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Novartis Institutes for BioMedical Research

BYM338/Bimagrumab

Clinical Trial Protocol CBYM338X2211

A randomized, subject- and investigator-blinded, placebo-controlled study to assess the safety, pharmacokinetics and efficacy of intravenous bimagrumab in overweight and obese patients with type 2 diabetes

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO & PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

γGT	Gamma-glutamyl transferase
ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatinine kinase
CL	Clearance
CMR	cardiac magnetic resonance imaging
COPD	chronic obstructive pulmonary disease
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization

CT	computerized tomography
CV	coefficient of variation
D5W	Dextrose 5% solution
DMC	Data Monitoring Committee
DPP4	Dipeptidyl peptidase-4 inhibitor

DXA	Dual energy X-ray absorptiometry
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of study
EoT	End of treatment

FBM	fat body mass
FDA	Food and Drug Administration

FPG	Fasting plasma glucose
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
h	hour
HbA1c	glycated haemoglobin test
hCG	Human chorionic gonadotropin

HIV	human immunodeficiency virus
HOMA2-IR	Homeostatic model assessment 2 – insulin resistance

i.v.	intravenous
IA	Interim analysis
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system

kg	kilogram(s)
LBM	lean body mass
LDH	lactate dehydrogenase

LFT	Liver function test

MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities

mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging

MTT	Meal Tolerance Test
NCDS	Novartis Clinical Data Standards
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamic(s)
PG	pharmacogenetics(s)
PK	pharmacokinetic(s)
PoC	Proof of Concept
PRO	Patient reported outcome
QTcF	Fridericia QT correction formula
QUICKI	quantitative insulin-sensitivity check index
RNA	ribonucleic acid
s.c.	subcutaneous
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
sIBM	sporadic inclusion body myositis
S	Source data

SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2D	Type 2 Diabetes
TBL	total bilirubin
TMDD	target mediated drug disposition

ULN	upper limit of normal
US	ultrasound
WHO	World Health Organization
WOC	Withdrawal of Consent

Pharmacokinetic definitions and symbols

Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Ctrough	The trough observed analyte concentration is the concentration that is just prior to the beginning of, or at the end, of a dosing interval
Tmax	The time to reach the maximum concentration after drug administration [time]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
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 other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further

	assessments are planned
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc
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
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol synopsis

Protocol number	CBYM338X2211
Title	A randomized, subject- and investigator-blinded, placebo-controlled study to assess the safety, pharmacokinetics and efficacy of intravenous bimagrumab in overweight and obese patients with type 2 diabetes
Brief title	Safety, pharmacokinetics and efficacy study of bimagrumab in overweight and obese patients with type 2 diabetes
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug, Diet, and Moderate exercise
Study type	Interventional
Purpose and rationale	The main purpose of this study is to evaluate the efficacy of bimagrumab to decrease total body fat and improve glycemic control by improving insulin sensitivity in overweight and obese subjects with type 2 diabetes. This study will enable decision making for the development of bimagrumab in overweight and obesity and/or metabolic indications.
Primary Objective(s)	To evaluate the treatment effect of bimagrumab on total body fat mass.
Secondary Objectives	To evaluate the treatment effect of bimagrumab on total body fat mass after 6 months of treatment. To evaluate the treatment effect of bimagrumab on glycemic control and parameters of insulin sensitivity. To evaluate the safety and tolerability of bimagrumab in overweight and obese subjects with type 2 diabetes. To evaluate the pharmacokinetics of repeat doses of bimagrumab in overweight and obese subjects with type 2 diabetes. To evaluate the immunogenic response to repeat dosing of bimagrumab in overweight and obese subjects with type 2 diabetes. To evaluate the treatment effect of bimagrumab on anthropometric body measurements and on lean body mass.
Exploratory Objectives	Company Confidential Information

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Study design	This is a randomized, subject and investigator blinded, placebo-controlled, parallel arms study, investigating a 48-week treatment period with intravenous bimagrumab in overweight and obese subjects with type 2 diabetes. Approximately 68 subjects are planned to be enrolled and randomized. Company Confidential Information Eligible subjects will be randomized in a 1:1 ratio to bimagrumab or placebo.
Population	Approximately 68 overweight and obese subjects (BMI: 28-40 kg/m^2 inclusive) with type 2 diabetes Males and females between the ages of 18-75 years inclusive
Key Inclusion criteria	• Male and female, age 18 to 75 years (inclusive), in stable health condition as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening. • Type 2 diabetes, with an HbA1c between 6.5% and 10% (inclusive) at screening • On any one of the following anti-diabetes regimens with stable treatment for approximately 3 months prior to randomization: 1) metformin monotherapy; 2) DPP4 inhibitor agent monotherapy; 3) combination therapy of metformin and DPP4 inhibitor agent; 4) no anti-diabetes therapy. • Body mass index (BMI) of 28.0 to 40.0 kg/m2 (inclusive) at screening. • Body weight between 65 and 140 kg (inclusive) at screening, and with a stable body weight (±5 kg) by history (patient report) and stable physical activity within 3 months prior to screening.
Key Exclusion criteria	• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation confirmed by a positive hCG laboratory test. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 6 months after stopping of investigational drug. • Diabetes other than type 2 such as type 1 diabetes, surgically induced-diabetes; "brittle" type 2 diabetes as per investigator judgment, history of severe hypoglycemic episodes in the year preceding screening, or hypoglycemic unawareness. Company Confidential Information
Study treatment	• Bimagrumab (BYM338) • Placebo

Efficacy/PD assessments	• DXA scan for whole body, trunk, appendicular fat and lean mass • HbA1c, HOMA2-IR, QUICKI and Matsuda Index for glycemic response • Anthropometric measurement of fat by weight, body mass index (BMI), waist circumference; hip circumference; waist to hip ratio Company Confidential Information
Key safety assessments	• Adverse events • Physical exam • Vital signs • Laboratory evaluations • ECG • Urinalysis
Other assessments	• PK samples Company Confidential Information • IG (immunogenicity) Company Confidential Information • Dietary intake – including but not limited to total calories, protein, fat, carbohydrate. Company Confidential Information
Data analysis	The primary aim of the study is to assess the effect of bimagrumab on body fat mass at Week 48 of the treatment period compared to baseline. The study design enables evaluation of efficacy based on the following dual criteria: 1) statistical significance (superior treatment effect, 1-sided 10% level) in fat mass; **and** 2) clinical relevance of the change in fat mass (median treatment effect of at least 5%). Weight loss of 5% has been shown to translate into clinical benefit in an overweight and obese population with T2D. Fat mass loss of a similar magnitude to 5% weight loss is expected to translate into similar clinical benefits, (such as on glycemic control) in a similar population. The randomization will be stratified by BMI category (>=28.0 kg/m^2 and <=33.0 kg/m^2, or >33.1 kg/m^2 to <=40.0 kg/m^2) in order to achieve an approximate balance of BMI distribution across the two treatment groups. The cutoff value of 33 kg/m^2 represents the expected median BMI in the population based on internal data; therefore, the two randomization strata are expected to be of similar size. However, equal size strata will not be enforced. A minimum of 10 subjects will be targeted for enrollment in the smaller stratum to ensure acceptable precision of the treatment effect in both strata (see Section 11.7). A longitudinal model describing fat mass over time will be used, using all of the data collected from both randomization strata and adjusting for baseline fat mass, treatment arm, baseline BMI. Variables indicating time and time by treatment interaction will be included. An unstructured within-subject covariance will be used. The change in fat mass at Week 24 will be estimated from that model. In addition, the proportion of subjects reaching at least 5% fat loss at Week 24 will be presented by treatment

	group.
Key words	Bimagrumab, type 2 diabetes, obesity, myostatin, MRI, DXA

1 Introduction

1.1 Background

More than just a consequence of poor lifestyle choices, obesity is now viewed as a disease that is complex, multifactorial, chronic and resistant to many forms of treatment (Mechanick et al 2016). Obesity is a risk factor for increased overall mortality and is estimated to have caused 3.4 million deaths worldwide in 2010 (Lim et al 2012). Many co-morbidities are associated with obesity, such as type 2 diabetes, hypertension, dyslipidemia and coronary heart disease (Apovian et al 2015). A body weight reduction of 5-10% has been associated with significant and clinically meaningful improvements in insulin sensitivity, glycemic control, hypertension and dyslipidemia (Goldstein 1992; Vidal 2002; Van Gaal et al 2005).

There are no approved obesity interventions that preserve or build lean mass while promoting fat mass loss.

The activin type 2 receptors (ActRIIA and ActRIIB, collectively abbreviated as ActRII) modulate signals for ligands belonging to the transforming growth factor beta (TGF-β) superfamily such as myostatin, GDF-11, and activin. Myostatin, activin A, and GDF-11 are negative regulators of skeletal muscle growth, acting via the ActRII receptor signaling pathway to inhibit muscle protein synthesis and myocyte differentiation and proliferation. Blockade of these ligands' action through blockade of ActRII is known to increase skeletal muscle mass, which in turn is hypothesized to improve peripheral insulin sensitivity, since skeletal muscle is one of the major glucose utilizing tissues in the body. Inhibition of ActRII with an antibody has been shown to reduce white adipose tissue in mice on a normal or high-fat diet, while increasing skeletal muscle mass, potentially by inducing a functional increase in brown fat (Fournier et al 2012).

