NOVARTIS

Clinical Development

MBL949

CMBL949A12201

ClinicalTrials.gov Identifier: NCT05199090

A randomized, placebo-controlled, participant-and-investigator-blinded, sponsor open-label study to evaluate the safety, tolerability, and efficacy with different dosing regimens of subcutaneously administered MBL949 in obese participants with or without type 2 diabetes mellitus

Statistical Analysis Plan (SAP)

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Commercially Confidential Information (CCI)

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List of abbreviations

	Commercially Confidential Information
AE	Adverse Event
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CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
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FAS	Full Analysis Set
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IA	Interim Analyses
MedDRA	Medical Dictionary for Drug Regulatory Affairs
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RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

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

Final study protocol amendment (v02) is available at the time of finalization of Statistical Analysis Plan.

1.1 Study design

This is a multi-center, randomized, placebo-controlled, participant-and-investigator-blinded, sponsor open-label study in obese participants with or without T2DM. The study comprises a screening/baseline period of up to 35 days (5 weeks), a 14-week treatment period in which participants will be administered MBL949 or placebo at 8 biweekly intervals starting on Day 1 and a 10-week follow-up period.

Approximately 106 participants will be enrolled to ensure at least 90 participants complete week 16 to assess the primary objectives of safety, tolerability, and efficacy.

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Participants will be randomized to one of five MBL949 arms (shown below), or placebo, administered by subcutaneous (SC) injection every 2 weeks during treatment period (8 doses):

MBL949 Arm 1: Commercially Confidential Information

MBL949 Arm 2: Commercially Confidential Information

MBL949 Arm 3: Commercially Confidential Information

MBL949 Arm 4: Commercially Confidential Information

MBL949 Arm 5: Commercially Confidential Information

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Screening (Days -35 to -15)

Consented participants will undergo a screening visit between Day -35 and Day -15 to determine their eligibility for the study. Participants who meet eligibility criteria will be scheduled for baseline assessments.

Baseline (Days -14 to -1)

Prior to dosing (Day 1), participants who are eligible for enrollment following screening will return to the clinic to undergo baseline assessments. To facilitate study conduct, participants may come to the clinic on multiple days to complete the required assessments prior to Day 1,
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Randomization and Dosing (Day 1)

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Eligible participants, based on screening and baseline assessments, will be randomized into MBL949 arms 1-5 and placebo arm Commercially Confidential Information

On Day 1, participants will come to the clinic after an overnight fast of at least 10 hours to complete the Day 1 assessments prior to dosing.

Administration of MBL949 or placebo will be given via a SC injection according to instructions provided in the Pharmacy Manual. Dosing will be followed by an observation period of at least one hour post dose administration.

Treatment period (Days 1-99)

Following Day 1, the study treatment will be administered SC at biweekly intervals for a total of eight dose administrations over 14 weeks. Participants will be evaluated regularly throughout the treatment period for safety, tolerability, efficacy, CCI . Participants in consultation with the Investigator may select to have selected visits throughout the study to be conducted at home by a visiting nurse or at the study site.

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Follow Up (Days 100-169)

Participants will have a 10-week follow-up period (Day 100 to Day 169) CCI in which they will continue to be monitored for safety, tolerability, efficacy,

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1.2 Study objectives, endpoints and estimands

Primary objective(s)

• To evaluate the safety and tolerability of different dosing regimens of MBL949 in obese participants with or without T2DM	• Frequency and severity of adverse events (AEs)
• To evaluate the effect of different dosing regimens of MBL949 on weight in obese participants with or without T2DM at week 16	• Weight

Exploratory objective(s)

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2 Statistical methods

2.1 Data analysis general information

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The final analysis will be conducted on all participant data at the time the trial ends. Details of these analyses are outlined in this document.

Data will be analyzed using SAS® version 9.4 (or higher).

Interim analyses

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Descriptive statistics

Descriptive statistics on continuous data will include mean, standard deviation, median, minimum, and maximum, while categorical data will be presented as frequencies and percentages.

In shift tables and tables of abnormal values all unscheduled assessments are included. Unscheduled assessments will be reported with the scheduled assessments in the listings.

2.1.1 General definitions

Study treatment refers to MBL949 Commercially Confidential Information or placebo.

The term ***'date of first administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the first time in the CMBL949A12201 study.

The term ***'date of last administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the last time in the CMBL949A12201 study.

The term ***'study day'*** refers to the Analysis Relative Day, Relative Start Day, or Relative End Day, as applicable. Day 1 is defined as the date of first dose of study drug (MBL949 or placebo).

