NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

BYM338/Bimagrumab

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

## Statistical Analysis Plan (SAP)


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# 1 Introduction

## 1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CBYM338X2211".***

The Statistical Analysis Plan (SAP) describes the implementation of the statistical analyses planned in the protocol.

## 1.2 Study reference documentation

Final study protocol (v05) is available at the time of finalization of SAP.

## 1.3 Study objectives

### *1.3.1. Primary objective(s)*

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

### *1.3.2. Secondary objective(s)*

| ***Secondary objective(s)*** | ***Endpoints related to secondary objective(s)*** |
|---|---|
| • 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 |
| • 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/obese patients with type 2 diabetes. | • Adverse events, Vital Signs, ECG, Laboratory Values, Immunogenicity |
| • To evaluate the pharmacokinetics of repeat doses of bimagrumab in overweight/obese patients 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 patients 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 |

### *1.3.3. Exploratory objective(s)*

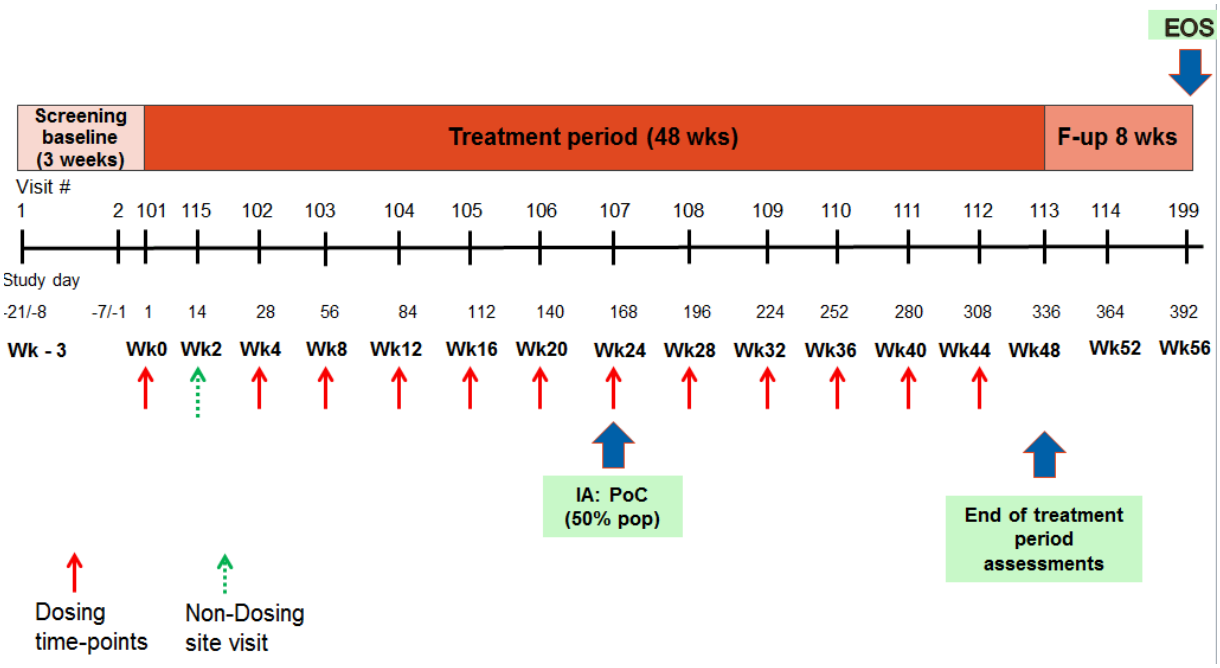
## 1.4 Study design and treatment

This is a non-confirmatory, randomized, subject and investigator blinded, placebo-controlled, parallel arms study, investigating a 48-week treatment period with intravenous bimagrumab 10mg/kg in overweight/obese patients with type 2 diabetes. Approximately 68 patients (34 receiving active treatment and 34 placebo) are planned to be enrolled and randomized. The randomization will be stratified according to baseline BMI in two strata:

- BMI between 28 kg/m$^2$ and 33 kg/m$^2$ (inclusive) and
- BMI above 33 kg/m$^2$ and up to 40 kg/m$^2$ (inclusive),

in order to achieve an approximate balance of BMI distribution across the two treatment groups.

**Figure 1-1: Study Design**




Based on the latest version of protocol amendment, an additional visit at week 2 has been added coded as Visit 115.

# 2 First interpretable results (FIR)

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# 3 Interim analyses

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# 4 Statistical methods: 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 experienced no protocol deviations that impact PK data.

The PD analysis set will include all patients with available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

For subjects for which the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis. The analysis sets and protocol deviation codes are related as follows:

**Table 2 Protocol deviation codes and analysis sets**

| Category<br>Deviation code | Text description of deviation | Data exclusion |
|---|---|---|
| **Subjects are excluded from PK analysis in case of these PDs:** | | Exclude subject from PK analysis set |
| **Subjects are excluded from PD analysis in case of these PDs:** | | Exclude subject from PD analysis set |
| **Subjects are excluded from PK and PD analysis in case of these PDs:** | | Exclude subject from PK and PD analysis sets |

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

# 5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

## 5.1 Variables

The following pharmacokinetic 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

## 5.2 Descriptive analyses

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PK parameters will be listed by treatment group, patient 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.

