safety monitoring introduced in this amendment and that the independent adjudication of image-based fracture healing complications will be performed by the central image reader only.

[redacted]

[redacted]

[redacted]

Section 7.2.1: SAE reporting

Amended to clarify that all X-ray based findings pertinent to delayed fracture healing (i.e. bone non-union at W36/W48) will have to be reported as SAE.

Section 8.4: DMC

Text has been updated to indicate that the DMC will review unblinded data outputs following recent changes in Guidelines to DMC activities.

Section 8.5: Adjudication

This section has been updated to reflect that an independent adjudication committee to re-assess and confirm pre-specified AEs/SAEs reported by investigators will be utilized for cardiovascular events only. The scope of adjudication which includes ischemic heart disease,

[redacted]

heart failure, cardiomyopathy, and certain cardiac arrhythmias, was clarified. The section also highlights that independent adjudication of image-based fracture healing complications will be done by the central image reader only.

Section 9: Data Analysis

Amended to highlight that the primary analysis (summary of W24 data) is planned to be supplemented by additional analysis of all efficacy data available at the time of the primary analysis to obtain preliminary insight into the robustness/durability of potential therapeutic effects

Section 9.1.1: Study medication

This section was amended to correct the calculation of exposure to last infusion date minus first infusion date plus 56 days (instead of 28 days).

Section 9.5.2.2: Bone Safety Analysis

Amended to reflect current focus of interest concerning orthopedic complication (fracture healing complications with focus on incidence of delayed bone-union).

[redacted]

Section 12: References
Updated by references used in the current amendment

[redacted]

[redacted]

Amendment 2

Amendment rationale

[redacted]

In order to properly assess dose response relationship of bimagrumab at least three doses are required, ranging from a potential minimally effective dose to a dose where maximal efficacy is expected. A lower dose arm of 70 mg i.v., which is expected to show suboptimal to minimal efficacy, has therefore been added to this study. This will facilitate an adequate dose-selection for phase III without the need for supportive data from another dose- response finding study.

[redacted]

[redacted]

[redacted]

[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 (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The main changes are the following:

- Addition of a treatment arm and change dosing regimen from weight based dosing (bimagrumab 3 mg/kg and 10 mg/kg) to fixed dosing (bimagrumab 70 mg, 210 mg and 700 mg)
- Changing the randomization ratio from 1:1:1 to 2:1:2:2 (1 referring to the lowest dose group of 70 mg)
- Reduction of the treatment epoch from 52 weeks to 24 weeks and the respective number of infusions from 13 to 6
- Increase of the post treatment follow-up epoch from 4 weeks to 24 weeks
- Increase of the screening epoch to be from 7 to 28 days to 3 to 42 days post-surgery
- Modification of the secondary objectives to address the shorter treatment duration

- Modification of the inclusion criteria
  - Lower limit of age has been decreased from 65 to 60 years
  - Lower limit of BMI has been decreased from 16 to 15 kg/m2

- Modification of the exclusion criteria
  - History of fracture was clarified to recent lower limb fracture or surgery with persistent negative impact. By doing so 2 criteria were merged
  - Various criteria on condition affecting the patient's ability to walk (e.g. some visual, psychiatric or respiratory disorders) were merged bringing 5 criteria into one
  - Criteria on disease affecting food absorption was clarified
  - Exclusion of rheumatoid arthritis patients was removed
  - Vitamin D deficiency exclusion is limited to patients not receiving an appropriate loading dose

  - Abnormal liver function test criteria was clarified and liver disease are limited to present conditions
  - Hypertension criterion was limited to uncontrolled with medication exceeding a systolic pressure of 180 mmHg and/or diastolic pressure of 90 mmHg
  - Ischemic heart disease was limited to ongoing unstable angina pectoris and recent myocardial infarction in the past 3 month prior to randomization
  - Type of excluded cancer was clarified
  - 2 criteria on excluded immunosuppressive therapies were merged and limited to the 3 months prior randomization period
  - Criteria related to the use of any therapies known to affect muscle mass was clarified
- Modification of prohibited medications
- Reduction of the number of visits in the post treatment follow-up epoch
- Elimination of the following assessments :
  - Alcohol test and drug screening

  [redacted]
  - Mediolateral sway test

  [redacted]
- Frequency reduction of the following assessments

  [redacted]
  - X-ray of the operated hip at (not done at W36 and W48, unless W24 result requires it)
  - DEXA (not done at Week 36 and W48)

  [redacted]
- Addition of the following assessment
  - Pre-albumin as part of Clinical Chemistry panel
- Removal of Appendix 4 with background material on SUSAR exemptions

[redacted]

Amendment 1

Amendment rationale

This protocol amendment is primarily issued for the following reasons:

- To add central laboratory serology testing, including HBV, HCV, and HIV, as well as urine drug testing at the screening visit. Results of these tests determine eligibility for the study, thus identification and documentation of status is required. Addition of these tests is necessary due to the limitations of relying on medical history or liver enzyme elevations when identifying patients with chronic viral infection (which may be asymptomatic) and inherent hepatic safety implications. Given the limited experience with longer-term (i.e. > 3 treatment months) testing of bimagrumab in the elderly frail population, it was deemed imperative to make every effort to minimize risk factors with major impact on hepatic safety assessment.
- To clarify and distinguish exclusion criteria 26 (chronic active hepatitis) from exclusion criteria 33 (chronic active virus or bacterial infection).
- To align the Decision Tree for Randomization with the cardiovascular exclusion criteria.
- To clarify that the physical exam may include additional rectal, external genitalia, breast, and pelvic exams if deemed necessary by the investigator. Such physical examinations may not be routinely performed by the orthopedist and are thus explicitly specified to indicate that reporting of findings is expected in case the patient presents with signs or symptoms pertinent to these organ systems.
- To add temperature to the vital sign assessments. It was deemed medically important to document and address, if necessary, high body temperature due to its potential interference with physical performance measurements.

At the time of this amendment, no patients have been enrolled into the study.

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 wording of various sub-sections to "Study design" (Section 3.1), "Exclusion criteria" (Section 4.2), and "Visit schedule and assessments" (Section 6) have been amended to reflect the rationale given above.

Additionally, this protocol amendment includes the correction of typographical, formatting, and numerical errors as well as editorial changes for increased clarity of the text. Consequently, changes were implemented throughout the protocol.

This amended protocol is being issued before any IRB / IEC / HA submission has been made.A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

Protocol synopsis

Protocol number	CBYM338D2201
Title	A 24-week double blind treatment and 24-week follow-up, randomized, multi-center, placebo-controlled, phase IIa/IIb study to evaluate the safety and efficacy of i.v. bimagrumab on total lean body mass and physical performance in patients after surgical treatment of hip fracture
Brief title	Study of safety and efficacy of bimagrumab in patients after surgical treatment of hip fracture.
Sponsor and Clinical Phase	Novartis, phase IIa/IIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the present proof of efficacy study is to identify at least one dose of bimagrumab that can increase lean body mass and improve physical function as compared to placebo when administered every 4 weeks over a 24-week treatment epoch in patients with disuse atrophy after surgical repair of a proximal femur fracture. Data from this study will be used to find the dose for further development in phase 3 and assess the safety and tolerability of bimagrumab in this indication.
Primary Objective(s)	To assess the effect of bimagrumab given intravenously every 4 weeks on total lean body mass (LBM) measured by dual emission X-ray absorptiometry (DXA) as assessed by change from baseline **at week 24** relative to placebo in patients with disuse atrophy after surgical treatment of hip fracture.
Secondary Objectives	To assess the effect of bimagrumab compared to placebo on improvement in mobility as measured by change from baseline **at week 24** in gait speed. To assess the effect of bimagrumab compared to placebo on improvement in physical performance as measured by change from baseline **at Week 24** in the Short Physical Performance Battery (SPPB). To evaluate the effects of bimagrumab vs. placebo on the incidence of falls To assess the post treatment effect of bimagrumab compared to placebo on physical performance and mobility as measured by SPPB and gait speed up to End of Study. To assess the clinical safety and tolerability of bimagrumab relative to placebo as assessed by measures such as vital signs, clinical laboratory variables, electrocardiogram (ECG), echocardiogram (on patient enrolled prior to Amendment #3), adverse events (AE), X-ray assessment of the surgical procedure and potential orthopedic complications.
Study design	This is a 24-week double blind treatment and 24-week follow-up, 4-treatment arms, parallel-group, randomized, placebo-controlled, multi-center clinical study. A screening epoch from Day 3 up to Day 42 post surgery will be used to assess eligibility. At baseline visit, eligible patients will be randomized to placebo, 70 mg, 210 mg, or 700 mg of bimagrumab in a ratio of 2:1:2:2 respectively. Randomized patients will be treated for

Protocol number	CBYM338D2201
	24 weeks and will receive investigational treatment every 4 weeks for a total of 6 doses. After completing the treatment epoch, patients will enter a 24-week post-treatment follow up epoch.
Population	Approximately 245 male and female patients ≥ 60 years old, who recently sustained a low-energy hip fracture that required surgical repair by either internal fracture fixation or joint replacement.
Inclusion criteria	Key inclusion criteria: • Patient must have had surgical fixation or arthroplasty of the proximal femur fracture (AO Classification 31 A-C (AO Foundation) as confirmed by radiography. • Patient must be mentally competent at , to have scored at least ≥ 21 on the Folstein Mini Mental State Examination (MMSE) • Patient must be able to complete a 4 m gait speed test • Patients must weigh at least 35 kg and must have a body mass index (BMI) within the range of 15 – 35 kg/m^2 at screening • Patient must have completed surgical wound healing
Exclusion criteria	Key exclusion criteria: • History of any other complicated lower limb fracture in the past 6 months or major lower limb surgery in the past 3 months prior to randomization that caused a persisting functional sequelae, which directly impacts gait speed and/or gait quality and is unlikely to recover during the study period • Isolated high-energy sub-trochanteric fracture • Active diseases known to cause malabsorption of protein • Vitamin D deficiency (25-OH-vitamin D < 12.0 ng/mL or < 30.0 nmol/L) not treated with vitamin D supplementation prior to randomization **Cardiovascular conditions (SAFETY):** • Ongoing ischemic heart disease or congestive heart failure (NYHA Class III/IV), or hypertension poorly controlled by medication. **Hepatic enzyme elevations and conditions (SAFETY):** • Abnormal liver function tests such as SGOT (AST), SGPT (ALT), or serum bilirubin (except if associated to Gilbert's Disease). **Other major medical conditions:** • Type I diabetes mellitus or uncontrolled type II diabetes mellitus (e.g. pre-surgical levels HgbA1c ≥ 8.5% or fasting blood glucose ≥ 9.0 mmol/l at more than one occasion) **Prohibited medications interfering with muscle metabolism/strength:** • Use of any therapy known to affect muscle mass via modulation of androgen or growth-hormone receptors or the synthesis of these hormones within **3 months** prior to randomization or current use of high-dose selective beta2-adrenergic drug therapy;) *For further detail on Inclusion and Exclusion criteria, please refer to*

[redacted]

Protocol number	CBYM338D2201
	Section 4.1
Investigational and reference therapy	Arm 1: Placebo i.v. every 4 weeks Arm 2: Bimagrumab 700 mg i.v. every 4 weeks Arm 3: Bimagrumab 210 i.v. every 4 weeks Arm 4: Bimagrumab 70 mg i.v. every 4 weeks
Efficacy assessments	• Total lean body mass assessed by DXA • Short Physical Performance Battery (SPPB) • Gait Speed (as a component of SPPB) • Falls
Safety assessments	• Evaluation of all AEs and SAEs including infusion site and hypersensitivity reactions • Physical examination • Vital signs, height and weight • Laboratory evaluations • Electrocardiogram (ECG) • Echocardiogram (on patient enrolled prior to Amendment #3) • X-ray assessment of surgical complications (if applicable) and complications of fracture healing [redacted]
Other assessments	[redacted]
Data analysis	The primary variable is change from baseline in Total LBM at Week 24. A mixed model will be used with change from baseline at all post-baseline visits (Week 12 and Week 24) as response variable, and treatment, visit, randomization strata and baseline measurements as covariates. Two interaction terms (treatment*visit and baseline LBM*visit) will also be included in the model. The two-sided p-value for the least square mean (LSM) difference between the bimagrumab and the placebo groups at

[redacted]

Protocol number	CBYM338D2201
	Week 24 (and at Week 12) will be reported for the difference. Holm-Bonferroni method will be used to adjust for type I error among the 2 comparisons (bimagrumab 210 mg vs. placebo and bimagrumab 700 mg vs. placebo). Total LBM data will be transformed with natural logarithm before this analysis. The bimagrumab 70mg group will not be used for hypothesis testing. [redacted] The change in gait speed from baseline will be analyzed similar to the primary variable. If the variable is not normally distributed, log transformation may be used if warranted. The change in summary performance score of SPPB and in each one of the component scores (balance test score, gait speed score, chair stand score) from baseline will be analyzed similar to the primary variable, assuming a normal distribution. If the variable is not normally distributed, log transformation may be investigated.
Key words	Bimagrumab, BYM338, hip fracture, elderly, controlled clinical trial, randomized, muscle wasting (atrophy)

[redacted]

1 Introduction

1.1 Background

Skeletal muscle is a dynamic and plastic tissue that responds rapidly to changes in frequency and duration of use (Musacchia et al 1988). An increase in muscle activity builds and maintains mass, while inactivity results in loss of muscle mass and hence muscle atrophy. Skeletal muscle atrophy is a change that may occur as a result of varied conditions, among others disuse (e.g., immobilization, denervation, muscle unloading).

Disuse muscle atrophy and related functional limitations are commonly seen in frail elderly patients following a hip fracture. Disuse atrophy is triggered by immobility caused by the fracture and subsequent major surgical operation extent of which can vary depending on numerous factor such as patient's age, gender, presence of comorbidities (such as diabetes, OA, cognitive impairment, etc), concomitant medications, and preoperative mobility status (Lyons et al 1997, Koval et al 1998).

Importantly, atrophy due to disuse primarily affects the lower limbs and accounts for poor mobility and challenged rehabilitation course. One of the most important goals of rehabilitation for hip fracture patients - beyond pain management - is to recover ambulation and prevent serious morbidities arising from impaired mobility or complete immobility. Current treatment modalities are largely limited to physical rehabilitation, which requires active participation, long-term dedication and persistence from the patient's side. Despite these efforts, significant achievement in terms of restoration of muscle mass and strength is not always guaranteed.

Approximately half of patients with hip fracture do not return to pre-fracture level of mobility by Month 6 after surgery (Vochteloo et.al 2013). About 30% may face injurious falls, 12% fractures and 5% a secondary hip fracture. This emphasizes the need for effective therapy to accelerate ambulation and highlights the relative ineffectiveness of existing therapeutic approaches.

Treatment with a muscle anabolic drug during the recovery phase may boost the recovery of muscle mass, strength and functional performance to drive overall improvement of physical function. Adunsky et al (2011) showed that a muscle anabolic agent (ibutamoren mesylate) was effective in improving physical function as measured by Short Physical Performance Battery (SPPB) and its component, gait speed. Moreover, knee muscle strength was an important modifiable predictor of falls in patients after hip fracture surgery (Yau et al 2013), further indicating that increase in muscle mass and strength leads to better functional outcomes. However, currently there is no approved pharmacological therapy available that helps patients in increasing their muscle mass and resuming their functional activity after surgical fixation of the hip fracture.

Myostatin, a member of the transforming growth factor beta (TGF-β) superfamily, is a secreted protein that negatively regulates skeletal muscle mass in animals and humans throughout the lifecycle. Myostatin acts via the activin receptor type II (mainly via ActRIIB) and its proposed signaling is through the SMAD 2/3 pathway, which is involved in the inhibition of protein synthesis, and myocyte differentiation and proliferation. Myostatin

[redacted]

inhibition or genetic ablation increases muscle mass and strength (Lee et al 2005, Lee and McPherron 2001, Whittemore et al 2003).

Bimagrumab is a fully human, monoclonal antibody (modified IgG1, 234-235-Ala-Ala, λ2) developed for the treatment of involuntary muscle loss associated with illness, injury, and aging. It binds with high affinity to the activin receptors type IIB (ActRIIB) and with a lower affinity to activin receptors type IIA (ActRIIA), competitively blocking the binding of natural ligands (including myostatin and activins), that act as natural inhibitors of skeletal muscle growth.

[redacted]

In summary, bimagrumab has yielded sufficient clinical data to support further investigation in the anticipated target populations such as patients with disuse atrophy and mobility limitations due to hip fracture fixation surgery.

1.2 Purpose

The main purpose of the study is to identify at least one dose of bimagrumab that can increase lean body mass and improve physical function when compared to placebo at Week 24. After completion of the 24-week treatment period, the study will continue to assess the potential sustained efficacy and the safety up to Week 48. Data from this study will be used to further assess the efficacy and safety of the selected dose(s) for further development in phase 3.