Bimagrumab (BYM338), a recombinant human, monoclonal antibody, binds competitively to ActRII with greater affinity than its natural ligands. Bimagrumab is in development for muscle wasting indications and has resulted in a significant increase in skeletal muscle mass in healthy volunteers, in patients with sporadic inclusion body myositis (sIBM), and in patients with sarcopenia. Bimagrumab single dose resulted in a profound impact on body composition with a maximal reduction in fat mass of ~ 8% and an increase in lean mass of ~ 3% (DXA), in overweight and obese pre-diabetic patients. The net effect on total body weight was neutral. Insulin sensitivity was improved by ~ 18% as measured with a two-step hyperinsulinemic euglycemic clamp. This effect was associated with an absolute reduction in HbA1c of 0.2%, an effect size which has been associated with prevention of progression to diabetes in a similar population (DeFronzo et al 2011, Knowler et al 2002).

The current study is designed in overweight and obese individuals with type 2 diabetes to evaluate the effect of bimagrumab on body composition and to enable evaluation of the metabolic impact of these changes on metabolic parameters. The intent is to evaluate whether loss of fat mass along with increased lean mass will favorably improve glycemic control. In addition, the impact of adiponectin, levels of which might increase in response to the enhanced muscle growth resulting from ActRIIB blockade (Suzuki et al 2008), on liver fat

and abdominal fat contents (through an hepatic insulin-sensitizing effect, enhanced fat oxidation and reduced lipid synthesis) will be studied.

1.1.1 Relevant data summary

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1.2 Nonclinical data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

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1.3.2 Human pharmacokinetic data

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1.3.3 Human pharmacodynamic data

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1.4 Study purpose

The purpose of this study is to enable decision making for the development of bimagrumab in overweight/obesity and metabolic indications.

2 Study objectives and endpoints

2.1 Primary objective

Primary objective	*Endpoints related to primary objective*
• To evaluate the treatment effect of bimagrumab on total body fat mass	• Body fat mass by DXA at Week 48

2.2 Secondary objectives

Secondary objectives	*Endpoints related to secondary objectives*
• To evaluate the treatment effect of bimagrumab on total body fat mass after 6 months of treatment	• Body fat mass by DXA at Week 24

Secondary objectives	***Endpoints related to secondary objectives***
• To evaluate the treatment effect of bimagrumab on glycemic control and parameters of insulin sensitivity.	• HbA1c, fasting glucose and insulin, HOMA2-IR, QUICKI, Matsuda index based on MTT at Week 24 and Week 48.
• To evaluate the safety and tolerability of bimagrumab in overweight and obese subjects with type 2 diabetes.	• Adverse events, Vital Signs, ECG, Laboratory Values, Immunogenicity.
• To evaluate the pharmacokinetics of repeat doses of bimagrumab in overweight and obese subjects with type 2 diabetes.	• PK samples – pre (Ctrough) and post dose during treatment and follow-up periods. Tmax and Cmax (Day 1, Day 168 and Day 308) will be derived.
• To evaluate the immunogenic response to repeat dosing of bimagrumab in overweight and obese subjects with type 2 diabetes.	• Anti bimagrumab antibodies pre-dose, during treatment and at the end of study.
• To evaluate the treatment effect of bimagrumab on anthropometric body measurements and on lean body mass.	• Body weight, BMI, waist circumference, waist-to-hip ratio, lean body mass (LBM) by DXA at Week 24 and at Week 48.

2.3 Exploratory objectives

3 Investigational plan

3.1 Study design

This is a non-confirmatory, randomized, subject and investigator blinded, placebo-controlled, parallel arm study, investigating a 48-week treatment period with i.v. bimagrumab 10 mg/kg in overweight and obese subjects with type 2 diabetes. Approximately 68 subjects are planned to be enrolled and randomized

Screening (Days -21 to -8)

Potential subjects will undergo an onsite screening visit to determine their eligibility for the study (see enrollment criteria Section 4). Subjects who qualify for enrollment following screening will be scheduled for baseline assessments.

The investigator must recommend a lifestyle intervention (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2008) that includes dietary counseling for weight loss with a daily caloric deficit of approximately 500 kcal, with a diet that follows the American Diabetes Association (ADA) guidance for optimal glycemic control, and with protein intake of at least 1.2 g/kg/day to support muscle anabolism.

Subjects must be encouraged to follow a diet containing approximately 45-50% of calories as carbohydrate, 20-25% protein, and 30% fat. Subjects will receive counseling for physical activity and will be encouraged to follow the ADA walking program guidelines (please refer to the SOM). These interventions will be initiated at screening after eligibility is confirmed.

Baseline (Days -7 to -1)

Prior to dosing (Day 1), subjects who are eligible for enrollment following screening will return to the clinic to undergo baseline assessments as defined in Section 8.1

(Assessment schedule). To facilitate study conduct, subjects may opt to be domiciled on Day -1 to complete baseline assessments prior to dosing on Day 1. Subjects will receive a mobility tracker device to monitor their physical activity.

Randomization and Dosing (Day 1)

Eligible subjects, based on screening and baseline assessments, will be randomized in a 1:1 ratio to receive either bimagrumab or placebo. Randomization will be stratified according to baseline BMI into 2 strata:

- BMI between 28.0 kg/m^2 and 33.0kg/m^2 (inclusive) and
- BMI above 33.1 kg/m^2 and up to 40.0 kg/m^2 (inclusive).

Administration of bimagrumab or placebo will be done via an intravenous infusion over 30 minutes, followed by approximately 15 minutes for flushing and then an observation period that will include safety and tolerability and PK sampling. Following all assessments, subjects may be discharged from the Investigator site when the Investigator judges them to be medically stable, in good general health and not needing further observation.

Treatment period (Days 1 - 336)

Subjects should continue on anti-diabetes background therapy as per eligibility criteria (see Section 4.1) throughout the study. If, however, during the course of the study, a subject experiences an improvement or a deterioration of his/her glycemic control, modification of his/her background therapy can be made as defined in Section 6.4 (Background therapy dose adjustments).

Administration of bimagrumab or placebo will be done via an intravenous infusion over 30 minutes followed by 10 to 20 minute observation period once every 4 weeks for a total of twelve doses. Bimagrumab will be dosed based on body weight at 10 mg/kg, with a dose cap of 1200 mg for body weight equal to and above 120 kg. Placebo will be provided by the site as 5% Dextrose solution (D5W) (see Pharmacy Manual for more details).

Subjects will receive regular monitoring and advice on diet and physical activity as part of their monthly site visits (please refer to Section 8.1 (Assessment schedule)) throughout the study, and will be contacted by telephone, or scheduled for an in-person assessment, once between each monthly site visit to provide a 24-hour dietary recall. Additional methods for promoting weight loss may be incorporated into or used in place of standard clinical care; these methods may include the use of electronic tools for reporting dietary intake, weight or physical activity, and for receiving feedback on weight trends and lifestyle changes.

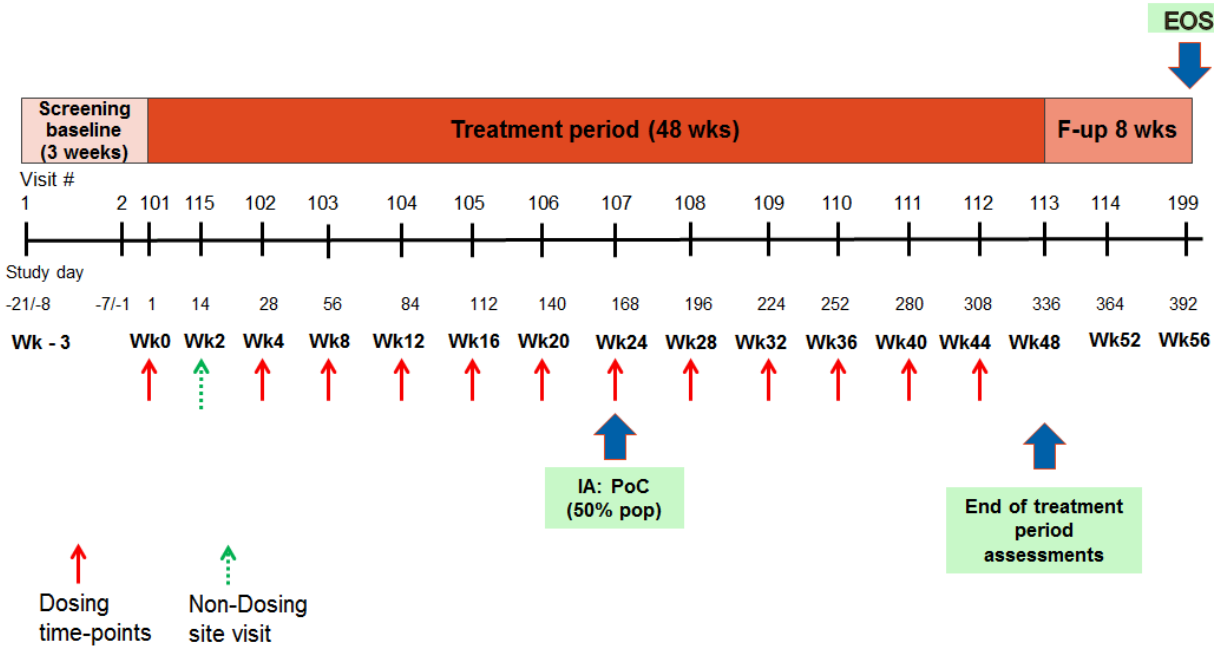
Subjects will be asked to return to the Investigator site for dosing approximately every 4 weeks during the treatment period. During these visits, subjects will be evaluated for safety, tolerability, PK and efficacy. The specific assessments for each of these visits are detailed in Section 8.1 (Assessment schedule).