Study day is defined as the number of days since the date of first dose of study treatment (Day 1).

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first administration of study treatment,

  Study day = Assessment date – Date of first dose of study treatment +1

- for dates prior to the date of first administration of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

The term ***'baseline'*** refers to the last non-missing assessment prior to the first dose of study drug, unless specified otherwise.

The term '***Treatment period***' refers to the 14 weeks period from Day 1 to Day 99.

The term ***'treatment-emergent adverse event'*** refers to any adverse event (AE) started after the first dose of study medication, or events present prior to the start of treatment but increased in severity based on preferred term (PT).

2.2 Analysis sets

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

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

The **full analysis set (FAS)** will include all randomized participants.

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2.2.1 Subgroup of interest

No subgroup analysis is planned.

2.3 Participant disposition, demographics and other baseline characteristics

Safety analysis set will be used for the below analyses.

2.3.1 Participant disposition

Subject disposition will be summarized by treatment group and disposition event.

The number and percentage of subjects screened, randomized, completed, and discontinued from the study will be summarized with reasons of discontinuation.

2.3.2 Demographics and other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographics: date or year of birth (if permitted), sex, race, predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we will assess the diversity of the study population as required by Health Authorities.

All prescription medications, over-the-counter drugs, and significant non-drug therapies prior to the start of the study must be documented. Details on concomitant therapy will be recorded on the appropriate page of the eCRF.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The safety analysis set will be used for the analyses below.

2.4.1 Study treatment / compliance

Administration of drugs for each treatment group will be summarized as a frequency table of number of doses received.

Dose administration records will be listed by treatment group, CCI and participant.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group and CCI as well as by ATC and treatment group.

2.5 Analysis supporting primary objective(s)

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All subjects within the safety analysis set will be included for the primary safety analyses.

The primary objectives of the study include assessing the efficacy of MBL949 in reducing weight and evaluating its safety and tolerability.

2.5.1 Primary endpoint(s)

Weight

The primary endpoint for efficacy is change-from-baseline in weight at week 16. Baseline weight is defined as the last weight measurement before dosing.

Adverse Events

Primary endpoints for safety and tolerability are occurrences and severities of adverse events.

2.5.2 Statistical hypothesis, model, and method of analysis

Weight

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Summary statistics will be provided by treatment, CCI and visit for weight and weight-change-from-baseline and also by treatment and visit CCI . Graphs will also be produced by treatment, and visit for weight and weight-change-from-baseline. Additional graphs may be produced for weight. Frequency tables of responders, who

are participants with ≥5% weight loss at a certain visit, will be provided by treatment, and visit as well as by treatment and visit only. CCI

2.5.3 Handling of intercurrent events

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2.5.4 Handling of missing values not related to intercurrent event

All participants with a baseline weight and at least one post-baseline weight measurement will be included in the primary efficacy analysis. Commercially Confidential Information

2.5.5 Sensitivity analyses

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2.5.6 Supplementary analyses

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2.6 Analysis supporting secondary objectives

N/A

2.7 Safety analyses

For all safety analyses, the safety analysis set will be used. All listings and tables will be presented by treatment group CCI .

2.7.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment group, CCI and participant.

The number (and percentage) of participants having treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- By treatment, primary system organ class and preferred term.
- By treatment, primary system organ class, preferred term, and maximum severity.
- By treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

2.7.1.1 Adverse events of special interest / grouping of AEs

N/A

2.7.2 Deaths

Deaths will be listed by treatment group, CCI and subject.

2.7.3 Laboratory data

All laboratory data will be listed by treatment group, CCI participant, and visit/time and if normal ranges are available, abnormal laboratory data will be flagged. Summary statistics of laboratory parameters will be provided by treatment group and visit/time. Urinalysis lab parameters will be further separated by gender.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

PR, QRS, QT, QTcF, RR intervals and HR will be obtained from single 12-lead ECGs for each participant during the study.

Abnormal ECG will be flagged and listed by treatment group, participant, and visit/time.

The total number and percentage of subjects with abnormal ECGs will be summarized by treatment group and visit.

2.7.4.2 Vital signs

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

Vital signs values outside normal range will be listed by treatment group, CCI and subject.

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2.12 Interim analysis

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3 Sample size calculation

3.1 Primary endpoint(s)

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At final analysis, MBL949 arms 1, 2, and 3 (if not terminated early) will each have 12 participants, and the placebo arm will have at least 24 participants who complete week 16 weight assessment. Therefore, MBL949 efficacy group will have a sample size of either 24 or 36. Conservatively assuming that the efficacy group and placebo arm each has 24 participants, the power for efficacy criteria is still 95%.