[redacted]

2 Study objectives

2.1 Primary objective

The primary objective is to assess the efficacy of at least one dose of bimagrumab given intravenously every 4 weeks on total lean body mass (LBM) measured by dual emission X-ray absorptiometry (DXA) as assessed by change from baseline **at week 24** relative to placebo in patients with disuse atrophy after surgical treatment of hip fracture.

2.2 Secondary objectives

Secondary objectives are as follows:

- To assess the effect of bimagrumab compared to placebo on improvement in mobility as measured by change from baseline **at week 24** in gait speed.
- To assess the effect of bimagrumab compared to placebo on improvement in physical performance as measured by change from baseline **at week 24** in the Short Physical Performance Battery (SPPB).
- To evaluate the effects of bimagrumab vs. placebo on the incidence of falls
- To assess the post treatment effect of bimagrumab compared to placebo on physical performance and mobility as measured by SPPB and gait speed up to End of Study
- To assess the clinical safety and tolerability of bimagrumab relative to placebo as assessed by measures such as vital signs, clinical laboratory variables, electrocardiogram (ECG), echocardiogram (only on patients enrolled before Amendment #3), adverse events (AE), X-ray assessment of the surgical procedure and potential orthopedic complications.

3 Investigational plan

3.1 Study design

This is a Phase IIa/IIb, 24-week, 4-treatment arms, parallel-group, randomized, double-blind, placebo-controlled, followed by a 24-week follow-up multi-center clinical study (Figure 3-1). The study consists of 3 epochs:

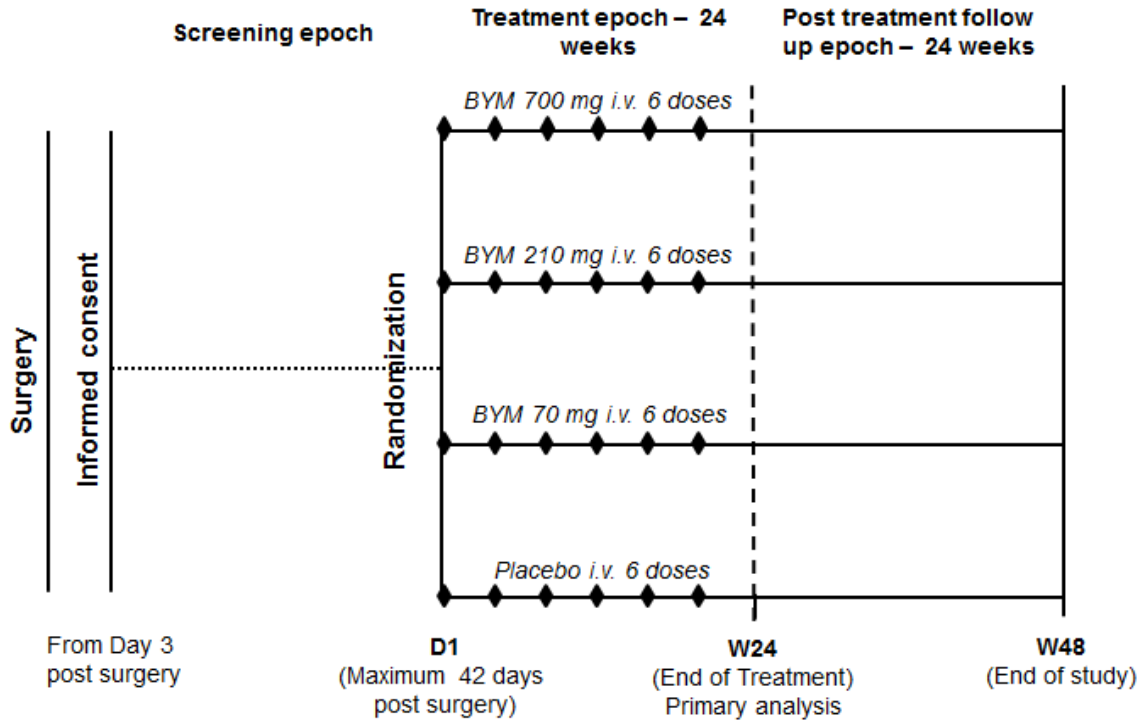
- A screening epoch of up to 6 weeks post-surgery will be used to assess eligibility.
- A treatment epoch of 24 weeks
- A post-treatment follow-up epoch of 24 weeks

At baseline visit, eligible patients will be randomized in a 2:1:2:2 ratio to either placebo, bimagrumab 70 mg, bimagrumab 210 mg, or bimagrumab 700 mg. Randomized patients will be treated for 24 weeks s and will receive investigational treatment every 4 weeks for a total of 6 doses. When all patients have completed the Treatment epoch (Week 24), the primary analysis will be conducted to assess the effects of bimagrumab on primary and secondary endpoints including key safety measures. After completing the treatment epoch, patients will enter a follow up epoch with two visits at Week 36 and 48, the latter representing the End of study (EoS) visit. The final analysis will be performed when all patients have completed their EoS visit.

Patients randomized prior implementation of protocol amendment #2 were converted to fixed dose regimen at their next scheduled visit. Patients on 3mg/kg bimagrumab converted to 210 mg bimagrumab fixed dose and patients on 10 mg/kg bimagrumab converted to 700 mg

bimagrumab. Patients who are beyond their week 20 visit had their EoT at the next scheduled visit and continued the study as per protocol amendment #2.

Figure 3-1 Study design



There are 3 study epochs:

Screening epoch: Informed consent will be obtained prior to implementing any study specific procedures. The screening epoch begins as early as day 3 post surgery and ends with randomization no later than 42 days post-surgery (Study Day -39 to Day -1). The screening epoch should ideally start as soon as the patient starts to walk [redacted]

All entry criteria must be fulfilled before randomization (and latest on Day 42). This implies that any screening assessment can be repeated, as needed, if timelines to collect results allow this.

It is recommended to perform simple screening assessments first (e.g. medical history, inclusion/exclusion criteria and vital signs) to identify non-eligible patients early, followed by the 4 meter gait speed test to demonstrate the ability to walk. Then, laboratory samples, which require shipping and analysis, should be collected along with the 12-lead ECG..

As soon as all inclusion criteria and none of the exclusion criteria have been met, the patient can be randomized.

The randomization date will be the 'Day 1' study visit (baseline/randomization) and used as reference for visit scheduling throughout the study period.

[redacted]

Treatment epoch: First dose of investigational treatment will be administered on the day of randomization (Day 1). Patients will receive 6 doses, one every 4 weeks. Final dose will be administered at the week 20 visit and the treatment epoch will end 4 weeks later at week 24, the EoT visit. Investigational treatment will be administered in addition to the local surgical standard of care for hip fracture [redacted]

Post treatment Follow-up epoch: After completing the End of Treatment visit, patients will enter a post-treatment follow-up with two visits at Week 36 and 48.

Following their study participation, patients will be further followed by their treating physician if required, according to the local standard of care.

3.2 Rationale of study design

There is no published Health Authority guidance to provide considerations for this study population or for the treatment of skeletal muscle disuse atrophy. The double-blind, randomized, parallel-group, placebo-controlled design used in this study will provide objective and unbiased data on the physical and functional improvements as a result of bimagrumab treatment.

Efficacy of bimagrumab will be tested [redacted] associated with surgical hip fracture repair. The working hypothesis is that increased muscle mass [redacted] will lead to increased muscle power and improved functional performance, which is a prerequisite of improvement of activities of daily living, avoiding living dependency, and occurrence of complications (falls, fractures, hospitalization).

The post treatment follow-up period will allow characterizing the potential effect of bimagrumab in terms of mobility and lower-extremity function even after stopping therapy.

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

The choice of doses, frequency, route of administration, and duration of treatment is based on results of three Phase I studies: the First in Human (FIH) study (CBYM338X2101 Part A), casting study in healthy male volunteers (CBYM338X2101 Part B) and the multi-dose study (CBYM338X2102) in healthy volunteers.

Dose and frequency

Results in healthy volunteers (CBYM338X2101 and CBYM338X2102) indicated that thigh muscle volume (TMV) increased comparably for single doses of 10 mg/kg and 30 mg/kg, but the effect of 30 mg/kg lasted longer (2 months versus 1 month). With 3 repeated every 4 weeks doses of bimagrumab, there was a comparable increase in TMV in healthy adults at 3 mg/kg and 10 mg/kg, even though duration of complete receptor occupancy (inferred from PK profile) with the 3 mg/kg dose is approximately half that observed with the 10 mg/kg dose. In healthy volunteers (CBYM338X2101), a limited and transient effect on the TMV was observed after infusion of a single dose of 1 mg/kg bimagrumab. This 1 mg/kg dose is therefore expected to be a non-effective or a minimally effective dose.

[redacted]

In order to identify at least one effective dose of bimagrumab and be able to evaluate a dose response curve, the study will evaluate 3 fixed i.v. doses of bimagrumab 70, 210, or 700 mg administered every 4 weeks. The fixed dose equivalent of the mg/kg doses used in previous studies was calculated based on the mean patients' weight and similar calculation was used for the current study based on the mean patients' weight rounded to 70 kg reported in literature for hip fracture patients (66±12 kg) (Mak et al 2014).

Since the 70 mg dose is expected to be a non-effective or minimally effective dose it will be used only for dose response modelling and not hypothesis testing, therefore fewer patients will be randomized to this group. The randomization ratio will be 2:1:2:2 to either placebo, bimagrumab 70 mg, bimagrumab 210 mg, or bimagrumab 700 mg.

Changing from weight-based to fixed dosing is expected to better inform of the variability of exposure data and improve the accuracy of dose-exposure-response relationship estimation. Of note it is not expected that randomized patients will be exposed to bimagrumab at Cmax levels exceeding those experienced with the highest tested dose in previous studies, i.e. 30 mg/kg. .

Dosing frequency every 4 weeks is based on observations from PK/PD studies where the efficacy reached the same plateau with both the 10 mg/kg every 4 weeks dosing and the 30 mg every 8 weeks i.v. dosing.

Route of administration

Study medication will be administered via intravenous infusion over 30 minutes, which was tested in study BYM338X2107 and shown to be well tolerated.

Treatment duration

Most recovery after a hip fracture has been shown to occur during the first 6 months after surgery, but many patients (44-60%) never regain prefracture level of mobility and physical functioning (Magaziner et al 2000, Vochteloo et al 2013, Shyu et al. 2004). Even with multidisciplinary postoperative rehabilitation, no more than 40% of patients completely regained their ability to perform activities of daily living during the 1-year follow-up (Stenvall et al 2007).

A recent study in hip fracture patients treated with an anabolic agent (ibutamoren mesylate) showed that a 6-month (but not a 3-month) treatment was effective in improving physical function as measured by SPPB and its component gait speed score (Adunsky et al 2011). Since increases in LBM are expected to reach their maximum after 2-3 months of treatment and functional benefits are observed with a delay, it seems reasonable to hypothesize that 6-month duration of therapy is sufficient for increasing the functional recovery of hip fracture patients.

Timing of first dose

The efficacy of bimagrumab is expected to be optimal when coupled with physical activity, therefore the timing of the first dose is aligned to be close to the start of physical therapy (ie. 2-4 weeks post-surgery).

A number of studies reviewed by Chudyk et al 2009 and English and Paddon-Jones D 2010 indicate that early mobilization/ambulation following surgical fixation of a hip fracture may

[redacted]

improve patient outcomes such as early physical function, rate of discharge to home and decrease the risk of immobility-related complications and hospital readmissions (e.g. infections and thrombotic events). Recent reviews also argue that early (and preferably more intensive) initiation of physiotherapy is critical for overcoming the early loss of muscle strength after hip fracture surgery (Bandholm and Kehlet 2012), which is an important predictor of the course of recovery.

3.4 Rationale for choice of comparator

The choice of placebo as a control agent is necessary to obtain information concerning the specific versus non-specific effects of the active treatment and provides the best way of evaluating the efficacy and assessing the safety and tolerability of bimagrumab.

In the absence of any approved pharmacological comparator (i.e., a 'gold standard') in disuse atrophy, placebo will be used. The placebo arm will account for functional recovery that would naturally occur over time with local standard of care [redacted].

After the primary analysis (Week 24), all patients will stop study medication and remain in the study to be seen twice at Week 36 and End of Study (Week 48) visits.

It is ethically justified to keep placebo patients without bimagrumab treatment during the 6 month follow-up as they will be treated with standard of care. Moreover, bimagrumab is unlikely to benefit significantly and in a timely manner when the treatment is initiated more than 24 weeks after surgery, when most of the spontaneous recovery has already occurred (Magaziner et al 1990; Vochteloo et al 2011).

3.5 Purpose and timing of interim analyses/design adaptations

The primary analysis will be performed when all patients have completed their Treatment epoch (Week 24, EoT visit) via an interim database lock (soft database lock), while an updated analysis will be conducted when all patients have completed their End of Study (Week 48). No interim analysis will be performed prior to the primary analysis at the Week 24 EoT visit.

3.6 Risks and benefits

Risks

The safety data from the completed Phase I and II studies do not highlight any specific safety risk or concern or any particular pattern of major adverse event clustering. From the standpoint of the overall risk-benefit assessment, the current study design and its trial-related risks (e.g., infusion, blood draws, exposure to radiation during imaging) with bimagrumab are justified.

As of 1st September 2017 approximately 1341 adults have been enrolled in clinical trials with bimagrumab of which approximately 900 have received the antibody as study medication. Cumulatively, a total of 556 adults have participated or are participating in the Phase I program, with approximately 361 subjects having received bimagrumab. Seven-hundred eighty-five patients participated or are actively participating in the Phase II/III program. Dose

[redacted]

levels have ranged from 0.01 mg/kg to 30 mg/kg as i.v. infusions and 2 mg/kg s.c. injections, with the majority receiving repeat doses of 10 mg/kg (equivalent to 700 mg) and 30 mg/kg i.v. bimagrumab. The current **safety profile** suggests that bimagrumab is well-tolerated with adverse events limited to minor, transient clinical symptoms. Transient cases of episodic, spontaneous muscle contractions, acne and diarrhea of mostly mild intensity have been observed in study participants with symptoms occurring more frequently in those participants receiving the highest doses of drug (30 mg/kg).

Preliminary data from the first studies in healthy volunteers and older patients indicate observations of diffuse acne on the face and less frequently on the back and chest in some adults receiving a single dose of 30 mg/kg. Treatment has been successful with good skin hygiene using a 4-10% benzoyl peroxide wash and over the counter topical treatments. On occasion, a prescription, topical or oral antibiotic (i.e., minocycline 100 mg bid), was used. The mechanistic link between bimagrumab and acne remains poorly understood. There were no relevant changes in total testosterone or testosterone-estrogen ratio to bimagrumab treatment that otherwise could have explained the skin findings (CBYM338X2108).

In approximately 20 - 48% of normal healthy volunteers and patients with sporadic inclusion body myositis (sIBM) treated with a single 30 mg/kg i.v. dose of bimagrumab, involuntary muscle contractions, referred to as ‘muscle twitching’ were reported. The reported muscle twitches were mild in intensity, transient, of short duration, self-limiting and did not require medical treatment. While twitching could theoretically be more pronounced in aging and atrophying muscle, this has not been observed in sIBM patients up to 78 years old. The biological explanation of twitching is being pursued by the bimagrumab Project Team using both internal and external resources.

In the recently completed CBYM338B2203 study on patients with sIBM, diarrhea was usually an early event, a single episode, and mild in severity. Mechanism of this is yet to be understood in full detail, yet rapid increases in activin might be a potential driver as this ligand in animal studies has been implicated in irritable bowel disease (Hübner et al 1997). There were three cases of diarrhea in the 10 mg/kg dose group, which were reported as serious adverse events, but responded well to treatment.

Cardiac effects

Preclinical studies in rats demonstrated a marked cardiac hypertrophy deemed compensatory to the substantial increase in skeletal muscle mass. Although inconsistently seen in monkey studies, the observed increase in ventricular muscle mass without any effect on left ventricular chamber size and, importantly, on global left ventricular systolic function in female monkeys is also supportive of a compensatory effect rather than a direct effect of bimagrumab.

In clinical studies to date, including the CBYM338B2203 study that exposed sIBM patients for 12-26 months, echocardiography has shown no evidence of significant change in posterior wall thickness, interventricular septum thickness, left ventricular and systolic or diastolic diameter, left ventricular mass, left ventricular mass index, end diastolic volume, end systolic volume and left ventricular ejection fraction when compared with placebo.

The echocardiography findings have recently been confirmed by a dedicated cardiac safety study (CBYM338X2109) that investigated the effects of 6 doses of 10 mg/kg bimagrumab in 68 elderly subjects (65-90 years old). Magnetic resonance imaging (CMR), revealed no

[redacted]

decrease in left ventricular ejection fraction, no increase in left ventricular mass index and no changes in regional myocardial thickness. Unlike the preclinical rat studies revealing up to 30% increase in body weight, these human subjects had relatively small increases in lean body mass (~6%), which does not seem to drive compensatory changes on the myocardium.