The treatment period will end approximately 4 weeks after the last dose administration.

Follow Up (Days 364 -392)

After completion of the treatment period, subjects will have a follow-up period of 8 weeks with regular monitoring for safety and efficacy beginning at Week 48 and continuing until the end of study visit (EOS) which will take place 12 weeks after the last study drug administration. The specific assessments for the follow up and end of study visits are detailed in Section 8.1 (Assessment schedule).

Figure 3-1 Study design



3.2 Rationale for study design

The rationale for key elements of the study design include:

- **Randomization**: To decrease the chance of an imbalance in subject characteristics (e.g., age, BMI) between treatment groups.
- **Stratification:** BMI was selected as a stratification parameter as it is an important predictor of response for parameters of body composition/body weight and HbA1c (internal data). The expected median value for BMI in this subject population is 33 kg/m^2 (internal data), therefore 2 strata above and below/inclusive of the median will ensure a balanced representation of subjects between placebo and active drug in each strata, i.e. strata of approximately similar size between the 2 arms.
- **Subject- and investigator-blinding**: To mitigate the risk of bias in treatment allocation, reporting and causality assessment of adverse events. Furthermore, this design decreases the potential confounding effect of intentional or unintentional behavioral changes made by subjects who are aware of their treatment assignment

- **Placebo arm**: Inclusion of a placebo group will allow the analysis of whether or not bimagrumab treatment is more effective than a standard treatment approach based on lifestyle intervention.
- **Lifestyle interventions:** Trials with anti-obesity agents have to demonstrate treatment benefits on body weight/composition on a background of first line-therapy with lifestyle interventions. The daily caloric deficit of 500 Kcal with approximately 45-50% calories from carbohydrate, 20-25% from protein and 30% from fat is a standard approach and is expected to induce weight loss over the treatment period. It may also enhance the effect of bimagrumab on body composition and body weight. The American Diabetes Association (ADA) walking program is tailored to the type of population in this study and is a gentle, easy to implement approach for physical activity.

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Electronic methods to support participants in making behavioral changes to promote weight loss may also be utilized.

- **Adequate protein intake:** Protein content of 1.2 g/kg/day is recommended to ensure adequate dietary intake during the period of muscle growth.
- **Standard of care diabetes therapy:** Subjects will remain on their standard of care treatment for diabetes, enabling the evaluation of added treatment benefit with bimagrumab on glycemic parameters. Anti-diabetes therapy is restricted to metformin and/or DPP4 inhibitors, as these medications are less likely to affect body weight and thus confound the study results.

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

Dose rationale

In healthy volunteers (HV) and sIBM patients, a 10 mg/kg dose of bimagrumab was shown to provide exposure levels (i.e. above 10 µg/mL) at which the anabolic effect is observed and maintained over dosing intervals of 4 weeks [CBYM338X2102 (N=6 subjects), CBYM338X2104 (N=47 subjects)], for up to six doses [CBYM338X2109 (N=35 subjects)] Company Confidential Information . The threshold for minimal target exposure for bimagrumab is approximately 10 µg/mL, a concentration below which nonlinear clearance is observed, suggesting loss of full receptor saturation and target-mediated drug disposition. In clinical studies to date, bimagrumab concentrations approximately at or above 10 µg/mL for at least 4 weeks in HV and more than one year in sIBM patients have been safe, well tolerated, and have demonstrated an increase in thigh muscle volume. The 26-week toxicology studies in cynomolgus monkeys showed a chronic exposure at NOAEL (300 mg/kg/week) of approximately 300-fold and 55-fold for AUC and Cmax, respectively, when compared to human exposures at 10 mg/kg at steady state.

Dosing in this study is weight-based for subjects with body weight up to 120 kg, and is capped at 1200 mg for subjects with body weight between 120 kg and 140 kg.

Body-weight based dosing has proven to reduce variability in exposure in subjects/patients, and will be implemented as applicable. Capped dose is selected for body weights > 120 kg because of the uncertainty of the effect of large body weight and body composition (% fat mass vs. % lean mass) on the exposure and safety profile of bimagrumab.

To date, the pharmacokinetic data is limited in obese subjects, and the maximal body weight in dosed subjects has been 116 kg, in studies conducted with bimagrumab in overweight to obese subjects with insulin resistance (N=10), and obese healthy subjects (N=6).

The maximal amount of bimagrumab administered to-date is 3500 mg (at a dose of 30 mg/kg), given i.v. and as a single dose for a maximal body weight of 116 kg. This dose did not show over-exposure and caused no safety concerns.

A capped dose for these subjects is selected to avoid over-exposure and to maintain bimagrumab levels around the threshold for safe anabolic effects over 4-week dosing intervals. Specifically, the selected amount of 1200 mg translates to a body weight based dose ranging from 10 to 8.6 mg/kg for the body weight range of 120-140 kg, which is predicted to result in exposure levels within the safe and efficacious range for bimagrumab and with minimal risk of over-exposure.

Rationale for duration of treatment

A treatment duration of 48 weeks is selected to capture the temporal profile as well as maximal effect of bimagrumab on body fat mass. While a ceiling effect is typically observed on lean mass gain with bimagrumab, the loss of fat mass does not seem to plateau over a period of 24 weeks and even up to 64 weeks (Internal data).

Rationale for follow-up period

An off-drug follow-up period is included to monitor the durability of treatment effect of bimagrumab on body fat mass, lean mass and glycemic control once off treatment. The EOS visit being performed 12 weeks after the last administration covers the wash-out period of bimagrumab exposure associated with anabolic effect (approximately 8 weeks).

3.4 Rationale for choice of comparator

A placebo will be used as a comparator in this study based on the following rationale:

- A placebo comparator is needed to assess bimagrumab efficacy over the standard treatment approach based on lifestyle intervention. Also a placebo comparator does allow maintaining the double blind design.

3.5 Rationale for choice of background therapy

This trial in overweight or obese patients with T2D has the primary goal of assessing the effect of bimagrumab on body composition.

While improvement in glycemic control may occur as a result of improved body composition, subjects should maintain their background T2D therapy throughout to avoid deterioration in glycemic control. If, however, improvement in glycemic control is observed during the study, reduction in or discontinuation of anti-diabetic treatment is allowed under the guidance of a medical professional to prevent hypoglycemia as specified in Section 6.4. T2D treatment is restricted to specific anti-diabetes therapy for homogeneity of the study population and to enable interpretability of the data. Anti-diabetes therapy is restricted to classes with minimal effect on body weight, including metformin, a first line therapeutic agent, and/or DPP4 inhibitors. Management of background therapy, including the potential need for managing worsening glycemic control, is presented in Section 6.4.

3.6 Purpose and timing of interim analyses/design adaptations

3.7 Risks and benefits

3.7.1 Potential benefits

Based on preliminary clinical data in a pre-diabetic population, bimagrumab is expected to result in improved body composition, with higher lean body mass and lower fat mass. Bimagrumab may also result in improved insulin sensitivity and glucose control during the trial. Although in a previous study in mostly overweight subjects, the effect of bimagrumab on body weight was neutral, in the presence of a negative energy balance and with a longer treatment period, bimagrumab may also induce body weight loss. All subjects enrolled in the study may benefit from the lifestyle interventions including diet and physical activity, and regular monthly visits.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and stopping rules.

There may be unknown risks of bimagrumab, which may be serious.

3.7.2 Bimagrumab related risks

Acne

Data from the prior proof of concept study in older adults with sarcopenia reported an incidence of acne in 10.5% (2/19) of patients administered two doses of 30 mg/kg bimagrumab.

Program-wide, single and multiple dose studies in healthy volunteers and patients with sarcopenia, sIBM and COPD cachexia demonstrated the occurrence of diffuse, transient acne on the face and scalp and less frequently on the back and chest in 18.3% of the population.

Earlier studies showed an increased incidence with the highest doses (Table 3-1). Conversely, acne was not observed in the multiple dose study (CBYM338X2102) after three i.v. doses of 3 or 10 mg/kg every 4 weeks.

Acne has been confirmed in these studies by dermatology consult and biopsy. 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 recommended. However, early standard of care intervention is recommended in participants when acne presents.