At final analysis, if MBL949 arm 4 has been triggered and completed, the weight change of this arm will be compared to MBL949 efficacy group.

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Weight change in MBL949 arm 4 will be compared against placebo arm and MBL949 efficacy group, respectively. Assuming that the true weight change in MBL949 arm 4 is -2kg, there is at least 77% probability of declaring MBL949 arm 4 having more weight loss than placebo, and at least a 99% probability of declaring MBL949 efficacy group having more weight loss than MBL949 arm 4, given sample sizes of 12, ≥24, and ≥24 in MBL949 arm 4, MBL949 efficacy group, and placebo arm, respectively, where type I error rate is 0.1.

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4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

N/A

5.1.1 Study drug

No imputation will be made to the start date and end date of study treatment.

5.1.2 AE date imputation

5.1.2.1 AE start date imputation

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), treatment start date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the treatment start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), treatment start date + 1 day).

If AE end date is available and the imputed AE start date is greater than the AE end date, then imputed AE start date should be set to the AE end date.

5.1.2.2 AE end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.3 Concomitant medication date imputation

5.1.3.1 Concomitant medication start date imputation

Rules for imputing the CM start date:

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:

a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the treatment start date year value:

a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.

b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).

c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.2 Concomitant medication end date imputation

Rules for imputing the CM end date (based on RAP M3):

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.2 AEs coding/grading

N/A

5.3 Laboratory parameters derivations

Clinically notable values for vital signs are as follows:

- Any significant increase or decrease in vital signs beyond inclusion/exclusion criteria:
  - Systolic blood pressure less than 95 mgHg or greater than 155 mgHg
  - Diastolic blood pressure less than 60 mgHg or greater than 95 mgHg
  - Pulse rate less than 56 or greater than 110 bpm

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

The weight of each participant at week 16 will be analyzed with a mixed model for repeated measures (MMRM) as described in Section 2.5.2. The model will be fitted using the SAS procedure "PROC MIXED". Unstructured covariance matrix will be used (TYPE = UN), thus allowing adjustment for correlations between time points within subjects. If not possible, other appropriate covariance structures will be explored.

Adjusted means and the corresponding variance covariance matrix will be estimated. The estimated treatment differences for treatment comparisons will be tabulated along with the associated 80% confidence intervals and two-sided p-value. No adjustment for multiplicity will be made. For calculation of denominator degrees of freedom Kenwood-Rogers method would be used (DDFM=KR).

The mathematical formula of this MMRM is given as follows:

$$\underline{y} = \beta_0 + \underline{\beta_1} treatment + \underline{\beta_2} time + \underline{\beta_3} treatment * time + \beta_4 baseline + \underline{\beta_5} glycemic + \underline{\beta_6} treatment * glycemic + \underline{\beta_7} time * glycemic + \underline{\beta_8} treatment * time * glycemic * + \underline{\varepsilon}$$

where,

- $\underline{y}$ is vector of the absolute change from baseline in weight
- β_0 the fixed effect intercept
- $\underline{\beta_1}$, $\underline{\beta_2}$, $\underline{\beta_3}$, and $\underline{\beta_5}$ the vector coefficients of the corresponding parameters and β_4 the coefficient of corresponding parameter.
    - $\underline{\beta_5}$,$\underline{\beta_6}$,$\underline{\beta_7}$ and $\underline{\beta_8}$ depends on the parameter level, if glycemic has two levels then β_5, β_6, β_7 and β_8
    - If glycemic parameter has one level, $\underline{\beta_5}$,$\underline{\beta_6}$,$\underline{\beta_7}$and $\underline{\beta_8}$ are dropped from the equation
- $\underline{\varepsilon}$ the vector of residuals where $\underline{\varepsilon} \sim N(0, \boldsymbol{R})$ with **R** is a $m \times$ m diagonal covariance matrix.

5.5 Considerations due to COVID-19

Due to the COVID-19 pandemic, it might not be possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed separately to other deviations and may be also tabulated.

Observations that were impacted due to COVID-19, may be excluded from the primary analyses and separately explored to identify if there is an impact of them on the analyses.

5.6 Variables derivation/calculation

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5.7 Rule of exclusion criteria of analysis sets

Table 5-1 Criteria leading to exclusion

Analysis Set	Deviation Code	Criteria that cause subjects to be excluded

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Analysis Set	Deviation Code	Criteria that cause subjects to be excluded

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Analysis Set	Deviation Code	Criteria that cause subjects to be excluded

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6 Reference