Thus based on an analysis of data from the entire bimagrumab clinical program, intensive cardiac monitoring by echocardiography has been judged as no longer required and therefore removed from this protocol. The omission of echocardiography and monitoring of potential effects on the myocardium (hypertrophy or decreased ejection fraction) has been approved by the independent DMC as well as the internal Novartis Medical Safety Monitoring Board.

In addition, standard and Holter ECG in the aforementioned study indicated no difference in the incidence of cardiac arrhythmias or changes in QTcF or heart rate. Moreover, there was no alteration of blood pressure, hematologic parameters or cardiac injury biomarkers either. In light of these recent findings and in agreement with both the Novartis Safety Monitoring Board and the external DMC, the QTcF-related exclusion criterion has been updated raising the QTcF threshold of exclusion to 500 msec for both genders. In addition, it also allows enrollment of patients, who have artificially prolonged QTcF due to widening of the QRS complex (presence of right or left bundle branch block or a ventricular pacemaker).

In this study, patients will continue have regular vital signs measurements, and multiple ECGs to monitor cardiovascular condition.

Reproductive hormone effects

Animal toxicity studies at weekly doses of 1, 10 and 100 mg/kg of bimagrumab in the 4- and 13-week studies resulted in reversible changes in the uterus, vagina and ovaries of the rat and to a much lesser extent to the ovaries of the cynomolgus monkey at the highest doses.

Recently, a dedicated hormone profiling study (CBYM338X2108) examined the effect of two doses of 10 mg/kg bimagrumab on hormone levels in older men and women. Results showed no increase in circulating testosterone levels and no effect on the pituitary-gonadal or pituitary-adrenal axes in either gender. The only finding was a significant decrease in FSH levels in post-menopausal women, which is consistent with the physiology of activin and the ActRII receptors in the pituitary. No statistically or clinically significant effects on FSH were seen in men. This expected effect on FSH reversed upon drug discontinuation by the end of the study. No biologic implications of these changes in FSH in elderly postmenopausal women have been described to date. Semen analysis data from the multiple dose study (CBYM338X2102) suggest that three doses of 10 mg/kg have no effect on fertility in males. Overall conclusions of the CBYM338X2108 study are corroborated by laboratory findings from prior studies as well as by the recently completed larger CBYM338B2203 study including 251 sIBM patients.

Overall the risk of changes in reproductive organs in this study is minimal due to the age range of study participants.

Body weight

Increase in lean body mass and decrease in body fat mass were observed in the first-in-human study. During 6 months treatment of healthy elderly subjects with 10 mg/kg bimagrumab (CBYM338X2109 study), the relative loss of fat mass exceeded the increases of lean body

[redacted]

mass thereby causing a net body weight decrease of ~1.5 kg. With longer term exposure, such as in the CBYM338B2203 study body weight tended to decrease further due to continuing decrease in body fat mass (average decrease at W52 was ~3.5 kg).

Body weight will be assessed regularly during the study and patients showing at least 5% decrease in body weight will be referred to consultation with a nutritionist or other health care professional for assessment of malnutrition and consideration of taking adequate measures, if needed

Lipase and amylase elevations

Observations of dose-dependent, transient, sub-clinical elevations of lipase and/or amylase have been identified in several studies in the bimagrumab clinical program. The biological explanation for this temporal rise in pancreatic enzymes seen in some individuals is not yet fully understood and the causality with bimagrumab treatment has not yet been established.

As of 1 Sep 2017, there have been two confirmed cases of acute pancreatitis among the 642 study participants from completed studies and an estimated 250 participants in ongoing (blinded) studies administered bimagrumab. There is no association of the temporary elevations in lipase and/or amylase with an increased risk for pancreatitis.

In order to fully evaluate these new safety findings, additional safety monitoring measurements are added. Safety monitoring guidance for patients who experience elevated lipase and/or amylase during the study is provided in Section 7.4.

Trial related risks

Infusion related reactions can occur with monoclonal antibodies. Hypersensitivity reactions can manifest as fever, chills, urticaria, dyspnea, headaches, myalgia and/or hypotension. A serious infusion reaction that results in anaphylaxis is a rare event in monoclonal antibody therapy. If a severe hypersensitivity reaction occurs, administration of bimagrumab must be discontinued and appropriate therapy initiated.

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 volume taken.

Radiation Exposure

This clinical study involves exposure to radiation from X-ray and DXA total body and contralateral (unaffected) hip scans. X-ray assessments at baseline and 6 months are part of standard medical care after hip fracture surgery. However, exposure at 9 and 12 months is usually not medically necessary. DXA radiation exposure is not necessary for medical care and it is intended for research purposes only. The total amount of radiation exposure per patient from X-ray and DXA scans will be about 3.65 mSv (365 mrem).

For effective radiation doses between 3 mSv (300 mrem) and 50 mSv (5000 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired (Stabin 2013).

The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and guidance for the investigators provided in the Investigator's Brochure. An adjudication committee will review cardiovascular events to confirm that these events have been evaluated appropriately and diagnosed correctly, while a Data Monitoring Committee (DMC) will monitor safety data from the study and the entire bimagrumab program for potential safety concerns.

As for any other investigational drug, there are unknown risks to bimagrumab, which may be serious and unforeseen.

Benefits

The benefits of bimagrumab treatment in the hip fracture population are still not known. However, it is expected that as seen in healthy volunteers and patients with sIBM, the hip fracture patients will have an increase in muscle mass that may translate to better recovery of lower extremity function and faster return to mobility. Over the course of the study, the number of falls might be reduced, which in turn reduces the risk of traumatic injuries and fractures, including secondary hip fractures.

4 Population

The study population will consist of male and female patients ≥ 60 years old, at time of randomization, who underwent surgical treatment for a low-energy fracture of the proximal femur. The study aims to screen approximately 400 patients. With an estimated screen failure rate of about 40%, approximately 245 patients, with successful surgery after hip fracture, will be randomized in more than 60 centers worldwide. Approximately 200 patients are expected to complete the 24-week treatment epoch and approximately 120 patients the full 48 -week study period.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed;
2. Males and post-menopausal females ≥ 60 years (as defined in Section 6.5.9);
3. Patient must have had surgical fixation or arthroplasty for a fracture of the proximal femur (AO Classification 31 A-C (AO Foundation 2013)) as confirmed by radiography;

[redacted]

4. Patient must be mentally competent, to have scored at least ≥ 21 on the Folstein Mini Mental State Examination (MMSE);
5. Patient must be able to complete a 4 m gait speed test
6. Patients must weigh at least 35 kg and must have a body mass index (BMI) within the range of 15– 35 kg/m^2 at screening;
7. Patient must have complete surgical wound healing.

4.2 Exclusion criteria

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

Central laboratory tests needed for eligibility assessment, i.e. GFR, AST, ALT, bilirubin, platelet count, hemoglobin, or ECG interpretations which fall outside of the **protocol-specified range** at screening can be repeated at an unscheduled visit during the screening epoch to confirm patient eligibility prior to randomization.

1. History of any other lower limb fracture in the past 6 months or any other major surgery to the lower limb in the past 3 months prior to randomization that caused a persisting functional sequelae, which directly impacts gait speed and/or gait quality and is unlikely to recover during the study period ;
2. Isolated high-energy sub-trochanteric fracture (AO Classification 32 A-C, (AO Foundation 2013));
3. Major mobility limitation (i.e. not able to walk 100 meters without stopping or getting help; unilateral help being fine) in the past 3 months prior to the hip fracture due to severe dyspnea, presence of permanent or progressive neurologic deficit (muscle weakness, spasticity, rigor or balance impairment), disabling joint or muscle pain in the hip or knee, intermittent claudication or major visual impairment.
4. Active gastrointestinal diseases/conditions known to cause malabsorption or increased enteric loss of protein, such as inflammatory bowel disease (unless complete remission), celiac disease (unless gluten-free diet), short bowel syndrome, pancreatic insufficiency (unless under good control by medication/enzyme supplements);
5. Severe renal insufficiency defined by either requiring dialysis or having an estimated glomerular filtration rate (GFR) < 30 mL/min using the modification of diet in renal disease (MDRD) equation which can be found in the *Study Manual*;
6. Uncontrolled hypothyroidism requiring a change in the dose of hormone replacement therapy in the last 6 weeks prior to randomization; uncontrolled hyperthyroidism;
7. Underlying muscle diseases, including history of or currently active form of inflammatory myopathies (e.g., dermatomyositis, polymyositis, etc) or muscular dystrophies;

Cardiovascular conditions

8. Hypertension uncontrolled with medication (i.e. systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mmHg
9. Known heart failure classified as New York Heart Association Class III and IV;

[redacted]

10. Ongoing unstable angina or history of myocardial infarction in the last 3 months prior to randomization;
11. Current presence of severe aortic or mitral stenosis, or septal defects;
12. Severe pulmonary hypertension uncontrolled with medication;
13. Confirmed diagnosis of restrictive or hypertrophic (obstruction) cardiomyopathy. Patients with dilative cardiomyopathy are allowed to enter the trial unless the diagnosis is associated with any of the conditions/events outlined in the list of exclusion criteria;
14. History of familial long QT syndrome or known family history of Torsades de Pointes
15. Prolonged QT syndrome or QTcF ≥ 500 msec (Fridericia Correction) (central reading); patients with QTcF ≥ 500 msec in the presence of right or left bundle branch block or ventricular pacemaker are permitted, if endorsed by the patient's treating physician.
16. Any current supra-ventricular arrhythmia with an uncontrolled ventricular response (mean heart rate >100 beats per minute [bpm]) as per ECG at rest despite medical or device therapy or
    - any history of spontaneous or induced sustained ventricular tachycardia (heart rate >100 bpm for 30 seconds) despite medical or device therapy or
    - any history of resuscitated cardiac arrest or
    - the presence of an automatic internal cardioverter-defibrillator;

Liver related conditions

17. Abnormal liver function tests such as SGOT (AST), SGPT (ALT), or serum bilirubin (except if accompanying Gilbert's Disease) as defined by;
    - Any single transaminase > 3 x the upper limit of normal (ULN). A single parameter elevated up to and including 3 x ULN should be re-checked as soon as possible, and in all cases, prior to randomization, to rule out any lab error.
    - Serum bilirubin > 1.6 mg/dL (27 μmol/L).
18. Presence of severe acute or chronic liver disease (e.g., cirrhosis) or conditions with hepatotoxic potential (e.g. known gallbladder or bile duct disease, acute or chronic pancreatitis);

Other medical conditions

19. History of hypersensitivity to therapeutically administered antibodies;
20. Lack of peripheral venous access;
21. Any type of active cancer (i.e. under current treatment) or cancer that required treatment in the last 5 years, except for secondary preventive measures (e.g. tamoxifen for breast cancer). -. Non-melanoma skin cancers or in situ cancers with excellent prognosis (e.g. carcinoma in situ of the uterine cervix) are permitted, if were excised or fully resolved by other means;
22. Type I diabetes mellitus or uncontrolled type II diabetes mellitus (e.g. pre-surgical levels as per patient file indicating HgbA1c ≥ 8.5% or if fasting blood glucose ≥ 9.0 mmol/l at more than one measures);
23. Significant coagulopathy, platelet count less than 75,000/mm^3, or anemia (hemoglobin less than 8.0 g/dL);

[redacted]

24. Active systemic infection requiring treatment with IV anti-infectives within 4 weeks of randomization;
25. Chronic active infection (e.g., HIV, hepatitis B or C, tuberculosis, etc). Patients with already diagnosed latent tuberculosis, who are receiving chemoprophylaxis, are eligible for the study.
26. Patient has any other condition (e.g. alcohol abuse), laboratory finding, or any post-operative condition or complication, which, in the investigator's opinion may affect the course or magnitude of recovery from surgery, interfere with participation in the study (poor compliance), may confound the results of the study, or pose additional risk in administering bimagrumab;

Prohibited medications:

27. Systemic use of vascular endothelial growth factor (VEGF) inhibitors within **6 months** prior to randomization; intravitreal administration is allowed
28. Use of immunosuppressive therapy within **3 months** of randomization;
29. Use of any therapies known to affect muscle mass via modulation of androgen or growth-hormone receptors or the synthesis of these hormones within **3 months** prior to randomization (or current use of high-dose selective beta2-adrenergic drug therapy;
30. Ongoing systemic corticosteroid use or history of systemic corticosteroid use for at least 3 months (in the last year) prior to randomization at a daily dose greater than or equal to 10 milligram (mg) prednisone equivalent;
31. Currently enrolled in, or discontinued within the last 30 days (or 5 half-lives, [redacted] whichever is longer or longer if required by local regulations) from a clinical trial involving an investigational drug or off-label use of a drug, or are concurrently enrolled in any other type of medical research judged to be scientifically or medically incompatible with this study.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply the following investigational drugs:

- **Bimagrumab:** BYM338 150 mg/1 ml liquid in vial--colorless glass vials with rubber stopper and aluminum flip-off caps.
- **Placebo:** BYM338 placebo/1 ml liquid in vial--colorless glass vials with rubber stopper and aluminum flip-off caps.

Note: To maintain the blind, the investigational treatments will be prepared by an unblinded pharmacist/designee and ***administered only by blinded study personnel****.*

[redacted]

5.1.2 Additional study treatment

5.1.2.1 Local standard of care therapy after hip fracture

Local standard of care therapy to manage patients peri/post operatively (such as for thrombosis prophylaxis, pain management, calcium supplementation, secondary osteoporosis prevention) is acceptable unless listed in Section 5.5.8 and may be used according to the national or local guidelines.

[redacted]

[redacted]

5.2 Treatment arms

Under the original protocol, patients were assigned in a 1:1:1 manner to one of the 3 treatment arms (placebo, bimagrumab 3mg/kg and bimagrumab 10mg/kg). After approval of Protocol Amendment 2, patients were assigned to one of the following 4 treatment arms in a ratio of 2:1:2:2

- Arm 1: Placebo i.v. every 4 weeks
- Arm 2:Bimagrumab 70 mg i.v. every 4 weeks
- Arm 3: Bimagrumab 210 mg i.v. every 4 weeks
- Arm 4: Bimagrumab 700 mg i.v. every 4 weeks

Patients will receive a total of 6 doses of bimagrumab or placebo. The first dose will be given on Day 1 and the last dose at week 20 visit. End of treatment assessments will be performed at week 24.

Patients randomized before the Protocol Amendment 2 were switched in a blinded manner via the IRT system to the corresponding fixed dose i.v. regimen at the next scheduled visit following amendment approval by their respective health authorities and ECs/IRBs:

- patients originally randomized to 10 mg/kg i.v. switched to 700 mg i.v.,
- patients originally randomized to 3 mg/kg i.v. switched to 210 mg i.v.,
- patients originally randomized to placebo remained on placebo.

Patients who are already beyond week 20 at the time of the protocol amendment #2 implementation performed their EoT assessment visit at their next scheduled visit and continued in the study as per protocol amendment #2.

[redacted]

5.3 Treatment assignment, randomization

At the randomization visit, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the four treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drugs.

Randomization will be stratified using the following three strata: 1) Japanese sites, 2) Non-Japanese sites for patients randomized 21 days or less from their hip fracture surgery date, and 3) Non-Japanese sites for patients randomized greater than 21 days from their hip fracture surgery date. This measure will balance the distribution of Japanese patients among bimagrumab treatment groups and the placebo group. Therefore it will support the analysis of comparison of key efficacy and safety endpoints for Japanese sub-population.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group. A separate randomization list was already created at the time of amendment 2.

5.4 Treatment blinding

Patients, investigators and their site personnel (with exception of the unblinded pharmacist), as well as Novartis agents in the countries as well as the global study team involved in the routine conduct of the trial will remain blinded to the identity of the individual patient treatment from the time of randomization until the final database lock (when all patients will have completed both the Treatment epoch and the Post Treatment Follow-Up epoch)..

For the study duration, the following method will be used to maintain the blind:

1. Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible to anyone else involved in the study with the following exceptions:
    - specific vendors whose role in trial conduct requires their unblinding [e.g., Interactive Response Technology (IRT)]
    - DSM (drug supply management)
    - members of the DMC
    - study bioanalyst [redacted]
    - an independent, unblinded pharmacist/designee at the investigator's site who will prepare investigational treatment infusion

[redacted]

- unblinded monitor who will perform investigational treatment accountability at the site
- An independent global clinical person will have access to individual randomization codes at the interim database lock for the primary analysis

2. The identity of the treatments will be concealed by the use of investigational treatments in forms of infusion bags filled with bimagrumab or placebo and covered with a sleeve that are identical in appearance, labeling and schedule of administration. However, the bimagrumab and placebo vials will be supplied "open-label" to the unblinded pharmacist.
3. Results of DXA scans and a mechanism of action related biomarker (activin A) as well as FSH that may reveal [redacted] effects of the study drug will not be shared by the central reader/laboratory to investigators, site staff or global study team but will be stored in a blinded part of the study data base.

Due to the difference in supply and preparation methods of the active drug and placebo, an independent, unblinded pharmacist or designee who is independent of the study team will be required to maintain the blind. The unblinded pharmacist will receive the medication numbers, prepare infusions with either investigational drug or placebo, without disclosing the identity to any other site personnel. Appropriate measures must be taken by the unblinded pharmacist to ensure that the study team remains blinded throughout the course of dose administration and the remainder of the study. No other person will have access to the medication and drug administration documentation, except the unblinded monitor.