Further analysis of skin reactions and their association with preexisting conditions, bimagrumab PK parameters, time to appearance from dosing and time to resolution will be performed in current and future studies. A possible mechanistic link between bimagrumab and skin reactions remains unclear.

Table 3-1 Skin reactions considered possibly related to bimagrumab from unblinded data*

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Muscle Symptoms

Involuntary muscle contractions, referred to as cramps, spasms or twitches, have been reported by participants in early studies receiving single or multiple doses of bimagrumab (Table 3-2).

The dose-frequency of muscle symptoms is not linear. In the multiple dose study, spasms were reported by one (of six) subjects receiving three i.v. doses of 3 mg/kg, and six (of six) receiving 10 mg/kg and four (of six) in the combination i.v. and s.c. cohort (greatest drug exposure). Most muscle spasms throughout the clinical study program have been mild in intensity, transient, painless, of short duration, and did not require medical treatment. Several cases of muscle spasms were moderate in severity.

In early studies, a smaller percentage of muscle symptoms were seen in older healthy volunteers 70-83 years of age than in young and middle aged adults. A case of spasm was reported by one subject (of 6) that received 3 mg/kg, while no cases were reported in the group receiving 30 mg/kg.

The etiology and clinical meaning of these observations are not known. Similar symptoms have been reported with at least one other anabolic molecule, a beta-2 adrenergic agonist (Tomlinson et al 1990) and are commonly reported by adults performing muscle building exercise. Data on twitches and the effects on people receiving bimagrumab are detailed in the Investigator's Brochure.

Table 3-2 Muscle symptoms considered possibly related to bimagrumab from unblinded data*

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Reproductive organs

Data from CBYM338X2108 demonstrate no clinically or statistically significant effect of bimagrumab on circulating testosterone levels and no effect on the pituitary-gonadal or pituitary-adrenal axes in either gender. Suppression of FSH levels in postmenopausal women and premenopausal women of non-childbearing potential has been observed with no associated safety risk identified. All effects were transient and resolved after bimagrumab exposure ended. Semen analysis data from the multiple dose study suggest that three doses of 10 mg/kg have no effect on sperm count or quality in males.

Women of childbearing potential may participate in this study as long as they use highly effective contraception as detailed in Section 4.2 (Exclusion criteria).

Immunogenicity

It is possible that anti-drug antibodies could develop against bimagrumab, which could neutralize or clear the drug more rapidly and attenuate its efficacy. A treatment related anti-drug antibody response has been observed in subjects treated with bimagrumab although it should be noted that high exposure to bimagrumab may mask the presence of an immune response. Nevertheless, there was no evidence of an infusion or hypersensitivity reaction that could be related to immunogenicity or any sign of immune complex formation in the clinical trials performed so far. No positive signal in the immunogenicity assay was accompanied by a change in the bimagrumab PK profile.

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.

As of 1 September 2018 there have been two confirmed cases of acute pancreatitis among approximately 1038 participants administered bimagrumab. There is no known association among participants receiving bimagrumab between the temporary elevations in lipase and/or amylase and an increased risk for pancreatitis. However, to reduce the potential risk of elevated pancreatic enzymes to study participants, volunteers with elevated amylase and lipase will be excluded as per Section 4.2.

Participants will be monitored throughout the study as detailed in the Assessment schedule. Safety monitoring guidance for participants who experience elevated lipase and/or amylase during the study is provided in Section 9.4.

3.7.3 Blood sample volumes

A maximum of 500 mL of blood is planned to be collected from each subject during the study over a period of 392 days (56 weeks). Additional samples for monitoring of any safety findings are not included. Blood collection is not considered to be a risk for this population.

During the collection of blood samples, subjects may experience pain and/or bruising at the insertion site of the needle/catheter. Although rare, localized clot formation, infections and nerve injury may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw. Patients will be observed following all blood draws and discharged only when the Investigator observes stable health status. In addition, liquids by mouth in the form of water, fruit juice or a similar product will be provided following the blood draw to replenish the blood volume removed.

Timings of blood sample collection are outlined in the Assessment Schedule, Section 8.1. A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage and shipment information.

See Section 8.9 regarding the potential use of residual samples.

3.7.4 Trial-related risks

Infusion risks

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

Diet-related

The daily caloric deficit of 500 Kcal with approximately 45-50% calories from carbohydrate, 20-25% from protein and 30% from fat is a standard approach and is expected to induce weight loss of approximately 450 gr (1 pound) per week over the treatment period. It may also enhance the effect of bimagrumab on body composition and body weight. The anabolic effect of bimagrumab requires adequate protein intake. Given the daily caloric deficit, the protein intake is increased to 1.2 g/kg/day to ensure an adequate protein supply for increasing lean mass.

A daily multivitamin/multimineral supplement is also recommended to ensure adequate intake of micronutrients involved in protein synthesis and glucose regulation. Over-the-counter supplements will be recommended at doses commonly consumed and recommended by recognized authoritative scientific bodies (for example, the US Institutes of Medicine). No adverse effects are anticipated.

Exercise-related

The ADA walking program is tailored to the type of population in this study and is a gentle, easy to implement approach for physical activity.

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No adverse effects are anticipated.

Imaging

Dual-Energy X-ray Absorptiometry (DXA)

This clinical study involves exposure to radiation from a DXA total body scan. The radiation exposure by DXA is not necessary for medical care but is intended for research purposes only. The effective dose of a DXA whole body scan on an adult is 2.1 microSv. Therefore, the total amount of radiation exposure per subject from five DXA scans will be about 10.5 microSv. This amount of radiation is equivalent to approximately 14 days of background exposure (approx. 0.03 microSv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be minimal (Albanese et al 2003). Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired (Stabin 2008). DXA measures are described as having no observable or biological effect and are similar to natural background levels of radiation in most countries; the study scans pose no safety risk.

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4 Population

Approximately sixty-eight (68) overweight/obese men and women 18-75 years old (inclusive) with type 2 diabetes will be enrolled in the study.

The investigator must ensure that all subjects being considered for the study meet the eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

4.1 Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female, age 18 to 75 years (inclusive), in stable health condition as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
3. Type 2 diabetes, with an HbA1c between 6.5% and 10% (inclusive) at screening.
4. On one of the following anti-diabetes regimens with stable treatment for approximately 3 months prior to randomization: 1) metformin monotherapy; 2) DPP4 inhibitor agent monotherapy; 3) combination therapy of metformin and DPP4 inhibitor agent; 4) no anti-diabetes therapy.
5. Body mass index (BMI) of 28.0 to 40.0 kg/m^2 (inclusive) at screening.
6. Body weight between 65 and 140 kg (inclusive) at screening, and with a stable body weight (±5 kg) by history (patient report) and stable physical activity within 3 months prior to screening by history (patient report).
7. Able to communicate well with the investigator; to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Conditions related to safety:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception until the termination of gestation, and confirmed by a positive hCG laboratory test at screening.
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant **unless** they are using highly effective methods of contraception during dosing and for 6 months after stopping of investigational drug. ***Highly effective contraception methods include:***
   - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject.
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

   In the case of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking the investigational drug.

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 been sterilized as specified above.

3. Any chronic active infection (e.g., HIV, hepatitis B or C, tuberculosis, etc) or has received anti-HCV treatments within the previous 6 months. Patients receiving chemoprophylaxis for latent tuberculosis infection are eligible for the study.
4. History of or known hypersensitivity to monoclonal antibodies or drugs similar to the study drug.
5. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.
6. Chest pain, severe shortness of breath, or occurrence of other safety concerns during the screening or baseline assessments.

Diabetes related conditions:

7. Diabetes other than type 2, such as type 1 diabetes, surgically induced-diabetes, "brittle" type 2 diabetes as per investigator judgment, history of severe hypoglycemic episodes in the year preceding screening, known hypoglycemic unawareness.

Liver or pancreas related conditions:

8. Abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin (except Gilbert's Disease), or abnormal lipase and/or amylase. The investigator should be guided by the following criteria:
    a. Any single transaminase may not exceed 3x the upper limit of normal (ULN).
    b. A single parameter elevated up to and including 3x ULN should be re-checked as soon as possible, and always prior to enrollment/randomization, to rule out any laboratory error.
    c. If the total bilirubin concentration is increased above the ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27μmol/L).
    d. Screening or baseline levels of lipase and/or amylase ≥ 2x ULN are exclusionary. Initial tests in either lipase or amylase of ≥ 2x ULN should be re-checked as soon as possible to confirm lab values, and **must** be available prior to randomization. Patients with confirmed lipase and/or amylase ≥ 2x ULN at screening or baseline are excluded.
9. Known history or presence of severe active acute or chronic liver disease (e.g., cirrhosis) or conditions with hepatotoxic potential (e.g. known gallbladder or bile duct disease, acute or chronic pancreatitis, or exocrine pancreatic insufficiency).