# 6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

## 6.1 Primary objective

The primary objective of this trial is to assess the effect of bimagrumab on fat mass at Week 48 of the treatment period.

### 6.1.1 Variables

The primary efficacy variable is the change from baseline in fat mass (kg) at Week 48 of the treatment period. No transformation of (logarithmic or otherwise) will be done for analysis.

Since the week 48 visit is the scheduled EOT visit, and since the EOT assessments are also performed in subjects who discontinue early, 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.

### 6.1.2 Descriptive analyses

The individual fat mass assessments will be listed by treatment group, patient and visit/time. Summary statistics will be provided for raw, change from baseline, and percentage change from baseline by treatment group and visit/time. Summary statistics will include mean (arithmetic), SD, CV, median, minimum, maximum.

Graphical methods will be employed to show group and individual summary plots over time by treatment.

### 6.1.3 Statistical model, assumptions and hypotheses

The primary analysis will be analyzed using a longitudinal mixed effects model. This model will have change from baseline in kg fat mass as the dependent variable, treatment arm, time, and a time*treatment interaction as fixed effects. Baseline fat mass and baseline BMI value may

be included in the model as covariates. Time will be modeled as a categorical variable. An unstructured within-subject covariance will be used.



#### 6.1.3.1 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.

Since the week 48 visit is the scheduled EOT visit, and since the EOT assessments are also performed in subjects who discontinue early, 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. Thus, we will only include patients in the final analysis where the EOS visit is within 8 weeks +/- 10 days from the week 48 assessment and did not discontinue early.

#### 6.1.3.2 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.

#### 6.1.3.3 Supportive analyses

## 6.2 Secondary objectives

### 6.2.1 Variables

The secondary variables are the:

1. Body fat mass: change from baseline in fat mass after 6 months of treatment at Week 24
2. HbA1c: change from baseline will be used for inferential analysis at Week 24 and Week 48. Baseline for HbA1c is defined at the Day 1 assessment.
3. Fasting insulin and glucose at Week 12, Week 36, and EOS: Baseline for these parameters is defined at the Screening assessment.
4. HOMA2-IR: homeostatic assessment model of insulin resistance at Week 12, Week 36, and EOS
5. QUICKI: quantitative insulin sensitivity check, under fasting conditions at Week 12, Week 36, and EOS. QUICKI index will be derived from glucose and insulin levels at study completion using the following formula:

$$\text{QUICKI} = \frac{1}{\{\log(\text{Fasting Insulin}) + \log(\text{Fasting Glucose})\}}$$

6. Matsuda Index based on MTT at Week 24 and Week 48. Matsuda Index will be derived from glucose and insulin levels using the following formula:

$$\frac{10000}{\sqrt{(\text{Fasting Glucose} \times \text{Fasting Insulin}) \times (\text{Mean Glucose} \times \text{Mean Insulin})}}$$

7. Anthropometric body measurements: body weight, BMI, waist circumference, waist-to-hip ratio and lean body mass (LBM) as measured by DXA at Week 24 and Week 48.

### 6.2.2 Descriptive analyses

The variables will be listed by treatment group, patient and visit/time. Summary statistics will be provided for raw, change from baseline and percentage change from baseline by treatment group and visit/time. Summary statistics will include mean (arithmetic), SD, CV, median, minimum, maximum.

Graphical methods will be employed to show group and individual summary plots over time by treatment. Other secondary efficacy variables will be summarized graphically and in summary tables.

### 6.2.3 Statistical model, assumptions and hypotheses

**HbA1c**

The secondary analysis of HbA1c will be analyzed using a mixed effects model with the same structure as the analysis of the primary variable, in Section 6.1.3.



**Other Secondary Variables**

Similar to the analysis of HbA1c, an MMRM model may be used to compare values between active and placebo groups for the remaining secondary variables.

#### 6.2.3.1 Supportive analyses

As a supportive analysis for metabolic changes, summaries of change in background anti-diabetic medication may be done. A change in background anti-diabetic medication is defined as a change in daily dose, any discontinuation, or the addition of a second agent.

## 6.3 Exploratory objectives

# 7 Statistical methods for safety and tolerability data

All subjects within the safety analysis set will be included in the safety data analysis.

## 7.1 Variables

Adverse events, vital signs (blood pressure, heart rate, body temperature), ECG intervals, clinical laboratory measurements, immunogenicity, hematology, blood chemistry as well as subject demographics, baseline characteristics, and treatment information.

## 7.2 Descriptive analyses

**Subject demographics and other baseline characteristics**

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

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

Demographic table will include a corresponding p-value for comparison of baseline values between BYM338 and placebo groups. T-test can be performed for continuous variables and chi-squared test for categorical variables. Demographic table will be generated for both sets of patients (completed/not completed treatment).

**Treatment**

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

**Vital signs**

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

**ECG evaluations**

All ECG data will be listed by treatment, subject 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, subject, and visit/time, and if normal ranges are available, abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

**Adverse events**

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

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

**Other safety evaluations**



**Immunogenicity**

All immunogenicity results will be listed by subject and visit/time.

## 7.3 Graphical presentation

Figures may be created, as needed, to explore safety data trends.

# 8 Statistical methods for Pharmacokinetic/Pharmacodynamic interactions

Scatterplots may be used to explore the relationships between systemic exposure to BYM338 and selected safety/PD endpoints. Other graphical exploration may be done as appropriate.

# 9 Statistical methods for biomarker data