The unblinded pharmacist is NOT allowed to administer the drug to the patient.

Unblinded monitors will be required to perform proper oversight for drug accountability. The unblinded field monitor will be responsible exclusively for drug accountability and must take appropriate measures to ensure the blind is preserved for the duration of the study.

Full unblinding (treatment and dose) will only occur in the case of patient emergencies and at the conclusion of the study.

In the case of unblinding, the patient will be discontinued from investigational treatment and enter the Post-treatment follow-up epoch. Discontinuation of investigational treatment and premature patient discontinuation are discussed in detail in Section 5.5.9.

Following the interim database lock, to perform the primary analysis, partial unblinding will occur as follows:

- An independent global clinical person will have access to individual randomization codes after the primary analysis.
- The Novartis global study team will be unblinded to the group level results only
- The study subjects and the site personnel will remain blinded until the final database lock

The study bioanalyst will have access to the randomization list to facilitate analysis of samples (i.e. to avoid the unnecessary analysis of placebo samples). [redacted] The bioanalyst will provide sample data to the team under blinded conditions [redacted]

[redacted]

[redacted] The unblinded bioanalyst [redacted] will keep treatment allocation information confidential until clinical database lock.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed of the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing of the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site should select the CRF book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient is a screen failure. The reason for not being randomized will be entered on the Screening Epoch Study Disposition CRF.

5.5.2 Dispensing the investigational treatment

The packaging of the investigational treatment will be open-label and not identical in appearance.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the investigational drugs. The unblinded pharmacist or designee will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before preparation of investigational treatment infusion, the unblinded pharmacist/designee will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

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

5.5.3 Handling of investigational treatment

Investigational treatment must be received by the unblinded pharmacist/designee at the study site, handled and stored safely and properly, and kept in a secured location to which only the unblinded pharmacist/designee has access. Upon receipt, all investigational treatment 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 Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The unblinded pharmacist/designee must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the unblinded field monitor during site visits and at the completion of the trial.

[redacted]

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

At the conclusion of the study, and as appropriate during the course of the study, the unblinded pharmacist/designee will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the unblinded Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.4 Instructions for prescribing and taking investigational treatment

Detailed instructions on the preparation and administration of the investigational treatment will be described in the *Pharmacist Manual* and provided to each site.

The unblinded pharmacist/designee will prepare the infusion according to treatment assignment (bimagrumab 700mg, 210mg, 70mg or placebo) based on the information provided by the IRT system (medication number and volume to be dispensed). The unblinded pharmacist/designee will withdraw the appropriate amount of investigational treatment from one or more vials and the drug product will be diluted with a dextrose solution to approximately 100 ml intravenous infusion solution. The infusion bag with the prepared investigational treatment solution will be covered with a sleeve and provided by the unblinded pharmacist/designee to the blinded investigator or assigned site staff.

The unblinded pharmacist/designee must not have any contact with the subject and must not be involved in any of the study assessments.

Study medication will be administered by blinded study center personnel.

The 100 ml of bimagrumab or placebo solution for i.v. administration will be administered as a slow infusion over approximately 30 minutes, followed by a flush with 50 ml.

Only the materials (infusion bag, administration set and filter) specified in writing by the sponsor should be used for administration of the study medication. All medication administered to the patient (in ml of infusion without the flush), the duration of the total infusion (including the flush), and all dose changes during the study must be recorded on the Dose Administration Record eCRF page. In case of an unintentional study treatment error, no AE needs to be reported unless symptoms, warranting AE reporting, are associated with it.

All kits of investigational treatment assigned by the IRT will be recorded in the IRT.

The investigator should promote compliance by instructing the patient to return to the site for investigational treatment administration as outlined in Table 6-1 and by stating that compliance is necessary for patient's safety and the validity of the study.

5.5.5 Permitted dose adjustments and interruptions of investigational treatment

Investigational treatment dose adjustments are not permitted.

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

[redacted]

If a patient misses two doses, the subject must be discontinued from the investigational treatment (refer to Section 5.5.9).

5.5.6 Rescue medication

Use of rescue medication is not applicable to this study.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy, dietary modification, protein supplements and blood transfusions) administered after the patient was enrolled into the study must be recorded on the Concomitant medications eCRF or Surgical and Medical procedures eCRF.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed from the start of Screening epoch until End of study visit at Week 48.

The following treatments are not allowed because of their biological effect on muscle anabolism or catabolism, or muscle strength, which would confound the assessment of efficacy.

Table 5-1 Prohibited treatment

Medication*	Action to be taken
Androgen modulators (e.g., testosterone, danazol, fluoxymesterone, methyltestosterone)	Discontinue investigational treatment
Anabolic steroids (e.g., Oxandrolone, stanozolol, DHEA, testosterone)	Discontinue investigational treatment
Anti-androgens (e.g. flutamide, nilutamide, cyproterone acetate, spironolactone)	Discontinue investigational treatment
Progestins with known androgenic component (e.g. norethindrone acetate, megestrol acetate, tibolone)	Discontinue investigational treatment *Note:* • *Norethindrone acetate use for 5-10 days to stop abnormal uterine bleeding due to hormonal imbalance is permitted.* • *Low-dose (1.25 mg or lower) tibolone treatment is permitted.*
Systemic glucocorticoids (e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone)	Discontinue investigational treatment *Note: Short term (defined as 20 mg/day prednisone equivalent for less than 14 days) or irregular use if medically indicated (e.g. Asthma, allergic reactions) is permitted.*
Oral selective beta2-adrenergic agonists (e.g. Albuterol)	Discontinue investigational treatment *Note: Intermittent use if medically justifiable and doses up to 16 mg/day*

[redacted]

Medication*	Action to be taken
	albuterol equivalent are permitted.
Gonadotropin-releasing hormone (GnRH) agonists or antagonists (e.g. leuprolide, nafarelin, ganirelix, degarelix)	Discontinue investigational treatment
Recombinant Human Growth hormone and/or mimetics (e.g. somatrem, somatropin) and Ghrelin	Discontinue investigational treatment
Immunosuppressive therapy	
Systemic use of vascular endothelial growth factor (VEGF) inhibitors	Discontinue investigational treatment *Note: Intravitreal administration is allowed*
Any investigational treatment or participation in any interventional trial	Discontinue investigational treatment
*In case of undue safety risk for the patient, the patient should discontinue investigational treatment at the discretion of the investigator.	

5.5.9 Discontinuation of investigational treatment or premature study discontinuation

Patients may voluntarily discontinue the investigational treatment for any reason at any time.

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

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

- Use of prohibited treatment as per Table 5-1.
- Any other protocol deviation that results in a significant risk to the patient's safety
- Breaking of the blind (inadvertently or for emergency reasons)
- Severe hypersensitivity reaction occurs
- Liver event definition met as per Appendix 2
- Deviations from the prescribed dose regimen for investigational treatment with 2 doses missed at any time
- Death
- Withdrawal of consent
- Sponsor decision to terminate (part of) the study

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

- Emergence of the adverse events that in the judgment of the investigator, taking into account the patient's overall status, prevent the patient from continuing participation 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 continuing participation in the study

At the time of protocol amendment #2 implementation, patients who have already received their Week 20 infusion of investigational treatment returned to the site at their next scheduled

[redacted]

visit and performed their End of Treatment visit. They continued as per the study visit schedule Table 6.1.

Patients who discontinue investigational treatment are NOT considered immediately withdrawn from the STUDY or to have withdrawn informed consent to participation (described in section 5.5.10). The patient must return approximately 28 days following the patient's last investigational treatment administration to complete the End of Treatment visit assessments (Table 6-1). If the patient was already off-treatment for a longer period, then the End of Treatment visit can be performed without delay. After completing the End of Treatment assessments, patients will enter a 4-week follow up and return for the End of Study visit. If the patient fails to return for these assessments for unknown reasons, every effort should be made to contact him/her as specified in Section 5.5.11.

Investigators or site personnel must contact the IRT to register the patient's discontinuation from treatment. In addition, the investigator will report the primary reason for treatment discontinuation on the End of Treatment Epoch eCRF.

5.5.10 Withdrawal of consent

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

Withdrawal of consent occurs when a patient does not want to participate in the study any more, does not want any further visits or assessments, does not want any further study related contacts, and 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 Withdrawal of Consent eCRF. Investigational treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.11 Loss to follow up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, 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.

Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignment are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using

[redacted]

the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational 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 (GTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable, redundant procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide protocol number, investigational treatment name if available, patient number as well as oral and written information to the subject on how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time in the case of emergency.

Investigational treatment must be discontinued after emergency unblinding (Section 5.5.9).

5.5.13 Study completion and post-study treatment

A patient will be considered to have completed the study when he/she has completed 48 weeks of the study including the End of Study Visit.

The study will be considered to be complete when the last patient completes 48 weeks of the study including the End of Study Visit.

Patients who are still in the screening process once planned enrollment is met will be allowed to complete screening and will be randomized into the study if eligible.

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

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a patient prematurely withdrawn from the study. 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 patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when they are to be performed. Patients should be seen for all visits on the designated day within the recommended "visit window" specified below, or as close to it as possible. The site should make every effort to help bring the patients to the clinic visits, including providing transportation if necessary. If any visits are delayed or missed, the site personnel should ensure alignment of future patient visits according to the originally planned visit schedule (i.e. rescheduled visit window needs to be calculated with reference to first dose received; day of randomization and first dose received may differ occasionally), and should ensure that 2 consecutive infusions are done at least 14 days apart.

[redacted]

Recommended visit windows:

Randomization/Day 1: + 2 days

Weeks 4-12: +/- 4 days

Weeks 16-24: +/- 7 days

Weeks 36-48: +/- 14 days

Some of the following principles should be taken into consideration when scheduling a visit:

- Assessments for a particular visit - including the randomization visit - may be split over several days.
- [redacted] physical performance tests should be considered early in the visit to avoid physical or mental exhaustion of the patient.
- Laboratory work in particular those requiring 8 hours fasting should be done early in order to allow the patients to eat and drink
- Patient dosing should be the last procedure to be performed

During the treatment epoch, patients may be seen at unscheduled visits for instance for AEs that in the opinion of the investigator need intervention or repeated laboratory testing. All relevant safety assessments may be performed as deemed necessary by the investigator. During these unscheduled visits, investigational treatment must **NOT** be administered.

During the post-treatment follow up epoch, safety and efficacy assessments will continue until the EoS visit at week 48. .

[redacted]

Table 6-1 Assessment schedule

Study Epoch	Screening	Treatment							Post-treatment follow up		Notes
Visit name/study week	Screening / Day -39 to -1	BL/ Rand Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	End of treatment / Week 24 *	Week 36	End of study / Week 48	
Days post-op or post 1st dose	D3 to 42 post- op	1	28	56	84	112	140	168	252	336	
Informed Consent	X										
Verify Inclusion/ Exclusion	X										
Randomization		X									
Demographics	X										
MMSE	S										Source documents only.
Hip fracture history	X										
Medical history	X										
Physical Examination	S				S			S		S	Source documents only.
Blood sample for serology	X										
Blood sample for hematology and chemistry	X		X	X	X			X		X	
Blood sample for hormones	X				X			X		X	
Urine sample	X		X	X	X			X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (triplicate)	X	X			X			X			
Echocardiography								(X)		(X)	Only for patients enrolled

[redacted]

Study Epoch	Screening	Treatment							Post-treatment follow up		Notes
Visit name/study week	Screening / Day -39 to -1	BL/ Rand Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	End of treatment / Week 24 *	Week 36	End of study / Week 48	
Days post-op or post 1st dose	D3 to 42 post- op	1	28	56	84	112	140	168	252	336	
											before Amendment #3. W48 is to be performed only if W24 reading indicates clinically meaningful abnormality as per central reader's assessment.
Gait Speed	S										Source document only.
SPPB (incl. gait speed)		X	X	X	X	X	X	X	X	X	
DXA		X			X			X			All centrally read.
X-ray	X							X	(X)	(X)	At screening local X-ray taken during or after surgery is to be used. If bone union is incomplete at W24 per central reading, X-rays need to be performed until this is achieved at W36 and potentially W48 as well.
Drug administration		X	X	X	X	X	X				
[redacted]											

[redacted]

Study Epoch	Screening	Treatment							Post-treatment follow up		Notes
Visit name/study week	Screening / Day -39 to -1	BL/ Rand Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	End of treatment / Week 24 *	Week 36	End of study / Week 48	
Days post-op or post 1st dose	D3 to 42 post- op	1	28	56	84	112	140	168	252	336	
[redacted]											
AE/SAE reporting	To be recorded as needed										
Medications and medical procedures	To be recorded as needed										

* In case of investigational treatment discontinuation during the Treatment Epoch, the patient should complete the EoT Visit 4 weeks after the last investigational treatment administration. After the EoT visit is completed, the patient should return after an additional 4 weeks for an EoS visit. In case of premature study discontinuation after the Treatment Epoch, the patient should return to an EoS visit (not earlier than 4 weeks after the EoT visit)

Rand = randomization; BL = baseline; Folstein Mini Mental State Examination =MMSE

[redacted]

6.1 Information to be collected on screening failures

Patients who sign the informed consent form for the study but fail to be randomized to treatment will be considered a screening failure. IRT must be notified within 3 days and the following eCRFs pages must be completed:

- Screening Phase Disposition eCRF,
- Informed Consent eCRF,
- Demography eCRF,
- Inclusion/Exclusion eCRF,
- Adverse Events eCRF should be completed for any serious adverse events that occurred after signing the informed consent. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data,
- Re-screening page (if applicable),
- Withdrawal of informed consent eCRF (if applicable),
- Death eCRF (if applicable)

Patients who were declared as screen failures that may improve with time after surgery (e.g. mobility or cognitive function) or may change at re-assessment (e.g. marginal deviation in laboratory or ECG findings), can be re-screened once, unless they are outside of the 3-42 days post-surgery window. These patients must be re-consented, and they receive a new patient number, after which all screening assessments done previously must be repeated. Therefore, given the additional burden of a re-screening, it is recommended to avoid screen failing a patient too rapidly, if the reason for screen failure is transient in nature and has a chance to improve within a short period of time.

6.2 Patient demographics/other baseline characteristics

6.2.1 Demographic information

Patient demographic data to be collected for all patients include: date of birth if permitted as per local regulations, sex, race, and ethnicity.

6.2.2 Medical history

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

The aim is to capture the diagnoses rather than symptoms.

In addition several specific eCRF pages will capture more details on a number of conditions such as:

- Fall history, which takes into account the last 12 months prior to the fall that led to the current fracture

[redacted]

- Cardiovascular and metabolic disease history including conditions such as cardiomyopathy, diabetes, hypertension, etc.
- All relevant orthopedic conditions and/or earlier surgical interventions that may affect lower limb function (e.g. prior factures, arthroplasty, arthrodesis)
- Perioperative information on the hip fracture surgery including the surgical method used

6.2.3 Eligibility assessments

In addition to the review of the patient's medical history and type of hip fracture, eligibility assessments must be performed and results reviewed by the investigator before a patient can be enrolled in the trial:

- 12-lead electrocardiogram (ECG) using the central reading
- Confirmed ability to complete a 4-meter gait speed test
- Central laboratory screening tests: GFR, AST, ALT, bilirubin, platelet count, and hemoglobin)
- Vital signs, including height and weight, BMI
- MMSE
- Confirm successful surgical intervention for fracture repair AND completed surgical wound healing
- Historical intra- or post-operative X-ray of the operated hip.

6.2.4 Other pre-treatment characteristics

- Physical exam (recorded as source data)

[redacted]

- Total/appendicular LBM via DXA [redacted]
- Serology (HIV Ab, HCV Ab, HbsAg)
- 25-OH vitamin D
- [redacted]
- Dietary assessment/[redacted] as per pre-albumin and albumin levels.

[redacted]

6.3 Treatment exposure and compliance

All dates and times of investigational treatment administration will be recorded on the Dosage Administration Record eCRF.

[redacted]

Drugs administered prior to start of treatment and continuing or started during the investigational treatment period will be entered in the Concomitant Medications eCRF page.

[redacted]

Compliance is expected to be 100% since investigational treatment will be administered by the investigator or study personnel, unless the patient misses clinic visits. Compliance will also be assessed by an unblinded monitor using vial counts and information provided by the unblinded pharmacist/designee.

6.4 Efficacy

Efficacy measurements in the study will include:

- Total LBM assessed by DXA to measure lean body mass
- SPPB to assess functional improvement
- Gait Speed (as a component of SPPB) to assess functional improvement
- Falls

6.4.1 Total Lean Body Mass (LBM) by DXA

DXA will be used to measure lean soft tissue, which is fat-free and bone mineral free component that includes muscle and other soft tissue like skin tendons and connective tissues.

The exam is quick (10-15 min, including preparations), precise (0.5-1%) and non-invasive. DXA scanners have the precision required to detect changes in muscle mass as small as 5%. These examinations will be performed as outlined in Table 6-1.