Other conditions:

12. Any medical condition or laboratory finding during screening (e.g. an unexplained or clinically significant laboratory result), which, in the opinion of the investigator, may interfere with participation in the study, might confound the results of the study, or pose an additional safety risk in administering bimagrumab.
13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
14. Active alcohol or drug abuse, or participation in an alcohol or drug treatment program within 1 year prior to screening. Subjects having successfully completed an alcohol or drug treatment program > 1 year prior to screening with sustained abstinence may be eligible.
15. Confirmed diagnosis of current, significant psychiatric disease (e.g. dementia, Alzheimer's disease, schizophrenia, depression or bipolar disorder). Individuals with adequately treated depression and stable treatment at least 3 months prior to screening are eligible for enrollment.
16. Chronic kidney disease [estimated glomerular filtration rate (GFR) < 30 mL/min].
17. Patient plans to move out of the study area within 12 months, or be out of the study area for > 4 weeks, continuously.
18. History of any type of bariatric procedure.

Temporary Exclusion criteria:

Subjects excluded for one of the temporary medical conditions listed below may be rescreened after a period that is considered clinically relevant by the investigator. The subject will need to re-sign informed consent and the full screening visit must be repeated under a new subject number.

20. Use of prohibited medications (found in Section 5.2).
21. Significant acute illness such as urinary tract infection or upper respiratory tract infection which has not resolved within two (2) weeks prior to screening.

22. Men with low fasting morning testosterone (<250 ng/dl) at screening; men receiving testosterone replacement therapy for low testosterone are eligible if on a stable dose of testosterone for a minimum of 3 months and if their testosterone level is in the normal range on 2 consecutive tests at least one month apart and not more than 6 months apart, the second one being performed at screening.
23. Systolic blood pressure > 180 or < 90 mmHg or diastolic blood pressure > 100 or < 50 mmHg at screening or baseline.
24. Currently enrolled in, or discontinued within the last 30 days (or 5 half-lives of enrollment or until PD effect is expected to return to baseline, 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.
25. Uncontrolled thyroid disease. Hypothyroid subjects with euthyroidism on stable thyroid replacement therapy for at least 3 months prior to screening are allowed.
26. Significant change in cigarette smoking within 3 months of screening, as judged by the investigator.
27. Use of any anti-obesity medications, nutritional supplements or over the counter products for weight loss within 3 months of screening. Use of medications known or suspected to induce weight gain, such as some anticonvulsant and psychotropic medications (excluding anti-depressant medication, refer to point 15) within 3 months of screening.
28. Use of skeletal muscle anabolic agents in any form such as medications, hormones (except stable testosterone replacement therapy for at least 3 months for hypogonadal men), over the counter products and nutritional supplements (other than protein) that are labeled as muscle anabolic agents for 3 months prior to screening.
29. Any dietary intervention, new exercise regimen or lifestyle modifications targeted for weight loss or diabetes control started within 3 months of screening.

Refer to Section 8.3 (Subject Screening) for information regarding re-screening.

Refer to Section 8.6 for a complete list of safety assessments.

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

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of childbearing potential are eligible for this study if they use highly effective methods of contraception during dosing and for 6 months after stopping study medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should be stable on the same contraceptive medication for a minimum of 3 months before taking study treatment.

Men are not required to use contraception because of the large size of the antibody which does not penetrate the blood-testes barrier.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

5.2 Prohibited treatment

- Use of skeletal muscle anabolic agents in any form such as medications, hormones, over the counter products and nutritional supplements (other than protein) that are labeled as muscle anabolic agents.
- Anti-obesity medications, nutritional supplements, dietary interventions other than described in the protocol, or over the counter products for weight loss.
- Chronic systemic steroid treatment or systemic steroids for > 7 consecutive days for worsening of an underlying condition are not allowed during the study and within 4 weeks of screening.
- Any anti diabetic medication other than metformin or DPP4 inhibitor agent. Injectable drugs such as exenatide or pramlintide are prohibited; insulin is allowed for up to one week at a time to correct for acute hyperglycemia.
- Any product or medication known or suspected to cause weight gain, unless it is a stable anti-depressant therapy for at least 3 months before screening.

5.3 Dietary restrictions and smoking

Patients will be counseled to follow a modest calorie restricted diet with a daily deficit of approximately 500 kcal and approximately 45-50% calories from carbohydrate, 20-25% from protein and 30% from fat intake throughout the study, in keeping with guidelines for daily recommended protein intake (at least 1.2 g/kg/body weight) for anabolism (WHO guidelines 2015). The amount of calories will be determined by a dietitian or physician for every patient according to their height, weight and calculated basal metabolism. A copy of

the diet with content and nutritional information will be provided to the Sponsor prior to study start upon request.

Once enrolled and throughout the study period, site personnel will query study patients to determine if there has been a change in dietary habits and to encourage dietary intake that will promote weight loss. Dietary monitoring will occur via:

- Monthly dietary counseling visits at which time a 24 hour recall will be obtained
- Collection of 3-day food records at 3 time points during the study
- One telephone or in-person contact per month, approximately midway between counseling visits, to obtain a 24-hour dietary recall and reinforce lifestyle intervention.

Subjects will be advised to consume a daily multivitamin/multimineral supplement.

Smoking is discouraged but not prohibited for participation in this trial. Patients should refrain from smoking for one hour prior to study visits and during the study visits.

On Day 1, no breakfast will be provided. Meals should be similar in caloric content and macronutrient distribution for all patients on the day of dosing.

5.4 Other restrictions

On any visit day where fasting is required, patients should withhold their anti-diabetic medication until after study blood draws are completed, ideally before 10 AM. Additionally, patients should restrict alcohol consumption for 24 hours prior to visits at which the lipid profile will be assessed.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual and Pharmacy Manual.

Refer to Section 5.3 'Dietary restrictions and smoking' for details of dosing and food intake.

6.1.1 Investigational treatment and control drugs

The investigational drug, bimagrumab, 150 mg LIVI (liquid in vial), will be prepared by Novartis and supplied to the Investigator site as open labeled bulk medication. Study drug preparation will be detailed in a separate pharmacy manual. Placebo will be a D5W infusion supplied by the site.

Table 6-1 Overview of study medication

Study drug name	Formulation	Appearance *(e.g., approximate size, color, etc.)*	Packaging	Provided by
BYM338 (bimagrumab)	liquid in vial	water infusion	open labeled bulk medication	Novartis
Placebo	Liquid	water infusion		Site

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

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

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

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.1.2 Additional study treatment

Not applicable.

6.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1.

Study treatments are defined as:

- Bimagrumab 10 mg/kg up to maximum 1200 mg, every 4 weeks (12 doses)
  Placebo, every 4 weeks (12 doses)

6.3 Permitted dose adjustments and interruptions of study treatment

Dose adjustments are not permitted.

6.4 Background therapy dose adjustments

Adjustments of T2D background therapy are allowed, according to the standard of care, but are restricted to the following:

- Either increased or decreased dosage, or discontinuation, of current medication is allowed under the guidance of a medical professional;
- The add-on of a second medication is allowed but restricted to metformin or DPP4-inhibitor;
- Insulin, as an acute treatment for severe or uncontrolled hyperglycemia, such as during an acute illness, is allowed but restricted to one week only;

The Investigator must emphasize to the subjects the importance to communicate ANY change in the background medication. In particular, the Investigator must inform the subjects that ANY change in the anti-diabetes medication that IS NOT LISTED above, will cause the subject to discontinue study treatment. Any modification to the background therapy during study participation must be reported by the Investigator.

6.5 Treatment assignment and randomization

Treatment is assigned by stratified randomization for two strata based on the patient's baseline BMI. The strata have the following randomization numbers:

- BMI between 28.0 kg/m^2 and 33.0 kg/m^2 (inclusive): 5101 – 5150
- BMI between 33.1 kg/m^2 and up to 40.0 kg/m^2 (inclusive): 5201 – 5250

The randomization number is used to identify which strata the patient belonged to at randomization and which treatment the patients have been randomized to receive.

The Patient number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on patient numbering, please see 'Subject numbering' section in the SOM.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by, or under the responsibility of, Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

BMI was selected as a stratification parameter as it is an important predictor of response on parameters of body composition/body weight and HbA1c (internal data). The expected median value for BMI in this patient population is 33 kg/m^2 (internal data); therefore, 2 strata above and below/inclusive of the median will ensure a balanced representation of patients between placebo and active drug in each strata, i.e. strata of approximately similar size between the 2 arms. Equal size strata will not be enforced, but a minimal size of 10 will be required for the smaller stratum in order to ensure adequate precision of treatment effect estimation in both strata.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.6 Treatment blinding

This is a subject- and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

- Unblinded pharmacist

Unblinding a single patient at site for safety reasons (necessary for patient management) will occur via an emergency system in place at the site (see Section 6.8 Emergency breaking of assigned treatment code).

IMPORTANT: Drug product will be supplied in bulk. Due to the difference in preparation methods between the active and placebo treatments, an unblinded pharmacist or other qualified trained personnel, who is independent of the study team, will be required. This unblinded pharmacist will receive treatment allocation cards from Drug Supply Management with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff. Any potential visible difference in treatments will be concealed by the use of an opaque sleeve.

Sponsor staff

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK blood)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
Independent committees used for assessing interim results	B	UI	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

NA Not applicable

UI Allowed to be unblinded on individual patient level

6.7 Treating the subject

Bimagrumab or placebo will be administered to the subject via the following route of administration: i.v. by infusion pump.

Administrations will be performed at the study site. See the Site Operations Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.8 Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible to the investigator 24 hours per day in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of study treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code must not be recorded on the CRF.** The investigator must also immediately inform the study monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the code break cards at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

In addition, the investigator must provide oral and written information to inform the subject 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.

An assessment will be done by the appropriate site personnel and sponsor after an emergency un-blinding to assess whether or not study treatment should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase (e.g., an unblinded extension).

6.9 Treatment exposure and compliance

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

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with bimagrumab, as detailed in Section 8.7.

6.10 Recommended treatment of adverse events

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

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

Diarrhea may be treated with over the counter remedies. In cases of prolonged occurrence, other treatments may be used at the Investigator's discretion.

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

Adverse events related to underlying disease of T2D: hypoglycemia or hyperglycemia events that are clinically significant based on the judgment of the principal investigator should be treated and managed according to local diabetes treatment guidelines and standard of care. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Elevated lipase and amylase levels that meet AE criteria should be monitored and managed according to Section 9.4.

6.11 Rescue medication

Not applicable.

6.12 Concomitant treatment

The investigator should instruct the subject to notify the study site about any NEW and changes to current medications he/she takes AFTER the start of the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria **prior to the start** of the study **and during** the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the eCRF.

Should a subject have an *incidental and limited* need for a medication to be taken within the restricted *pre-dose* timeframe (e.g., ibuprofen for a headache, antibiotic prophylaxis prior to dental surgery, etc.), the sponsor should be advised, as administration of any concomitant medication *may* require the subject to be discontinued.

Administration of acetaminophen on an occasional basis is acceptable, but must be documented. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Medications allowed in the study as chronic therapy:

- Low dose aspirin is allowed.
- Oral anti-diabetic therapy (limited to metformin and/or DPP4 inhibitor agent), with stable treatment for approximately 3 months prior to randomization, for diabetes management during the trial. Insulin is allowed for one week only in case of acute deterioration of glycemic control.
- Stable regimen of testosterone replacement therapy for at least 3 months prior to randomization.
- Thyroid replacement therapy that is stable for at least 3 months prior to randomization.
- Antihypertensive medication must be on a stable regimen for at least 3 months prior to randomization.
- Medications for dyslipidemia must be stable for at least 3 months prior to randomization.
- Vitamin D and multivitamin/mineral supplementation (see below)
- Antidepressant medications must be stable for at least 3 months prior to randomization.
- Chronic therapy for hyperuricemia must be stable for at least 3 months prior to randomization.
- Other chronic therapy medications not listed above require Sponsor approval

6.13 Vitamin and mineral supplementation

- The subject must consume an oral multivitamin/multimineral supplement.
- In subjects with 25-OH vitamin D level between 12.0 and 50.0 ng/mL inclusive at screening:
  - Daily administration of vitamin D as part of the multivitamin/multimineral supplement (800 IU to 4000 IU, D3 preferable but D2 also acceptable per local availability); or,
  - Equivalent weekly or monthly formulation if deemed to be of advantage for the individual subject's compliance.
- In subjects with 25-OH vitamin D level ≥ 50.0 ng/mL at screening: supplementation recommendations may be made at the investigator's discretion.
- In subjects with 25-OH vitamin D level <12.0 ng/mL at screening and with no symptoms of osteomalacia or low serum calcium: administration of loading dose of oral vitamin D (recommended minimum 50 000 IU of vitamin D3, but according to local guidance) will be allowed. Different formulations of vitamin D3 are allowed based on the approved therapy in the subject's country. Vitamin D2 is permitted where D3 is not available.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

If subjects discontinue early and are not able to return for their End of Treatment and End of Study visits, they should have a safety follow-up call conducted 30 days after the last dosing visit, per Section 7.2. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

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

Study treatment *must* be discontinued for an individual subject under the following circumstances:

- Withdrawal of consent
- An infusion reaction that is considered severe
- One or more symptomatic hypoglycemic events necessitating third party rescue and suspected to be related to study drug; if diabetes medication can be appropriately reduced, the study drug may be resumed after stabilization of FPG at the Investigator's discretion
- A serious adverse event (SAE) thought to be related to study drug
- Pregnancy: a positive urine pregnancy test after start of study treatment requires immediate interruption of study treatment until serum hCG is performed and found to be negative
- Any protocol deviation that results in a significant risk to the subject’s safety
- Emergence of one or more adverse events that in the judgment of the investigator, taking into account the subject’s overall status, prevent the subject from safely continuing in the study

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

- Breaking of the blind (inadvertently or for emergency reasons)
- Use of prohibited treatment as described in the protocol

Subjects who discontinue study treatment should **NOT** be considered withdrawn from the study UNLESS they withdraw their consent. They should return approximately 4 weeks after their last dose for the EoT visit (Visit 113). The EoS visit (Visit 199) should be scheduled

4 weeks after EoT. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 7.4.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment schedule (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.4 Lost to follow-up

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

7.5 Study Stopping rules

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

- Data from this study is judged by the Investigators and Sponsor to indicate a clinically significant risk of using bimagrumab in the diabetic obesity patient population.

- Two or more subjects develop at least one event of symptomatic hypoglycemia necessitating rescue that is not self-administered, and judged to be related to study drug.
- Two or more subjects develop a significant hypersensitivity reaction (grade severe) believed to be related to bimagrumab treatment.
- The Sponsor unilaterally requests a stoppage.

7.6 Early study termination by the sponsor

The study may be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. 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 IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

After the Screening period, visits are scheduled every 4 weeks, except during the first month of the treatment period since a visit needs to be performed at Week 2 to comply with the safety monitoring for circulating amylase and lipase.

The Assessment Schedule below lists all of the assessments and indicates with an “x” the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. Assessments marked with an “S” should be assessed and documented in the patient’s source documentation but no data needs to be entered into the eCRF.

Patients should be seen for all visits on the designated day as specified in the Assessment Schedule. Until randomization, the visits should be calculated relative to the calendar date of the previous visit. After randomization, visits should be calculated relative to the calendar date of the randomization visit.

Table 8-1 Assessment schedule

Epoch	Screening		Treatment and Primary Follow-Up											
Visit Name	Screening	Baseline[1]	Treatment											
Visit Numbers	1	2	101			115	102	103	104	105	106	107		
Days	-21 to -8	-7 to -1	1			14	28	56	84	112	140	168		
Time (post-dose)	-	-	Pre-dose	0min	45min[6]	-	-	-	-	-	-	Pre-dose	0min	45min[6]
Informed consent	X													
Company Confidential Information														
Genetic Informed Consent	X													
Inclusion / Exclusion criteria	S	S[2]												
Subjects domiciled[3]		S												
Study drug administration				X			X	X	X	X	X		X	
Demography	X													
Medical history/current medical conditions	X													
Concomitant therapies	X	X	X			X	X	X	X	X	X	X		
Body Height	X													
Body Weight	X	X	X				X	X	X	X	X	X		
Waist circumference	X	X										X		
Hip measurement		X										X		
Vital Signs	X	X	X				X	X	X	X	X	X		
Physical Examination	S		S									S		
ECG evaluation	X											X		
Alcohol Test and Drug Screen	S													
Hepatitis and HIV Screen	S													
Pregnancy test	X	X	X				X	X	X	X	X	X		
Fasting insulin and glucose[5]	X								X					
HbA1c	X		X									X		
Mixed Meal Tolerance Test[5]	See Table 8-2 below													
Company Confidential Information														
Blood chemistry[5]	X	X				X	X	X	X			X		

Epoch	Screening		Treatment and Primary Follow-Up											
Visit Name	Screening	Baseline[1]	Treatment											
Visit Numbers	1	2	101			115	102	103	104	105	106	107		
Days	-21 to -8	-7 to -1	1			14	28	56	84	112	140	168		
Time (post-dose)	-	-	Pre-dose	0min	45min[6]	-	-	-	-	-	-	Pre-dose	0min	45min[6]
Hematology	X	X										X		
Urinalysis		X										X		
25-Hydroxy Vitamin D	X											X		
Testosterone	X													
TSH	X													
FSH LH	X											X		
Immunogenicity			X									X		
PK blood collection			X		X				X			X		X
DXA scan		X						X				X		
Adverse events		X												
Dietary Counseling[8]	X	X		X			X	X	X	X	X		X	
3-day Food Record		S											S	
24-hour recall dietary assessment[10]		X		X			X	X	X	X	X		X	
Study completion information														
Comments	X													