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 the same 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.

DXA Data Collection and processing

DXA and reading will be performed according to the procedures described in the *Imaging Manual*. Prior to the examination, the patient will be checked for absence of removable metal objects on his/her body, such as snaps, belts, underwire bras, jewelry, and so on. The patient will then be positioned so that his/her body is straight on the mat and the site personnel must ensure that the positioning is consistent from scan to scan. A whole body array scan will then be initiated on the patient.

Total LBM can be predicted from whole body DXA scan and it is comprised of the protein and water mass that make up skin, connective tissue and muscle from the appendicular, head and trunk regions of interest (ROIs).

[redacted]

6.4.2 Short Physical Performance Battery

The short physical performance battery evaluates lower extremity function by measuring the time to rise from a chair five times, ability to maintain standing balance, and the 4-meter gait speed which can provide useful qualitative information on the nature of mobility limitation.

A five-level categorical score can be created for each test, with 0 representing inability to complete the test and 4 representing the highest level of performance. A summary performance score is created by adding the individual scores, which yields a maximum of 12, where 10-12 denotes normal, 7-9 moderately impaired and 0-6 poor functional performance (Quadri et al 2005).

Details of the test administration are provided in the *Study manual*. The results of each test will be recorded on the SPPB eCRF.

6.4.3 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. Gait speed assesses a person's usual walking speed, which is defined as the speed a person normally walks from one place to another (e.g., walking from one store to another). The participant will perform two recorded trials of walking across the defined course. The fastest time in seconds (to the nearest 0.01 sec) a participant takes to complete the assessment will be scored and used to calculate the total SPPB score.

The patient should ideally complete the test without walking aids, unless he/she feels unsafe about completing the test without balance support (fears of fall). All types of walking aid(s) – except for wheeled walker / rollator – can be used during the treatment period (from Day 1 to EOS).

SPPB gait speed test performance will be captured in the eCRF including any potential usage of walking aids.

Details of the test are provided in the *Study manual.*

6.4.4 Falls

Detailed information on falls will be collected via patient interviews at each visit. The investigator will capture each fall and report any injuries, fractures, hospitalizations, change in

ambulatory status (e.g. needs for walking aids), impairment of activities of daily living or transfer to long term care facility.

Patients should be instructed and reminded at each visit to call their site and report fall events as they occur. Sites will provide patients with a diary to be used as "aide-memoire" to help them remembering the date, time, place and circumstances of sustained falls. This diary will not be used as source document but will be used to support the patient's interview at the time of the site visit.

Fall is defined as an event, which results in the person coming to rest inadvertently on the ground, floor, or lower level, and other than as a consequence of the following conditions: sustaining a violent blast, loss of consciousness, sudden onset of paralysis, or an epileptic seizure.

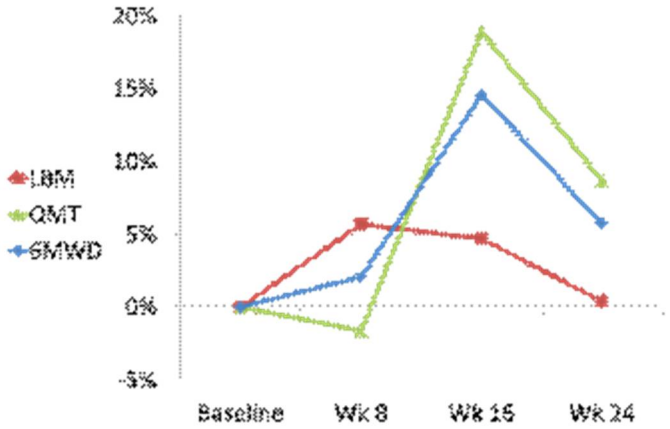
All falls will be recorded in the Adverse Event eCRF, with any associated injury recorded as a separate adverse event.

6.4.5 Appropriateness of efficacy assessments

Total LBM [redacted] by DXA

Previous work on testosterone supplements demonstrated that clinically meaningful increases in total LBM [redacted] are prerequisites of enhancing muscle strength and physical performance (Sattler et al 2011). In line with this previous observation, preliminary data on sIBM patients receiving a single dose of bimagrumab (30 mg/kg) showed that drug-induced increases in LBM (plateau reached at 8-12 weeks) were followed by significant increases in physical performance as quantified by the 6-minute walk distance (6MWD) at Week 24 (Figure 6-1). Moreover, when LBM declined upon drug withdrawal and returned to baseline, the functional benefits also vanished. Thus, increases in LBM are clinically relevant reflections of the expected functional benefits.

Figure 6-1 Sequence of LBM [redacted] changes to a single dose of bimagrumab 30 mg/kg in patients with sporadic inclusion body myositis (BYM338X2205 study)



Dual-energy X-ray absorptiometry provides a recommended alternative method for estimating skeletal muscle mass with advantages of inexpensiveness, short scan-time, much lower

[redacted]

radiation exposure to patients and more widespread availability in clinical and research settings as compared with the gold-standard methods, e.g. computerized tomography (CT) and MRI.

Studies document that the DXA-based approach gives mean total body skeletal muscle estimates that agree closely with muscle measured by CT or MRI, although DXA tends to systematically overestimate total body skeletal muscle by about 5% (Wang et al 1996, Chen et al 2007). This is due to the fact that DXA may also take into account organ lean mass of the trunk, the skin, and non-fat components in the adipose tissue when measuring total LBM (Wang et al 1976).

[redacted]

Furthermore, the relative inaccuracy of total LBM to estimate total skeletal muscle mass is of less concern in the monitoring setting, because the promyogenic drug bimagrumab has no known effect on parenchymal organs, skin, or the non-fat components of fat mass. In support, our observations in the BYM338X2102 study indicated a high degree of correlation (r=0.94) between the percent changes of total LBM (DXA) and percent changes of thigh muscle volume (MRI).

While total LBM is the preferred choice to quantify the primary [redacted] effect of the drug and establish the dose-response relationship, the measurement [redacted] will be of increased interest for the exploration of how drug-induced changes in skeletal muscle mass predict/reflect the anticipated functional benefits of the treatment.

Short Physical Performance Battery (SPPB)

The Short Physical Performance Battery (SPPB) is one of the most commonly used instruments for measuring physical performance in population studies of aging (Guralnik et al 1995). The SPPB is a composite measure of mobility including standing balance, chair stand and gait speed. 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.

Recently, it has been demonstrated that the SPPB can be feasibly and safely used to evaluate the functional status of acutely ill geriatric patients admitted to the hospital for serious medical conditions and that the SPPB score can provide important short-term prognostic information (Volpato et al 2008).

Beyond its strong predictive value, composite score of SPPB has also been used to monitor changes of physical performance over time (Kwon et al 2009) in observational studies as well

[redacted]

as in interventional trials and during strength or power training or treatment (Drey et al 2012) with a promyogenic agent (Adunsky et al 2012). The study by Bean et al (2010) showed for the first time that an increase in leg power, independent of strength, can make important contribution to clinically meaningful improvements in SPPB as well as gait speed.

Best estimate of small and large meaningful changes for SPPB are 0.5 point and 1.0 point, respectively (Kwon et al 2009, Perera 2006).

Gait Speed

While gait speed is imbedded in the full performance battery as a score between 0 and 4, it has also been subject of considerable research as a stand-alone continuous measure of physical performance / mobility. In fact, most studies have found that gait speed is the strongest predictor of health-related adverse events compared with the two other SPPB components (chair rise and balance tests), or it has performed almost as well as the full battery in predicting disability (Cesari et al 2009, Guralnik et al 2000). Gait speed alone has been associated with physical activity levels, changes in the isometric force of lower extremity muscles, frailty and falls (Newman et al 2003, Chandler et al 1998, Cesari et al 2005).

Gait speed is not only a well-established measure of physical function but it may also predict future disability in diverse community-dwelling elderly populations and is sensitive to reflect changes in physical status in response to changes in physical activity, including short-term rehabilitation (Barthuly et al 2012). Poor functional performance as measured by slow or declining gait speed is related to 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 often been quoted as a global indicator of health in the geriatric population.

Falls

Hip fracture patients experience a substantial reduction of mobility following fracture, with most (40-60%) patients discharged from the hospital after a hip fracture also experience another fall within the first year, mainly in the first 6 months (Bischoff-Ferrari et al 2010). A fall event can trigger fear of falls, restricted mobility, worsening of frailty and in extreme cases complete social isolation. Falls, however also account for 25% of hospitalizations and 40% of all nursing-home admissions. Given the continuing presence of fragility, falls often cause injuries, including recurrent fractures. Non-injurious falls may also be the source of morbidities/hospitalizations. Nearly half of non-injured frail fallers are not be able to stand up from the ground without assistance. This inability may lead to a period of immobility on the floor, which may lead to various adverse health outcomes depending on the time spent immobile. Treatment with bimagrumab in the period after fracture is likely to accelerate muscle volume gain, and may improve strength and mobility, which is likely to result in improved physical function and potentially a reduction in mobility-related adverse events.

6.5 Safety

All blood draws and safety assessments must be done prior to investigational treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs including any immediate infusion reactions) must be repeated after the dose is administered.

Safety assessments in this study will include:

[redacted]

- Evaluation of all AEs and SAEs including infusion site and hypersensitivity reactions
- Physical examination
- Vital signs, height and weight
- Laboratory evaluations
- Electrocardiogram (ECG)
- Echocardiogram, for patients enrolled prior to study protocol amendment #3
- X-ray assessment of surgical complications (if applicable) and hip fracture healing

[redacted]

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin (including paying special attention to telangiectasias of the skin or nail-folds), head and neck (including thyroid 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, neurological, and musculoskeletal system, at timepoints indicated in Table 6-1. Rectal, external genitalia, breast, and pelvic exams will be performed **only if indicated** based on medical history and/or symptoms.

Additional orthopedic examination, as per the standard of care, will be performed at the discretion of the investigator.

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. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after signing the informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.

6.5.2 Vital signs

Vital signs, blood pressure and pulse measurements will be assessed at every scheduled visit as indicated in Table 6-1.

After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an appropriate validated device, with a correct sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used (Mean systolic/diastolic value is used for eligibility).

If possible, assessments should be performed by the same study site staff member throughout the study.

Clinically notable vital sign measurements are listed in Appendix 1.

[redacted]

6.5.3 Height and weight

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

In addition, BMI will be calculated according to the formula:

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

If capturing a body weight decrease from baseline (Day 1) of 5% or more at any visit during the study, please refer to Section 6.5.8 for further actions to be taken to ensure patient's safety.

6.5.4 Laboratory evaluations

Bone marker results are influenced by the patients' fasting status. Therefore, it is important to ensure that blood samples for bone marker assessments are collected after **8 hour of fasting** (D1, W12, W24 (EoT)). This fasting status is preferable for the other blood samples as well, but this is not a requirement.

A central laboratory will be used for analysis of all specimens collected [redacted] Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the *Laboratory manual*. Reference to the Laboratory Manual should be made for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values.

Key laboratory test values that are clinically notable are defined in Appendix 1.

All abnormal values will be assessed by the investigator who will decide what action needs to be taken, taking into account the overall status of the patient.

In the case where a laboratory assessment listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening, the assessment may be repeated once for the purpose of inclusion. The repeated result must be within protocol-specified range prior to randomizing the patient. Investigators will have the discretion to record abnormal test findings on the medical history eCRF, whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.5.4.1 Hematology and serology

Hematology assessments listed in Table 6-2 will be measured at each scheduled visits as specified in Table 6-1.

Serology assessment (Table 6-2) will be done at screening only.

Table 6-2 Hematology and serology tests

Hemoglobin	
Hematocrit	
Red blood cell (RBC) count	Reticulocyte count
White blood cell (WBC) count with differential	Mean corpuscular volume
HIV Ab (screening only)	Mean corpuscular hemoglobin concentration
HbsAg (screening only)	Platelet count

[redacted]

HCV Ab (screening only)

6.5.4.2 Clinical chemistry, [redacted] and muscle integrity markers

Clinical chemistry, [redacted] and muscle integrity marker assessments listed in Table 6-3 will be conducted at the scheduled visits specified in this same Table 6-3. [redacted]

Table 6-3 Clinical chemistry tests, [redacted] and muscle integrity markers

Clinical chemistry parameters measured at Screening, W4, W8, W12, W24 (EoT) and W48 (EoS)	
Blood urea nitrogen (BUN)	Troponin I
Creatinine	Creatine kinase –MM
Calculated creatinine clearance	Creatine kinase –MB
Total bilirubin	Myoglobin
Aspartate aminotransferase (AST/SGOT)	Aldolase
Alanine aminotransferase (ALT/SGPT)	Fasting glucose
Gamma-glutamyltransferase (GGT/γGT)	HbA1c
Alkaline phosphatase	Cholesterol (total and HDL)
Total protein	Triglycerides
Albumin	Pre-albumin
Vitamin 25-hydroxy D	
High sensitivity C-reactive protein (hsCRP)	
Haptoglobin (if total bilirubin > 2ULN)	Amylase
	Lipase
Electrolytes (sodium, potassium, chloride, calcium, phosphorous, magnesium)	Uric acid
Activin A	estimated Glomerular Filtration Rate
Hormonal parameters measured at Screening, W12, W24 (EoT) and W48 (EoS)	
Sex hormone binding globulin (SHBG)	Luteinizing hormone (LH)
Estradiol	Follicle stimulating hormone (FSH)
Testosterone	Free thyroxine
	Thyroid stimulating hormone (TSH)
[redacted]	

6.5.4.3 Urinalysis

Urinalysis assessments listed in Table 6-4 will be conducted at each scheduled visit as specified in Table 6-1.

[redacted]

Table 6-4 Urinalysis tests

Specific gravity	Bilirubin
Protein	Ketones
Glucose	White blood cells (WBC)
pH	Blood

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after approximately 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs. The Fridericia QT correction formula (QTcF) will be used for clinical decisions.

A standard 12-lead electrocardiogram will be performed in triplicate (3 tracings of at least 10 sec duration to be obtained within a 2-5 min window) at visits indicated in Table 6-1. All ECGs must be performed on the ECG machines provided to the study site by an assigned vendor.

Patient management will be performed on the basis of the local assessment of the ECG by the investigator. Interpretation of the tracing must be made by a qualified physician that must also sign the tracing and review the findings. **The study code, patient number, patient initials, the date and actual time of the tracing must appear on each page of the tracing.** Original ECG tracings, appropriately signed, will be archived at the study site as source.

The tracings will be transmitted to a central reading vendor for independent review. Instructions for the collection and transmission of the ECGs to the independent reviewer are provided in the *ECG manual*.

Screening

The central reading results at screening will determine the eligibility of the patient for the trial. If two (or all three) of the three ECGs are outside the allowed limit of QTcF ≥ 500 msec, the patient must not be randomized. Patients having a ventricular pacemaker or showing the presence of a left or right bundle branch block a QTcF ≥500 msec is not exclusionary. Patient can be enrolled if endorsed by the patient's physician.

If a clinically relevant abnormality noted on the **screening ECG** is one of the pre-specified terms listed on the Cardiovascular eCRF, that abnormality should be recorded on the Cardiovascular eCRF. All other clinically significant abnormalities should be recorded on the Medical History eCRF.

Triplicate central ECGs may be repeated once at an unscheduled visit during the screening epoch to confirm patient eligibility prior to randomization. The repeated result must be within protocol-specified range prior to randomizing the patient.

Randomization (Baseline/Day 1)

Any clinically significant abnormalities noted **after screening visit ECG**, should be reported as adverse events on AEs CRF page.

The tracings must be locally reviewed for major abnormalities before randomizing the patient and before every dose administration. If the ECG findings are clinically relevant

[redacted]

and would prevent the patient from participating in the study, the patient should not receive the investigational treatment.

6.5.6 Echocardiography

Two-dimensional echocardiography monitoring will be performed on all patients enrolled prior Amendment #3. as per Table 6-1. The images will be transmitted to a central reading vendor for independent review. Sites will receive appropriate training as needed as well as the *Imaging manual* that includes detailed instructions and data transfer procedures.

Central assessments

Aligned with recommendations of the American Society of Echocardiography concerning the use of echocardiography in clinical trials (Gottdiener et al 2004), the following standard parameters - pertinent to the assessment of changes in cardiac muscle mass and/or contractile function - will be monitored during the study:

- Left ventricular wall (posterior) and septal thickness
- Left ventricular mass and mass index
- Left ventricular end-diastolic volume
- Left ventricular end-systolic volume
- Left ventricular ejection fraction
- Left ventricular diastolic and systolic diameter
- Left atrial size and volume
- Right ventricular wall thickness and dimension

If echocardiography indicates clinically meaningful abnormalities of cardiac mass or contractile function, patients will be followed up at W48 (at the end of the off-drug post-treatment period).

6.5.7 X-ray assessment of surgical procedure

A historical X-ray done by local practice during or after surgery (in some cases prior to the initiation of screening) will be used by the investigator for eligibility assessment. The summary of the local assessment will be recorded in the Perioperative eCRF and must confirm adequate surgical execution of internal fixation or arthroplasty for fracture repair. Images do not need to be submitted to the central reader vendor.