Epoch	Treatment & Primary Follow-up									
Visit Name	Treatment								Follow-Up	End Of Study
Visit Numbers	108	109	110	111	112			113[9]	114	199
Days	196	224	252	280	308			336	364	392
Time (post-dose)	-	-	-	-	Pre-dose	0min	45min[6]	-	-	-
Informed consent										
Genetic Informed Consent										
Inclusion / Exclusion criteria										
Subjects domiciled[3]										
Study drug administration	X	X	X	X		X				
Demography										
Medical history/current medical conditions										
Concomitant therapies	X	X	X	X		X		X	X	X
Body Height										
Body Weight	X	X	X	X	X			X	X	X
Waist circumference									X	X
Hip measurement									X	X
Vital Signs	X	X	X	X		X		X	X	X
Physical Examination									S	S
ECG evaluation								X		
Alcohol Test and Drug Screen										
Hepatitis and HIV Screen										
Pregnancy test	X	X	X	X	X			X		X
Fasting insulin and glucose[5]			X							X
HbA1c								X		X
Mixed Meal Tolerance Test[5]	See Table 8-2 below									
Blood chemistry[5]								X		X
Hematology								X		X

Company Confidential Information

Epoch	Treatment & Primary Follow-up									
Visit Name	Treatment								Follow-Up	End Of Study
Visit Numbers	108	109	110	111	112			113[9]	114	199
Days	196	224	252	280	308			336	364	392
Time (post-dose)	-	-	-	-	Pre-dose	0min	45min[6]	-	-	-
Urinalysis								X		X
25-Hydroxy Vitamin D								X		
Testosterone										
TSH										
FSH LH								X		X
Inflammatory markers								X		X
Immunogenicity								X		X
PK blood collection			X		X		X	X	X	X
DXA scan								X		X
Adverse events	X									
Dietary Counseling[8]	X	X	X	X	X			X		
3-day Food Record								S		
24-hour recall dietary assessment[10]	X	X	X	X	X			X		
Study completion information										X
Comments	X									

[1] Assessments expected at Baseline can be done on separate days between Day -7 and Day -1
[2] Criteria that have to be re-checked at baseline (refer to Section 4.2)
[3] Optional to be domiciled prior to day 1 to facilitate DXA
[4] Company Confidential Information
[5] Assessments need to be performed after a fast of approximately 12 hours
[6] Time point should be calculated based on the start of the infusion
[7] Company Confidential Information
[8] Assessment to be conducted in-person
[9] In the event of subject early discontinuation, visit assessments to be performed for the End of Treatment (EoT) visit
[10] See Table 8-3 for schedule of 24-hour recall dietary assessments performed in between monthly site visits

Table 8-2 Mixed Meal Tolerance Test

Epoch	Visit Name	Visit Numbers	Days	Time	Glucose and Insulin
Treatment And Primary Follow-Up	Treatment	101	1	0min*	X
				30min	X
				60min	X
				90min	X
				120min	X
				150min	X
				180min	X
		107	168	0min*	X
				30min	X
				60min	X
				90min	X
				120min	X
				150min	X
				180min	X
		113	336	0min*	X
				30min	X
				60min	X
				90min	X
				120min	X
				150min	X
				180min	X

* Sample collection must be performed while subject is fasted prior to start of meal ingestion

Table 8-3 24-hour dietary recall

Epoch	Treatment And Primary Follow-Up											
Visit Name	Treatment											
Days	14	42	70	98	126	154	182	210	238	266	294	322
24-hour recall dietary assessment via telephone call or in-person visit	x	x	x	x	x	x	x	x	x	x	x	x

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the patient agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Novartis will review the investigator's proposed informed consent form to ensure it complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure subjects are informed of the contraception requirements outlined in Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.3 Subject screening

In general it is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

Inclusion/exclusion criteria assessment will not be entered in the CRF, however, data should be available as Source data.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects and include: date of birth, age, sex, race, predominant ethnicity. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.4.1 Alcohol Test and Drug Screen

Subjects will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opiates).

Results will be available as source data and will not be recorded within the eCRF.

8.4.2 Hepatitis and HIV Screen

All subjects must be tested for Hepatitis B, Hepatitis C, and HIV at the screening visit. Hepatitis B will be evaluated using the Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies and if positive, HCV RNA levels should be determined. Evaluation for HIV positive status should be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot or as specified by local regulation.

Results will be available as source data and will not be recorded within the clinical database.

8.4.3 Testosterone and TSH

The following hormones will be measured at screening only: total testosterone (for males only) and thyroid stimulating hormone (TSH). If TSH is abnormal, free thyroxine (free T4 - not total T4) should be reported. For testosterone refer to Exclusion criteria for more details.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Site Operations Manual (SOM). Assessments will be performed/samples collected at the time point(s) defined in the Assessment schedule.

DXA images will be centrally read by a CRO.

Pharmacodynamic (PD) samples will be obtained and evaluated in all patients.

8.5.1 Diabetes parameters

8.5.1.1 Fasting insulin and glucose

Samples for fasting insulin and glucose will be collected after a fast of approximately 12 hours at time points specified in the Assessment schedule.

The Homeostatic model assessment 2 – insulin resistance index (HOMA2-IR) is a derived insulin resistance index that must be calculated by the sites and entered in the CRF. Please refer to the SOM for the details on the calculation.

The quantitative insulin-sensitivity check index (QUICKI) is another insulin resistance index that will be calculated at the end of the study and will not be entered in the CRF (Yokoyama et al 2004; Hrebícek et al 2002).

8.5.1.2 HbA1c

HbA1c will be measured at time points defined in the Assessment schedule.

8.5.1.3 Meal Tolerance test and Matsuda Index

The meal tolerance test will be performed in the morning, after a fast of approximately 12 hours. The meal will consist of a mixed liquid-solid food and frequent blood sampling will be conducted as indicated in Table 8-2 and in the SOM. The meal tolerance test will be conducted at time points defined in the Assessment schedule and results will be used at the end of the study to calculate Matsuda Index and other insulin sensitivity parameters (Matsuda and DeFronzo 1999).

8.5.2 Imaging

8.5.2.1 DXA Scan

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

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

Data collection and processing is explained in the imaging charter written by the imaging CRO supporting the study. DXA data need to remain blinded to investigator and patient until database lock.

8.5.3 Anthropometric measurements

- Height
- Body weight
- Waist circumference
- Hip circumference
- Waist to hip ratio will be calculated at the end of the study
- Body mass index (BMI) will be calculated by the site (Body weight (kg)/ [Height (m)]^2)

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems. If indicated based on medical history and/or symptoms, additional exams may be performed.

Skin-related issues will be assessed by the investigator or assigned clinician at each physical exam time point. Particular attention should be devoted to the assessment of acne at baseline and all follow-up visits due to the previously noted increased incidence of acne in people treated with bimagrumab. Information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

8.6.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse rate

All readings should be recorded on the CRF.

8.6.3 Pregnancy test

Serum pregnancy test is required at screening for all female subjects regardless of reported reproductive/menopausal status.

Urine pregnancy tests will be used at other visits as per the Assessment Schedule and will be performed in women of child-bearing potential only. The result of this test must be received before the patient may be dosed at the current visit.

8.6.4 ECG evaluation

A standard 12-lead ECG will be performed with the subject in a supine position. Interpretation of the tracing must be made by a qualified physician and documented on the ECG and in the ECG section of the CRF. Each ECG tracing should be labeled with the study number, patient initials, patient number and date, and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant medical history CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the sponsor.

The CRF will contain:

- date and time of ECG
- PR interval
- QT interval
- QTcF
- QRS duration
- RR interval

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

As applicable, QTcF may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. See the Site Operations Manual for additional details.

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

8.6.5 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes), erythrocyte sedimentation rate, platelet count, aPTT, PT, INR will be measured.

8.6.6 Blood chemistry

Blood chemistry should be assessed after a fast of approximately 12 hours. Blood chemistry will include: Sodium, potassium, calcium, magnesium, bicarbonate/HCO_3, chloride, phosphate or phosphorus, creatinine, BUN or urea, uric acid, albumin, total protein, alkaline phosphatase, total bilirubin, LDH, γGT, AST, ALT, amylase, lipase, CK (CK-MM, CK-MB), myoglobin.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Additional safety labs may be performed at the Investigator's discretion for clinically/medically significant abnormalities in glycemic control.

8.6.7 Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Required assessments include: occult blood, pH, specific gravity, ketones, glucose, protein, bilirubin, nitrite and leukocytes.

8.7 Pharmacokinetics (PK)

PK samples will be collected at the time points defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PK samples will be obtained and evaluated in all patients.

Concentrations will be expressed in mass per volume units.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined from the serum concentration-time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher):

- On Day 1, 168 and 308: Cmax, Tmax
- On Days 84, 168, 252, 308 and 336: Ctrough

8.8 Other assessments

8.8.1 3 day food record

Subjects will be asked to keep a 3-day food record at time points indicated in the Assessment schedule, and according to guidance provided in the SOM. These records will provide detailed information regarding dietary intake over the course of the study. Results will be available as source data and will not be recorded within the clinical database.

8.8.2 24 hour dietary recall assessment

A 24 hour dietary recall will be used at time points defined in the Assessment schedule to monitor the dietary intake and guide the dietary counseling.

Dietitians may contact the subject prior to a scheduled visit in order to collect the data, and will also contact subjects once between monthly in-person counseling visits as defined in Table 8-3.