During the trial, an X-ray of the operated hip will be taken at Week 24 (EoT) visit - as indicated in Table 6-1- to assess whether fracture healing has been completed (bone union) and whether there are any potential late complications of the surgery. If bone-union is not achieved at Week 24, patient will be followed up at Week 36 and also potentially at Week 48 (EoS), if bone union is still not achieved at Week 36. Additional unscheduled X-rays may also be required if there is any clinical suspicion of delayed/improper fracture healing. Any findings on X-ray need to be reported as adverse events. Specifically, bone non-union seen at Week 36 (delayed fracture healing) needs to be reported as an SAE.

All scheduled and unscheduled X-rays performed after enrollment will be transferred to a central reader (details provided in *Imaging Manual*). Two independent readers of the assigned

[redacted]

vendor will perform a blinded assessment of the images for bone union and a number of pre-specified orthopedic complications. In case of discordant medical opinions regarding the presence or absence of these complications, a third reader will settle a final decision. The central reader may request sites to provide additional X-rays, if available, to support overall assessment of the specific finding.

6.5.8 Dietary Assessment

The investigator should ensure that patients are consuming adequate protein amount and must determine whether the patient is malnourished as it may affect his/her muscle recovery.

If body weight decrease by 5% or more and/or the laboratory results are outside of the respective normal ranges, the investigator should evaluate the patient overall condition, refer the patient to a nutritionist or other health care provider for further evaluation and consideration of dietary supplements as per local standard of care.

6.5.9 Pregnancy and assessments of fertility

Not applicable as only post-menopausal women will be included.

As per definition: women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

[redacted]

6.5.12 Appropriateness of safety measurements

The safety measures used in this study, as detailed in Table 6-1, are reliable and relevant standard safety measures.

In line with the direct skeletal muscle effects of the drug, tolerability will be monitored closely using chemical/[redacted] measures of muscle damage including changes of serum levels of creatine kinase MM, myoglobin, aldolase, ALT, AST and potassium. Interpretation of any changes in these biomarkers will take into account simultaneous presence or absence of clinical symptoms such as spontaneous muscle contractions and related pain.

In preclinical studies on rats or monkeys reversible hypertrophic changes of the heart have been described, but these changes are considered compensatory in response to the marked changes in muscle mass and hence body mass (up to 30%). Alteration of myostatin expression has not been associated with alteration of cardiac systolic function in mice overexpressing or lacking the active protein. Nevertheless the effects of bimagrumab in the pathologic heart are yet to be understood. For this reason, patients with severe cardiac conditions (see respective exclusion criteria) need to be excluded from the trial.

Echocardiography has been used in studies on healthy volunteers and patients to monitor changes in cardiac structure and contractile function in response to the preclinical findings of a compensatory hypertrophy mentioned above. The current cardiac safety profile reflects the absence of any finding in any clinical study (approximately 900 adults received bimagrumab since September 2017) and the recent results from a dedicated cardiac safety study (CBYM338X2109). Using multiple technologies including cardiac magnetic resonance imaging (CMR) and Holter monitoring, there was no effect of 6-month exposure to 10 mg/kg (equivalent to 700 mg in this study) i.v. bimagrumab on left ventricular ejection fraction, cardiac mass, QTc, blood pressure or heart rate. Based on this safety profile, regular echocardiography is no longer required for studies in the bimagrumab clinical development program. These changes in cardiac safety monitoring were approved by the independent data monitoring committee (DMC) and internal Novartis safety and scientific review committees.

[redacted]

Two preclinical studies in rats undergoing osteotomy of the fibula indicate that repeated administration of high doses of bimagrumab (up to 100 mg/kg) may be associated with slight decreases in immature callus size and bone mineral content in skeletally immature (young) animals 4 weeks after surgery, but not in skeletally matured (old) animals. In addition, there were no differences in the size of the mature callus, the radiographic progression of fracture healing, the morphology and biomechanical competency of the fibula when comparing vehicle and bimagrumab treated animals. It is well known in the literature that animal findings do not necessarily translate into clinical findings (Geusens P et al Rheumatol 2013).

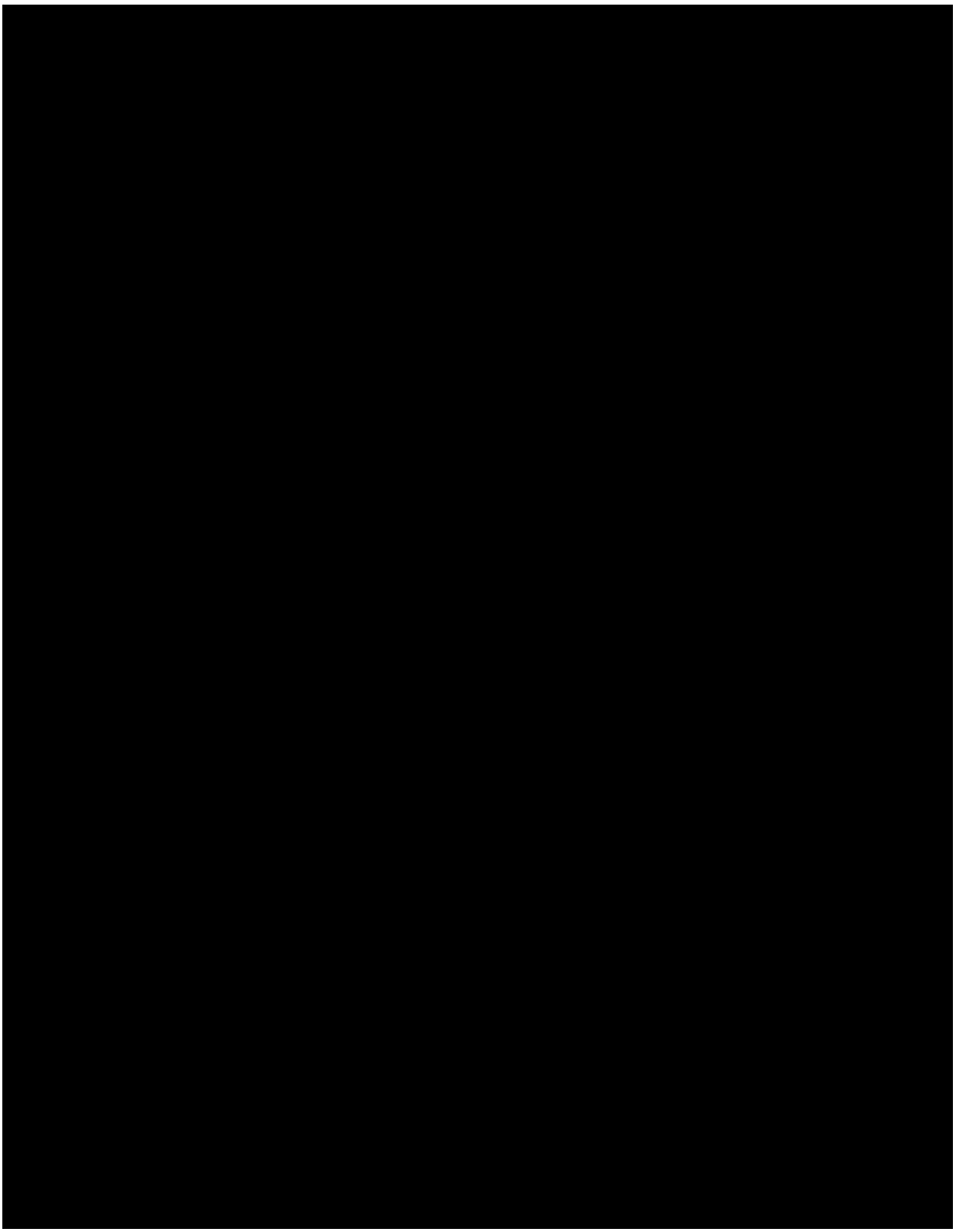
However, given the first-time testing of bimagrumab in patients undergoing major surgery after a hip fracture, the study will monitor the region of interest with X-ray taken at Week 24. Two independent radiologists (central readers) will assess these images and to confirm completed fracture healing (i.e. bone union) and exclude a number of postoperative orthopedic complications. If bone-union is not achieved at W24, additional X-rays are to be collected at W36, and if needed at W48. Data will be regularly reviewed by an external DMC that is empowered to alert the clinical study team in case of any unexpected safety finding (i.e. trend for delayed fracture healing or increased rate of orthopedic complications).

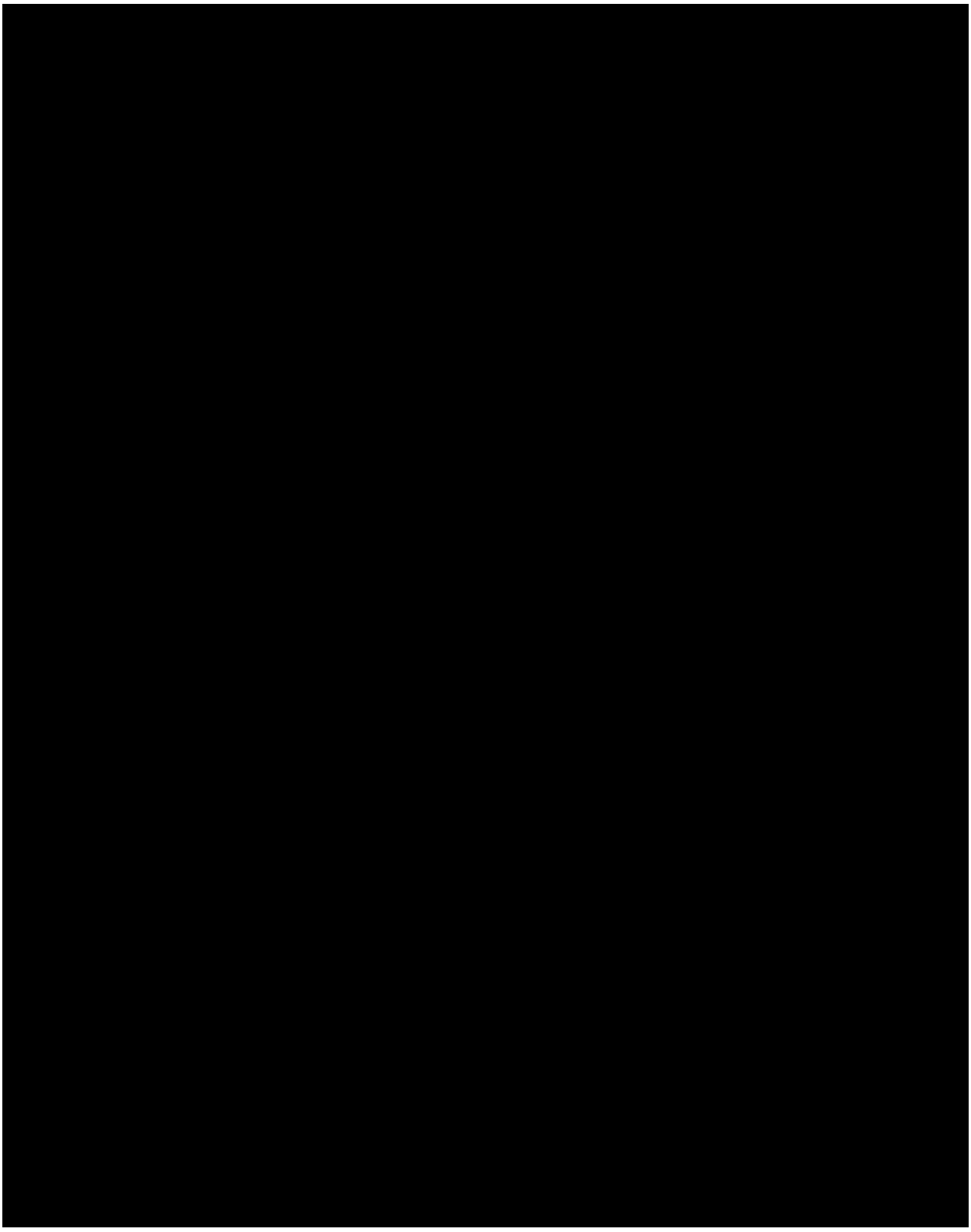
Fracture healing as well as osseointegration of non-cemented implants, are both critically dependent on intact bone formation and bone resorption. [redacted]

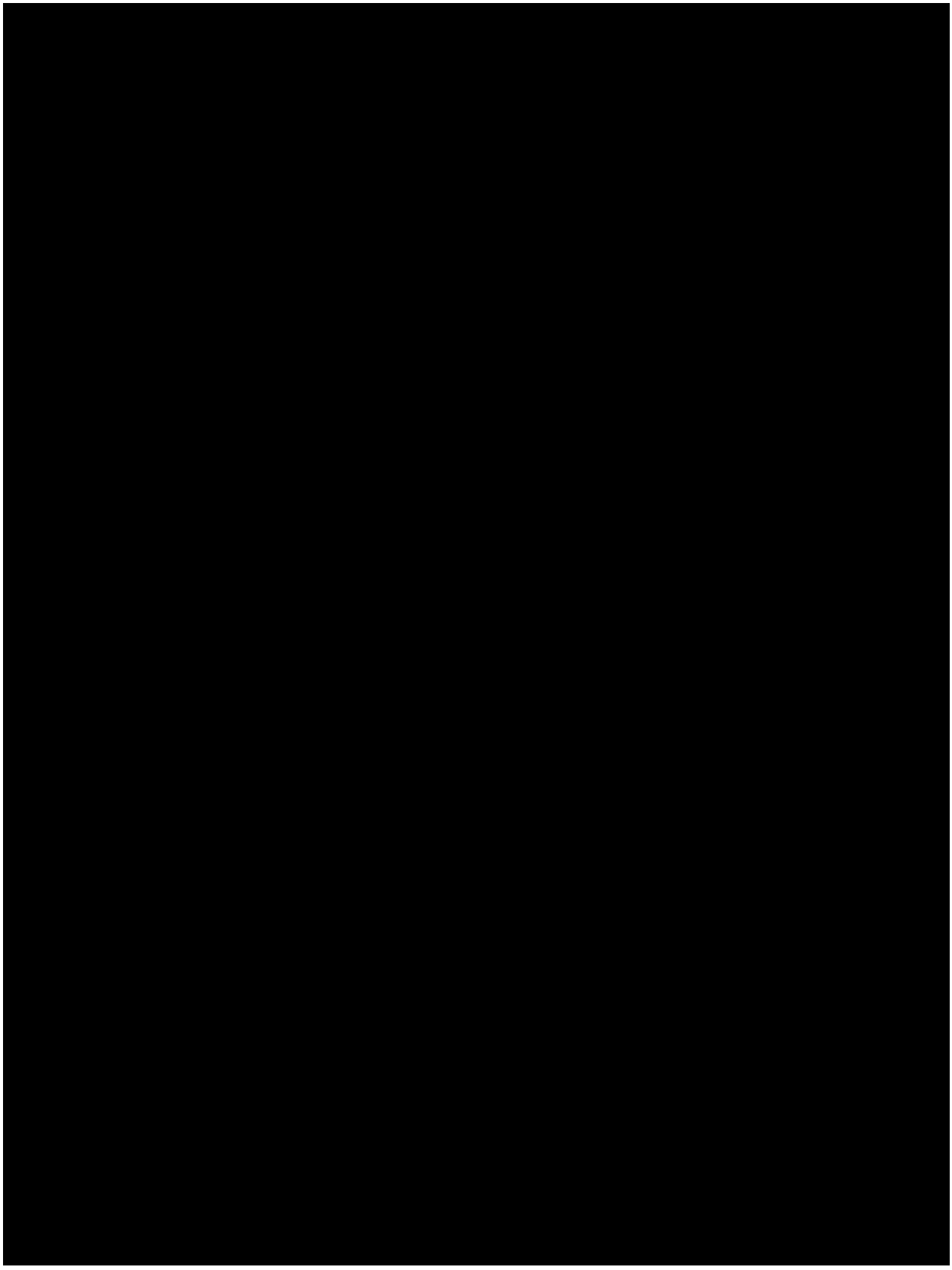
Although asymptomatic, in order to properly evaluate the increase in lipase or amylase observed in some bimagrumab treated patient and rule out any potential case of pancreatitis, additional monitoring procedure commonly used for pancreatitis diagnostic are included (i.e. laboratory works, clinical presentation and imaging).