Subjects will be asked to report: time of day, food/beverage, method of preparation, portion size/amount consumed and details of the item, as defined in the Site Operations Manual.

Data will be entered in the CRF as total amount of calories, protein (g/kg and % calories), fat (g and % calories), and carbohydrate (g and % calories).

8.8.3 Immunogenicity

Immunogenicity (IG) samples will be collected at the time points defined in the Assessment schedule and analyzed by a Novartis CRO.

Further details on sample collection, numbering, processing and shipment can be found in the SOM.

A validated bridging enzyme-linked immunosorbent assay (ELISA) will be used for screening and confirmation of the presence of anti-bimagrumab antibodies in human serum. Confirmed immunogenicity samples will be further characterized for presence of neutralizing antibodies using a validated ligand binding assay. The detailed method description to assess immunogenicity of bimagrumab will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

IG samples remaining after immunogenicity analysis may be used for exploratory assessment or other bioanalytical purposes (e.g., cross check between different sites). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

8.9 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

9 Safety monitoring

9.1 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 patient after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 9.6 for an overview of the reporting requirements.

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

Abnormal laboratory values or test results constitute AEs 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual patients and identifying AEs. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively. Other laboratory values to check are markers of muscle distress (CK, myoglobin) and pancreatic enzymes (amylase and lipase).

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

1. The severity:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment:
   - Yes or
   - No
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met.

5. Action taken regarding investigational treatment. All AEs must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the patient during the study as needed. Once an adverse event is detected, it must 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 investigational drug, the interventions required to treat it, and the outcome.

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

In this study, investigators will be asked to provide additional details on selected adverse events of special interest such as but not limited to events of spontaneous muscle contraction with associated pain, diarrhea or diarrhea-like events.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any AE (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 (any diabetic-related complications)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

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 also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 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 last study visit must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by patients deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the paper SAE Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department,

notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source 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 Electronic Data Capture 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. Study site personnel must also inform the Clinical Trial Leader.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the patient continued or withdrew from study participation. Each recurrence, complication, or progression of the original event must 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 study 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 study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

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

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below.

Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT, INR, ALP and γGT) to confirm elevation within 48-72 hours.
- Repeat laboratory test results must be reported as appropriate via an electronic data transfer (if applicable), or entered on the appropriate unscheduled local laboratory CRF.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the patient if appropriate.
- Causality assessment of the liver event.
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT, INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in Table 15-3.
  - Imaging such as abdominal US, CT or MRI, as appropriate.
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

9.4 Lipase and amylase elevations

To ensure subject safety and enhance reliability in determining the potential for pancreatic events with bimagrumab, a standardized process for identification, monitoring and evaluation of pancreatic events should be followed (Table 9-1).

Table 9-1 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., 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., CT or MRI) to evaluate for presence of pancreatitis. • Study drug interruption based on findings of additional assessments and at discretion of investigator.

Medically significant pancreatic events which are considered as serious adverse events (SAEs) should follow the **standard procedures for SAE reporting** as described in Section 9.2. 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.

9.5 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

9.6 Reporting medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-2 summarizes the reporting requirements.

Table 9-2 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.7 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

The study drug must be discontinued immediately, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

9.8 Early phase safety monitoring

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

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

10 Data review and database management

10.1 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 Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site 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 ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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).

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 eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.2 Data collection

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

After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis 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 or CRO working on behalf of Novartis who 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. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

For laboratory samples processed centrally, the results will be sent electronically to Novartis (or a designated CRO).

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

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

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

DNA samples (optional):

10.4 Data Monitoring Committee

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

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

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

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

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

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

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

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

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

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

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

10.5 Adjudication Committee

Not required.

11 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

The safety analysis set will include all patients that received any study drug.

The PK analysis set will include all patients with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact PK data.

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

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

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

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and patient.

11.4 Analysis of the primary variable(s)

The primary aim of the study is to assess the effect of bimagrumab on fat mass at Week 48 of the treatment period.

11.4.1 Variable(s)

The primary efficacy variable is the change from baseline in fat mass (kg) at Week 48.

Since the week 48 visit is the scheduled EOT visit, and since the EOT assessments are also performed in subjects who discontinue early (see Section 7.2), only EOT assessments on subjects who completed a full treatment regimen (i.e., those who did not discontinue early) will be included in the primary analysis.

11.4.2 Statistical model, hypothesis, and method of analysis

The study design enables evaluation of efficacy based on the following dual criteria 1) statistical significance (superior treatment effect, 1-sided 10% level) in fat mass; and 2) clinical relevance of the change in fat mass (estimated median treatment effect of 5% or more). Weight loss of 5% has been shown to translate into clinical benefit in an overweight/obese population with T2D (Franz et al 2015). Fat mass loss of a similar magnitude to the weight loss is expected to translate into similar clinical benefits (such as on glycemic control) in a similar population.

The randomization will be stratified by BMI category (>=28.0 kg/m^2 and <=33.0 kg/m^2, >33.1 kg/m^2 to <=40.0 kg/m^2) in order to achieve an approximate balance of BMI distribution across the two treatment groups. The cutoff value of 33 kg/m^2 represents the expected median BMI in that population (based on internal data); therefore the two randomization strata are expected to be of similar size. However, equal size strata will not be enforced. A minimum of 10 patients will be targeted for enrollment in the smaller stratum to ensure accurate precision on the treatment effect in both strata (see Section 11.7).

The primary endpoint will be analyzed using a mixed effects model. This model will have change from baseline in kg fat mass as the dependent variable, treatment arm, time, time*treatment interaction as fixed effects, and a subject level random intercept. Baseline fat mass and baseline BMI value may be included in the model as covariates. Data collected from both randomization strata (BMI category at randomization) will be included in the model. The change from baseline (absolute) in kg fat mass at Week 48 will be estimated from that model and will be summarized graphically and in tabular form. No transformation (logarithmic or otherwise) of body weight will be done for analysis. An unstructured within-subject covariance will be used.

The evaluation of efficacy is based on the following dual criteria:

1. statistical significance (superior treatment effect, 1-sided 10% level) in fat mass; and
2. clinical relevance of the change in fat mass (estimated median treatment effect of 5% or more) at Week 48.

11.4.3 Handling of missing values/censoring/discontinuations

The primary analysis model described above is valid under the assumption of data missing at random. If the dropout rate is greater than 10% in any arm, other analysis methods will be used to assess the sensitivity of the results to different methods for missing data handling.

11.4.4 Sensitivity analyses

Other models may be used (such as pattern-mixture models) if the dropout rate is higher than expected, in order to assess sensitivity of the primary efficacy conclusions to missing data. If a treatment effect in fat mass or HbA1c materializes, then it will be investigated whether this finding is robust under an assumption of informative drop-out; that the subjects who drop out would likely not have experienced a treatment benefit.

11.5 Analysis of secondary variable(s)

Company Confidential Information

11.5.1 Efficacy / Pharmacodynamics

Company Confidential Information

11.5.2 Safety

Vital signs

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

ECG evaluations

All ECG data will be listed by treatment group, patient and visit; abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

Other safety evaluations

Company Confidential Information

11.5.3 Pharmacokinetics

Bimagrumab serum concentration data will be listed by treatment, patient, and visit/sampling time point.

PK parameters will be listed by treatment group, patient, visit/sampling time, and dose number. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, maximum and 90% CI. A geometric mean will not be reported if the dataset includes zero values. An exception to this is Tmax where median, minimum and maximum will be presented. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Graphical exploration of bimagrumab PK parameters versus fat mass will be provided. Other graphical exploration may be done as appropriate.

11.5.5 Other assessments

Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit.

11.6 Analysis of exploratory variables

Company Confidential Information

11.7 Sample size calculation

A sample size of 68 recruited subjects (34 receiving active treatment and 34 placebo) is selected to enable at least 48 completers, assuming a dropout rate of maximum 30%.

A sample size of 24 completers per group (total of 48 patients) provides about 70% power (see Table 11-1) to pass the criteria described above for fat mass (significant reduction at the 1-sided 10% level (compared to placebo) and an estimated median placebo-adjusted reduction of at least 5%). Assumptions used for these calculations include a true placebo-adjusted fat loss of 6% (standard deviation 6.5%, CBYM338X2206). The associated type I error is about 1% (Table 11-1).

Because weight loss interventions in overweight/obese diabetic patients result in ~ 15% lower magnitude of response compared to overweight/obese non-diabetic patients (Franz et al 2007), we made the assumption that bimagrumab could have a 6% true effect on fat loss in overweight and obese diabetic patients (this is about 15% lower than the 7.2% effect observed in overweight and obese pre-diabetics (CBYM338X2206)).

11.8 Power for analysis of key secondary variables

The power to pass the criteria for HbA1c (significant reduction and an estimated median placebo-adjusted reduction of at least 0.5%) is about 73%. Assumptions used for these calculations include a true placebo-adjusted HbA1c reduction of 0.7% (standard deviation 1.11%, internal data). The associated type I error is about 6%.

11.9 Interim analyses

12 Ethical considerations

12.1 Regulatory and ethical compliance

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

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, 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 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

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.

13 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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, γGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase > 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.