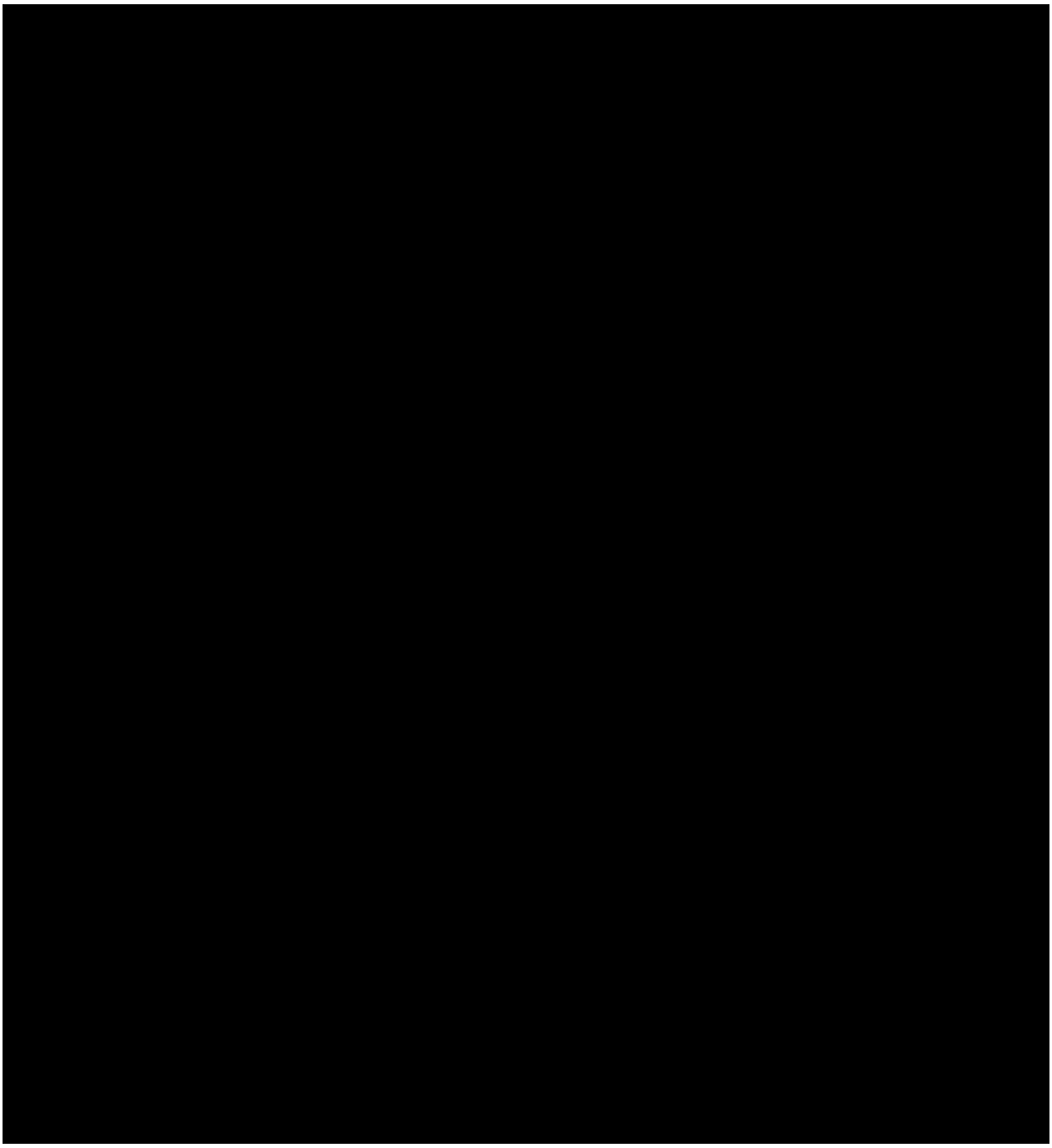
[redacted]

[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 patient 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 adverse events **occurring after informed consent is signed and until the last study visit** will be recorded on the Adverse Event CRF for all patients who enter the treatment epoch.

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

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Clinically notable labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
- its relationship to the investigational treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding investigational treatment
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- investigational treatment temporarily interrupted
- investigation treatment permanently discontinue due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged.

[redacted]

The action taken to treat the adverse event should be recorded on the CRF.

In this study, investigators will be asked to provide additional details on selected adverse event of special interests such as but not limited to events of spontaneous muscle contraction potentially associated pain or events that may require adjudication (see Section 8.5).

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 treatment, the interventions required to treat it, and the outcome.

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

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) 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 (specify what this includes)
  - 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
  - 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 patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

[redacted]

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 more severe (see Annex IV, ICH-E2D Guideline).

All malignant neoplasms and delayed fracture healing (i.e. bone non-union seen at X-ray at W36 or later) will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF. SAEs are monitored continuously and also require individual reporting requirements to DS&E as per Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the End of 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.

SAEs reported until Week 48 End of Study visit or early discontinuation will be captured in both clinical and safety databases. SAEs reported after this time-point will only be captured in the compounds safety database.

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (where available). 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) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder

[redacted]

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.

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

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 patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected, exempting the SUSARs in Table 7-1 below, and will be 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. .

Table 7-1 SUSARs exempt from expedited reporting

	SUSAR	Definition	Reason
	Falls (including injurious)	A sudden and unexpected loss of balance resulting in an event in which the participant comes to rest on the ground, floor, or lower level.	Pre-specified endpoint and common procedural complication after hip fracture surgery.
Implant-related	Implant loosening/migration and potential late mal-alignment of the joint	Implant loosening is a change in the position of the implant or a progressive radiolucent line at the bone-cement transition visualized by radiography. Symptomatic mal-alignment including significant leg shortening resulting in functional deficit	One of the most common procedural complication after hip fracture surgery.
Implant-related event	Implant fracture	Fracture of one part of the implant, e.g. stem, plate or screws	Rare but acknowledged procedural complication after hip fracture surgery.
Bone-related event	Periprosthetic fracture	Near-implant fracture on femoral or acetabular site	Relatively rare but severe procedural complication after hip fracture surgery.
Bone-related	Avascular necrosis of	Cellular death (necrosis) of bone	Rare but acknowledged

[redacted]

	SUSAR	Definition	Reason
event	head / trochanter major	components in the femoral head due to interruption of the blood supply, especially after medial fractures	procedural complication after hip fracture fixation
Bone-related event	Osteolysis	Biologic reaction of the bone to wear particles resulting in expansile lytic lesion adjacent to one of the implants (>1 cm in any one dimension or increasing in radiographs).	Relatively common (long-term) procedural complication after THA
Bone-related event	Hip dislocation	Dislocation of the ball of the femoral component from the acetabular cup during the healing of bone (needs to be radiologically confirmed), which requires closed or open reduction	Rare (early) but acknowledged procedural complication after THA
Soft-tissue related	Heterotopic ossification	The development of bone outside its normal location in the skeleton (e.g. para-articular soft tissue) and causing pain and restriction of hip motion	Relatively common procedural complication following a severe hip fracture. May cause functional impairment, if extensive
Soft-tissue related	Neural deficit	Postoperative nerve palsy (sciatic, femoral or obturator nerves) related to the index surgery (cut, stretch, cauterization), which may cause muscle weakness, limited ambulation, and persistent dysesthesia	Rare but acknowledged procedural complication after THA
Procedure related	Bleeding	Bleeding during the course of healing (most often associated with anticoagulant therapy) requiring surgical treatment	Relatively common procedural complication after hip fracture surgery.
Procedure related	Deep infections (including deep wound & periprosthetic infections)	There is a sinus tract communicating with the prosthesis, or A pathogen is isolated by culture from at least 2 separate tissue or fluid samples obtained from the affected prosthetic joint; or 4 of 6 independent infection criteria: elevated ESR or CRP concentration elevated synovial WBC elevated synovial neutrophil % presence of purulence in the joint isolation of the microorganism in 1 culture of periprosthetic fluid or tissue Greater than 5 neutrophils per high power field in 5 high power fields observed from histological analysis of periprosthetic tissue at 400 x magnification	Rare but acknowledged procedural complication after hip fracture surgery

[redacted]

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events will be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard liver CRF page

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeat laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient 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 on appropriate eCRF pages, including the liver event overview eCRF pages.

7.4 Lipase and amylase elevations

To ensure patient safety and enhance the reliability in determining the potential for pancreatic events with bimagrumab, a standardized process for identification, monitoring and evaluation of pancreatic events has to be followed (Table 7-2).

[redacted]

Table 7-2 Safety monitoring guidance for amylase and lipase elevations

Event	Follow up monitoring
Lipase and/or amylase < 3x ULN	• If asymptomatic, follow up at discretion of investigator. • If clinical symptoms (e.g., abdominal pain, nausea, diarrhea) suggest pancreatic involvement, re-check enzymes (amylase, lipase) and inflammatory markers (C-reactive protein) and consider pancreatic imaging (i.e., abdominal ultrasound or CT or MRI) to evaluate for presence of pancreatitis.
Lipase and/or amylase ≥ 3x ULN	• Re-check enzymes (amylase, lipase) and inflammatory markers (C-reactive protein) independent of presence of clinical symptoms. • Assess subject for clinical symptoms. • Conduct pancreatic imaging (i.e. abdominal ultrasound or CT or MRI) to evaluate for presence of pancreatitis. • Study drug interruption based on findings of additional assessments and at discretion of investigator.

As defined in Section 7.1, medically significant events which are considered as serious adverse events (SAEs) should follow the standard procedures for SAE reporting as described in Section 7.2. Every pancreatic event reported as an SAE should include a causality assessment of the event via exclusion of alternative causes (e.g., gallstones, co-medication).

An investigation of the pancreas needs to be followed up until resolution. A gastroenterology consult can be included at the investigator's discretion. All follow-up information, and the procedures performed, should be recorded in the appropriate CRFs.

7.5 Pregnancy reporting

Not applicable in this study where only post-menopausal women will be enrolled.

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 CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that investigational treatment 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 patient 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 CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

[redacted]

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary 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 patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. 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 copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis will review the data entered into the CRFs 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. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies 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).

ECG readings, all imaging (echocardiography, DXA and X-ray) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes 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.

[redacted]

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

At the time of the primary analysis, which will occur when all patients will have completed the double-blind treatment epoch (Week 24 visit), similar actions will be completed and the treatment codes will be made available to the Novartis global study team for data analysis..

8.4 Data Monitoring Committee

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

The DMC will periodically review the safety information throughout the study to monitor the trial's progress for unexpectedly large differences in the incidence of AE/SAE 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 must 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 unblinded information with anyone outside of the DMC. Particularly, the Sponsor will remain fully blinded to any results throughout the study unless the DMC recommends changes in the conduct of the study (for example, early termination due to negative safety findings).

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

[redacted]

- 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 cardiovascular adjudication committee will be used to re-evaluate and confirm the investigator-reported diagnostic term of specific safety events (e.g. ischemic heart disease, heart failure, cardiomyopathy, or cardiac arrhythmias). Events will be reviewed blindly as they occur during the trial. Details regarding the adjudication process will be available in the relevant Adjudication Committee charter. The committee may provide expert reports at the end of the study.

The clinical database will be regularly searched by the clinical team for targeted adverse events including but potentially not limited to cardiac safety events. When an adverse event in these categories is identified, a follow-up form will be sent to the clinical site to document the adverse event in detail and to request the submission of any applicable supplemental data, which may be available, including copies of source documents. Source documents include, but are not limited to, relevant clinical notes, radiographs, ECGs, ultra-sonograms, operative and pathology reports, hospital discharge summaries. In addition, an interview with the patient conducted by the site (in person or via telephone) may be needed to fully clarify the circumstances of the event.

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

9 Data analysis

The primary analysis for this study will be conducted when all patients have completed the (double-blind) treatment epoch (Week 24 visit). All post-treatment follow-up data on efficacy endpoints (SPPB and gait speed) available at the time of the primary analysis will also be summarized to address the durability of functional benefits during the off-drug follow-up period. The final statistical analysis will be performed when all patients have completed Week 48 of the study.

All details regarding the statistical analysis will be documented in the statistical analysis plan which will be finalized prior to the data extraction for the primary analysis (Week 24) at interim database lock and the global study team group level unblinding.

9.1 Treatments

Study medication and concomitant medication will be analyzed with the safety analysis set.

[redacted]

9.1.1 Study medication

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

Duration (days) of study medication administration will be summarized. For each patient, the number of days of drug exposure = last infusion date – first infusion date + 56 based on the infusion schedule for the study (intravenously every 4 weeks).

9.1.2 Concomitant medications

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

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

9.2 Analysis sets

The Full Analysis Set (FAS) used for all efficacy analyses will consist of all randomized patients who received at least one dose of investigational treatment. Patients will be analyzed according to the treatment they were assigned to at randomization. Patients who entered the study before Amendment 2 will be pooled with fixed-dose patients as follow: bimagrumab 3 mg/kg patients will be analyzed as member of the 210 mg group, bimagrumab 10 mg/kg patients will be analyzed as member of the 700 mg dose group.

The safety (SAF) Analysis Set will consist of all patients who received at least one dose of study medication. Patients will be analyzed according to the treatment received. Patients who entered the study before Amendment 2 will be pooled with fixed-dose patients as detailed for the FAS.

Per-protocol (PP) Analysis Set will include all FAS patients who complete the study without major deviations from the protocol procedures. Major protocol deviations and the definition of the PP set will be identified and finalized based on blinded review of the data, prior to the data extraction for the primary analysis (EoT) and the global study team group level unblinding.

For patients who entered the study before Amendment 2 and have been treated for more than 6 months, data collected after the Week 24 visit will be listed.

9.3 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment and patient and summarized by treatment. Patient demographics will include age, sex, race, ethnicity, height,

[redacted]

weight and BMI. Other baseline disease characteristics include medical history, falls history, orthopedic history, perioperative assessment, blood transfusion history, tobacco history, cardiovascular risk factors, gait speed, LBM, [redacted] and SPPB.

Summary statistics will be presented for the patients in the FAS. Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, and the number of non-missing observations.

Categorical data will be displayed via absolute and relative frequencies for each category (including a category labeled as 'missing' when appropriate).

9.4 Analysis of the primary variable

The primary analysis set for efficacy will be FAS.

9.4.1 Variable

The primary variable is change from baseline in Total LBM at Week 24.

9.4.2 Statistical model, hypothesis, and method of analysis

The aim of the study is to show that at least one bimagrumab treatment arm will increase Total LBM (change from baseline) compared with placebo at Week 24 by rejecting the null hypothesis described below at significance level α=0.05 level (two-sided):

$$H_0: \mu_T = \mu_P \text{ vs. } H_1: \mu_T \neq \mu_P$$

where μ_T and μ_P are mean change from baseline of Total LBM at Week 24 for the bimagrumab dose group of interest (700mg or 210mg only) and placebo.

A mixed model will be used with change from baseline at all post-baseline visits (Week 12, and Week 24) as response variable, and treatment, visit, randomization strata as defined in Section 5.3 and baseline LBM measurement as covariate. Two interaction terms (treatment*visit and baseline LBM*visit) will also be included in the model. An unstructured within subject correlation structure will be used for covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. REML (residual/restricted maximum likelihood) method will be used to estimate parameters.

The two-sided p-value for the least square mean (LSM) difference between the bimagrumab and the placebo groups at Week 24 (and at Week 12) will be reported for the difference. For the primary endpoint, the Holm-Bonferroni method will be used to adjust for type I error among the 2 comparisons at Week 24. No control for multiplicity will be made at Week 12. Total LBM data will be transformed with natural logarithm before this analysis.

9.4.3 Handling of missing values/censoring/discontinuations

The above analysis will be performed using all available data under the assumption that the probability of missing values of total LBM is independent of unobserved measurements (missing at random). Therefore the missing values will not be imputed for primary analysis.

The following sensitivity analysis will be performed to check the robustness of the primary analysis results.

[redacted]

- Fit the analysis model only to the completed cases (patients without missing LBM)
- Missing value imputation:

For this sensitivity analysis, we assume a "missing not at random" (MNAR) process meaning that missingness depends on the unobserved data. Suppose that patients in the bimagrumab arms who discontinue due to adverse events (AE), death (D) or unsatisfactory therapeutic effect (UTE) behave like placebo arm patients after study discontinuation. This assumption implies that the drug effect diminishes once bimagrumab arm patients discontinue from the study. To perform this analysis, a Bayesian multivariate normal imputation model using non-informative priors is fitted to the repeated total LBM measurements at baseline and Weeks 12, and 24 for all placebo patients. Based on this model, the conditional distribution of missing data given the observed data can be used to create multiple imputations for the missing values of patients in the bimagrumab arms who discontinue due to AE, D, UTE.

Missing data for all other subjects will be imputed under a MAR assumption, that is missing data are imputed based on the treatment-specific information for the repeated total LBM measurements at baseline and Weeks 12 and 24.

For each imputed and thus completed data set, the primary analysis model is then fitted as specified in Section 9.4.2. The resulting sets of parameter estimates and associated covariance matrices are then combined to derive overall estimates, confidence intervals that adequately reflect missing data uncertainty as well as associated p-values using Rubin's rules (Little RJA and Rubin DB 2002).

The results from all analyses will be discussed with reference to the plausibility of their respective underlying assumptions.

9.4.4 Supportive analyses

As supportive analysis, the primary analyses will be repeated using the PP analysis set.

In addition, dose response modeling will be performed using the MCP-Mod approach, which considers the following models:

1. Three parameter Emax: $f(d) = E_0 + E_{max}d/(ED_{50} + d)$
2. Sigmoidal Emax with h=2: $f(d) = E_0 + E_{max}d^h/\left({ED_{50}}^h + d^h\right)$
3. Exponential: $f(d) = E_0 + E_1\exp(d/\delta) - 1$
4. Linear: $f(d) = E_0 + \beta * d$

Where d is the dose level, ED_{50} the dose that gives 50 percent of the maximum effect, h the hill coefficient; δ and β the rate of change for the exponential and linear models respectively, E_0 the basal effect at d=0 and E_1 the scale parameter in the exponential model.

In the MCP-Mod approach, all statistically significant models listed above will be averaged in order to estimate the median dose for a given targeted response via inverse prediction along with corresponding 95% intervals using a bootstrap re-sampling method.

Since the design of this study is limited to having only 3 active doses, another dose response sigmoidal Emax model will also be considered which allows for estimation of the Hill coefficient (h). In this model, the fixed dose of 70 mg, 210 mg, and 700 mg from each patient will be normalized by their baseline weight in kg (i.e., the fixed dose will be divided the

baseline weight) to form a mg/kg dose regressor. The specific model to be applied to the mg/kg regressor will be the non-standardized sigmoidal Emax model. The mean dose response and corresponding asymptotic 95% confidence intervals (i.e., fiducial intervals) will be provided using the inverse prediction approach again.

The non-standardized sigmoidal Emax model is parameterized as follows:

$$f(d) = E_0 + E_{max} d^h / \left({ED_{50}}^h + d^h \right)$$

In choosing which dose response model to select for estimating dose as well as characterizing the entire response profile, the MCP-Mod approach is the default under the rule of parsimony, provided it fits the data well and results in intervals for estimating dose that are smaller than the 4 parameter Emax model.

To evaluate the homogeneity of the estimates within subgroups, forest plots displaying treatment group differences (or ratios) and corresponding 95% confidence intervals by subgroup, together with the relative position of the overall treatment effect, will be produced. In the statistical models, a treatment by subgroup interaction term will be added to allow for the analysis of the treatment effect within a subgroup. Subgroup analyses will include for example analyses of patients enrolled under original protocol versus those enrolled under protocol amendment 2.

9.5 Analysis of secondary [redacted] variables

9.5.1 Efficacy variables

9.5.1.1 Gait speed and Short Physical Performance Battery (SPPB)

The change from baseline at Week 24 and Week 48 in gait speed and in SPPB will be analyzed similar to the primary variable. A log transformation may be used if warranted. An unstructured within subject correlation structure will be used for the covariance matrix.

In addition, dose response modeling will be performed for both gait speed and SPPB using the MCP-Mod approach.

The following testing strategy will be used to control for multiplicity of endpoints and doses to be tested: if both doses (210 and 700 mg) are statistically significantly different from placebo at α=0.05 two-sided for the primary endpoint, then a fixed sequence approach will be applied for both Gait Speed and Short Physical Performance Battery (SPPB) at week 24 using the same linear mixed model for repeated measures and α=0.05 two-sided at each stage. The first inference will compare the 700 mg group to placebo for Gait Speed, followed by a second inference comparing the 210 mg group to placebo for Gait Speed. The third inference will compare the 700 mg group to placebo for SPPB, followed by a fourth inference comparing the 210 mg group to placebo for SPPB. Additionally, the fifth inference will compare the combined 700 mg and 210 mg group to placebo for the incidence of fall observed till the time of the interim analysis. The analysis conducted at Week 24 for falls will include available incidence of falls also collected from patients with visits beyond Week 24. The analysis of the fall data will be performed based on the assumption that the differences in incidences of fall within the active bimagrumab doses (700 mg and 210 mg) is small compare to the differences of those doses to the placebo arm.

[redacted]

The sequence of the endpoints has been decided based on the anticipated probability of showing statistical significance of bimagrumab over placebo, the clinical importance is not considered for this sequence determination, as each endpoint is clinically important.

[redacted]

9.5.1.3 Falls

The frequency of having at least one fall up to Weeks 24 and 48 will be summarized by treatment group. The time to the first fall may also be assessed using a plot of the Kaplan-Meier product limit estimates and a log rank test provided there are a sufficient number of events. Negative binomial regression may also be used to analyze fall event rates. All details regarding the analyses of falls will be documented in the statistical analysis plan. The numbers of patients meeting the criteria for the responder endpoint derived from SPPB, Gait Speed and incidence of falls by Week 24 and 48 will be summarized by treatment group. A logistic regression may be used to determine the treatment effect.

9.5.2 Safety variables

All safety evaluations will be performed on the safety set (SAF). Some safety analyses might be repeated on the subset of patients randomized after Amendment 2 that is patients who received a fixed dose of investigational treatment.

9.5.2.1 Cardiac Safety Analysis

The frequency of experiencing at least one cardiac event of special interest (AESI) – cardiomyopathy, ischemic heart disease, heart failure, or cardiac rhythm disturbances (brady/tachyarrythmias) - will be summarized by treatment group. In addition, the relative risk (to placebo) of experiencing at least one AESI (based on the confirmed events) will be calculated with 95% confidence intervals for each of the bimagrumab treated groups versus placebo. The results of these analyses will be presented in tabular form. If a substantial number of events occur, data may also be summarized graphically using adverse events dot plots (incidences and relative risks) per experimental dose.

Depending on the rarity of the events, a Kaplan-Meier plot for time-to-the first event with a censored adjusted median time and corresponding 95% confidence intervals may be presented for each treatment group. Differences between placebo and each of the bimagrumab treated groups will be further assessed by a log-rank test if the Kaplan-Meier plots provide a clinically warranted rationale.

9.5.2.2 Bone Safety Analysis

The incidence of orthopedic complications (i.e. with focus on bone non-union as per X-ray imaging) will be summarized through frequency counts by treatment group. The treatment contrasts will be presented as odds ratios and/or absolute risk differences with corresponding 2-sided 95% confidence intervals depending on the rarity of the event.

[redacted]

9.5.2.3 Adverse events

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

Incidence of potential cases of safety risks as defined in the case retrieval strategy with frequency counts by treatment arm and estimated rates with corresponding 95% confidence intervals regardless of investigational treatment relationship will be provided to compare each of bimagrumab treatments with placebo group.

Separate summaries will be performed for study medication related events, death, serious adverse events, adverse events leading to discontinuation of the investigational study drug , and other adverse events of interest.

Additional analyses utilizing the beta binomial model may be used to summarizing absolute rates by treatment group in the case of sparse data or if it is clinically warranted. The beta binomial model will utilize a non-informative beta (1/3, 1/3) prior. Summaries may include posterior probabilities for a clinically relevant difference(s), point estimates under the posterior distribution with corresponding 95% credible intervals (i.e., equal tail) and/or a graphical presentation of the entire posterior distribution itself.

9.5.2.4 Laboratory data

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

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

Newly occurring or worsening liver as well as pancreatic enzyme abnormalities will be summarized.

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

9.5.2.5 ECG

Summary statistics will be presented for ECG variables by visit and treatment group utilizing Novartis standard algorithms and reporting formats. All ECG data will be listed by treatment, patient and visit, abnormalities will be flagged.

9.5.2.6 Echocardiography

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

- Left ventricular wall (posterior) and septal thickness

[redacted]

- Left ventricular mass and mass index
- End-diastolic volume
- End-systolic volume
- Left ventricular ejection fraction
- Left ventricular diastolic and systolic diameter
- Left atrial size and volume
- Right ventricular wall thickness and dimension

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

9.5.2.7 Vital signs

Summary statistics for vital sign variables and for the change from baseline in vital signs will be presented. Abnormalities according to clinically notable criteria will be identified and the incidence of abnormalities will be tabulated. All vital signs data will be listed by treatment, patient, and visit and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged.

[redacted]

9.5.2.9 Other safety variables

Other safety variables will be summarized by visit and treatment group and will be listed by treatment, patient, and visit. Other safety variables include death, pain scores for AEs of spontaneous muscle contraction, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.6 Interim analyses

The primary analysis will be performed when all patients have completed their EoT visit (Week 24) via an interim database lock (soft database lock); while an updated analysis will be conducted when all patients have completed their EoS visit (Week 48). No interim analysis will be performed prior to the primary analysis at the Week 24 EoT visit.

[redacted]

9.7 Sample size and power calculation

A total sample size of approximately 245 patients at the time of randomization is planned (calculated using NQuery 7.0). Specifically, there will be 70 patients randomized to the placebo, bimagrumab 210 mg, and bimagrumab 700 mg groups for hypothesis testing purposes. An additional 35 patients will be randomized to the bimagrumab 70 mg group for the purpose of conducting formal dose response modeling described in the supportive analysis (section 9.4.4), but not for hypothesis testing. .

Total lean body mass

The primary objective of the study is to demonstrate that bimagrumab induces increases in Total LBM (change from baseline) compared to placebo at Week 24. A meaningful difference in LBM (change from baseline) increase has been identified as being 1.0 kg over placebo.

Study BYM338X2102 cohort 1&2 data showed that at Week 12, 5 subjects in 10 mg/kg bimagrumab group had LBM change from baseline mean = 1.48 kg (std = 0.86 kg); 6 subjects in 3 mg/kg bimagrumab group had LBM change from baseline mean = 2.22 kg (std = 1.13 kg).

Assuming that at Week 24 total LBM (change from baseline) difference between bimagrumab and placebo will be 1.0 kg and common SD = 1.0 kg, then sample size of 70 per group will show the power of 99%. Table 9-1 shows the power of detecting a significant difference between bimagrumab and placebo in LBM at Week 24 by two-sided test at alpha level = 0.025 (adjusted for 2 comparisons).

Table 9-1 Power calculation for total LBM (sample size = 70 per arm)

Common SD [kg]	Total LBM difference (bimagrumab – Placebo) [kg]				
	0.8	**0.9**	**1.0**	**1.1**	**1.2**
1.0	99	99	**99**	99	99
1.2	95	98	99	99	99
1.4	86	93	97	99	99
1.6	75	85	92	96	98

Gait Speed

One of the secondary objectives is to characterize for each bimagrumab treated group the placebo-corrected change in gait speed (GS) from baseline to Week 24. A treatment effect of 0.1-0.2 m/s between bimagrumab and Placebo has been deemed to be a clinically meaningful difference (Alley et al 2011).

The references in Table 9-2 were consulted in order to understand the variability and magnitude of treatment effect to be anticipated in 6 months on 4 m gait speed.

[redacted]

Table 9-2 Key references used to ascertain the variability in gait speed

Reference	Study Design	Population	Information
Latham et al (2008)	Randomized, double-blinded, placebo-controlled trial	Patients>65 years undergoing surgical repair of a hip fracture	Gait speed at baseline 0.50 (0.28) m/sec. Gait speed at Week 12 0.77 (0.35) m/sec
Alley et al (2011)	Prospective study patients presenting for hip fracture repair	217 women > 65 y able to walk before hip fracture.	Gait speed at month 2 0.36 (0.17) m/Sec. Gait speed month 12 0.52 (0.24) m/Sec Standard deviation of gait speed change score ranging from 0.19 to 0.25 m/sec (*) in an analysis stratified for self-reported improvement perception outcome
Hardy et al (2007)	Prospective cohort study without intervention	439 community dwelling adults> 65 y. No use of assisted devices. Gait speed between 0.2 m/sec and 1.2 m/sec	Baseline Gait speed 0.88 (0.24) m/sec 1 year Gait speed 0.91 (0.29) m/sec Change scores 0.03 (0.19) m/sec

Based on the references above, in particular Latham et al (2008), it is anticipated that the difference from baseline in gait speed will have a standard deviation between 0.2 and 0.3 m/Sec.

Assuming that at Week 24 gait speed (change from baseline) difference between bimagrumab and placebo will be 0.15 m/sec and common SD = 0.25 m/sec, then sample size of 70 per group will give a power of 94% using a two-sided test at alpha level = 0.05 (based on testing strategy). The assumed standard deviation of 0.25 is the best available estimate given the literature review.

Short physical performance battery (SPPB)

The other secondary objective is to demonstrate that bimagrumab induces increases in SPPB (change from baseline) compared to placebo at Week 24. Perera et al (2006) estimated that, the meaningful change using effect size analysis, SPPB score changes corresponding to small and moderate effect sizes were 0.54 and 1.34 points respectively. Hence a meaningful difference in SPPB (change from baseline) increase has been identified as being 1.0 point over placebo.

The references in Table 9-3 were consulted in order to understand the variability and magnitude of treatment effect to be anticipated on SPPB in 6 months. Common standard deviation for change from baseline at month 6 in SPPB have been estimated based on 95% confidence interval for the changes from baseline in SPPB from Latham et al (2014). When assuming respective group sample sizes of 95 and 100 and using a multiple imputation technique to address missing data, SD is estimated to 1.5. When assuming respective group sample sizes of 95 and 100 and using a multiple imputation technique to address missing data, SD is estimated to 1.4.

[redacted]

Table 9-3 Key references used to ascertain the variability in SPPB

Reference	Study Design	Population	Information
Latham et al (2008)	Randomized, double-blinded, placebo-controlled trial	Patients>65 years undergoing surgical repair of a hip fracture	SPPB at baseline 4.7 (2.8) SPPB at Week 12 7.9 (2.6)
Latham et al 2014	Randomized, double-blinded, placebo-controlled trial	232 functionally limited older (78-79 years) adults who had completed traditional rehabilitation after a hip fracture	SPPB at baseline 5.9 (2.8). SPPB at Week 24 6.2 (3.0) and 7.2 (3.0) in the placebo and exercise intervention groups, respectively Changes in SPPB from baseline at Month 6 was 0.2 (95% CI 0-0.5) in the control and 1.0 (95% CI 0.8-1.3) in the exercise group
Adunsky et al 2012	Randomized, double-blinded, placebo-controlled trial	123 patients 60+ years old with maximum 4 days after a non-complicated surgical hip fracture repair	SPPB at baseline was 9.1 (2.2) in the treated and 8.9 (2.6) in the placebo group, respectively Changes in SPPB from baseline were 4.5 (2.2) and 3.3 (2.7), respectively

Assuming that at Week 24 SPPB (change from baseline) difference between bimagrumab and placebo will be 1.0 point and common SD = 1.5 point, then sample size of 70 per group will give the power of 97% using a two-sided test at alpha level = 0.05 (based on testing strategy).

Falls

A secondary objective of the study is to evaluate the effects of bimagrumab vs. placebo on the incidence of falls when the primary analysis is conducted. The analysis conducted for falls will include all available information collected in patients including information from visits after Week 24. Patients randomized to the active doses of 700mg and 210mg will be combined and compared to placebo, with the assumption that the differences in the incidences of fall within the bimagrumab doses (700 mg and 210mg) are minimal than the differences with the placebo arm. The annualized placebo fall rate is considered as 30% and a clinically meaningful ratio in the fall rate of the active doses relative to placebo is considered as 0.7 (Gillespie et. al. (2012)).

Table 9-4 shows the power of detecting a significant difference between the active doses of bimagrumab and placebo in falls at Week 24, assuming sample sizes of 140 and 70 patients, respectively, negative binomial rates (Zhu and Lakkis 2014) with over dispersion parameter k=1 and using a two-sided test at alpha level = 0.05. It is also assumed that the average follow-up per patients will be 9 months.

[redacted]

Table 9-4 Power calculation for falls (sample size: BYM combined (210mg and 700mg) arm=140 and Placebo= 70)

Active bimagrumab annual fall rate	Placebo annual fall rate	Rate Ratio	Power, %
0.21	0.30	0.7	16.3
0.15	0.30	0.50	42.9
0.10	0.30	0.33	72.7
0.28	0.40	0.7	19.5
0.20	0.40	0.50	52.0

If the background placebo rate for the incidence of fall is 30% and if the rate reduction for the combined bimagrumab arm is 30% then the study will have less than 20% power. However, if the rate reduction is 67% (assuming the background placebo rate as 30%) then the study will have approximately 73% power.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 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 patients 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 patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient 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 patient 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.

[redacted]

[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(s), consent form updates, patient 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. **Only amendments that are required for patient safety may be implemented prior to IRB/IEC**

[redacted]

approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

[redacted]

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13 Appendix 1: Clinically notable laboratory values and vital signs

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 13-1 Clinically Notable Lab Values and Vital Signs

Laboratory Variable	Notable Criteria
Lipase	≥3x ULN
Amylase	≥3x ULN
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
Vital Signs	
Systolic blood pressure	>180 mm Hg
	<90 mm Hg
Diastolic blood pressure	>100 mm Hg
	<50 mm Hg
Pulse	>100 bpm
	<60 bpm
ECG	
QTcF**	≥450 msec for males
	≥460 msec for females

**Estimated Glomerular Filtration Rate using Modification of diet in Renal Disease (MDRD) equation*

***QT interval with Fridericia correction*

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

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold

[redacted]

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 *

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

Table 14-2 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 • Repeat LFT within 48 hours • 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	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Complete liver CRF	
> 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 syndrome)	• Repeat LFT within 48 hours • If elevation persists, 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) 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)

[redacted]

Criteria	Actions required	Follow-up monitoring
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]