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Novartis Research and Development

MBL949

Clinical Trial Protocol 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

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## List of abbreviations

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| Commercially Confidential Information | |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate Aminotransferase |
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| BLRM | Bayesian Logistic Regression Model |
| BMI | body mass index: weight kg / height $m^2$ |
| BUN | Blood Urea Nitrogen |
| Commercially Confidential Information | |
| CD-ROM | Compact Disc – Read Only Memory |
| Commercially Confidential Information | |
| CDP | Clinical Development Plan |
| CDS | Core Data Sheet |
| CK | Creatinine Kinase |
| Commercially Confidential Information | |
| CMO&PS | Chief Medical Office and Patient Safety |
| CO | Country Organization |
| $CO_2$ | carbon dioxide |
| COA | Clinical Outcome Assessment |
| COVID-19 | Coronavirus Disease-19 |
| CQA | Clinical Quality Assurance |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CSR | Clinical study report |
| CTC | Common Terminology Criteria |
| CV | coefficient of variation |
| DBP | Diastolic Blood Pressure |
| DIN | Drug Inducted Nephrotoxicity |
| DLT | Dose Limiting Toxicity |
| DMC | Data Monitoring Committee |
| DPP-4 | Dipeptidyl Peptidase 4 |
| DQF | Data Query Form |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCOA | Electronic Clinical Outcome Assessment |
| EDC | Electronic Data Capture |
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| ELISA | Enzyme-linked immunosorbent assay |

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|---|---|
| EOS | End Of Study |
| eSAE | Electronic Serious Adverse Event |
| eSource | Electronic Source |
| FDA | Food and Drug Administration |
| Commercially Confidential Information | |
| FIH | First in Human |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| GCS | Global Clinical Supply |
| GDF-15 | Growth Differentiation Factor-15 |
| GFRAL | Glial-derived neurotrophic Factor Receptor Alpha-Like |
| GGT | Gamma-glutamyl transferase |
| Commercially Confidential Information | |
| h | Hour |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HED | Human Equivalent Dose |
| HEOR | Health Economics & Outcomes Research |
| HFpEF | Heart Failure with preserved Ejection Fraction |
| HIV | Human immunodeficiency virus |
| Commercially Confidential Information | |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IN | Investigator Notification |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IUD | IntraUterine Device |
| LDH | lactate dehydrogenase |
| LFT | Liver function test |
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| MedDRA | Medical dictionary for regulatory activities |
| mg | milligram(s) |

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| mL | milliliter(s) |
| Commercially Confidential Information | |
| MRSD | Maximum Recommended Starting Dose |
| MTD | Maximum Tolerated Dose |
| Commercially Confidential Information | |
| NCDS | Novartis Clinical Data Standards |
| NOVDD | Novartis Data Dictionary |
| Commercially Confidential Information | |
| OHP | off-site Healthcare Professional |
| PA | posteroanterior |
| PC | Personal Computer |
| Commercially Confidential Information | |
| PPD | Premature Participant Discontinuation |
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| PSD | Premature Subject Discontinuation |
| PT | prothrombin time |
| PTT | Partial Thromboplastin Time |
| QD | Once a day |
| QMS | Quality Management System |
| QTcF | QT interval corrected by Fridericia's formula |
| R Value | ALT/ALP x ULN |
| RAP | The Report and Analysis Plan |
| RBC | red blood cell(s) |
| RDC | Remote Data Capture |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SC | subcutaneous |
| sCR | serum creatinine |
| SD | standard deviation |
| SGLT-2 | Sodium-Glucose coTransporter-2 |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T2DM | Type 2 Diabetes Mellitus |

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| TD | Study Treatment Discontinuation |
| TZD | Thiazolidinedione |
| ULN | upper limit of normal |
| Commercially Confidential Information | |
| UTI | Urinary Tract Infection |
| VAS | Visual Analogue Scale |
| WBC | white blood cell(s) |
| WHO | World Health Organization |
| WHR | Waist to Hip Ratio |
| WoC | Withdrawal of Consent |

## Glossary of terms

| | |
|---|---|
| Additional treatment | Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy) |
| Assessment | A procedure used to generate data required by the study |
| Biologic Samples | A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant |
| Cohort | A specific group of participants fulfilling certain criteria and generally treated at the same time |
| Control drug | A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Dosage | Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care |
| End of the clinical trial | The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol |
| Enrollment | Point/time of participant entry into the study at which informed consent must be obtained |
| eSource (DDC) | eSource Direct Data Capture (DDC) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate |
| Estimand | A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable. |
| Intercurrent events | Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. |
| Investigational drug/ treatment | The drug whose properties are being tested in the study |
| Medication number | A unique identifier on the label of medication kits |
| Mis-randomized participants | Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study |

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| Other treatment | Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy) |
| Participant | A trial participant (can be a healthy volunteer or a patient) |
| Participant number | A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc. |
| Period | The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis |
| Personal data | Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples. |
| Premature participant withdrawal | Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or 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 participant |
| Screen Failure | A participant who did not meet one or more criteria that were required for participation in the study |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource |
| Start of the clinical trial | The start of the clinical trial is defined as the signature of the informed consent by the first participant |
| Study treatment | Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy |
| Study treatment discontinuation | When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation |
| Treatment arm/group | A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. |
| Treatment of interest | The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment. |
| Variable (or endpoint) | The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event. |

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| Withdrawal of study consent (WoC) | Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data |
| Withdrawal of study consent (WoC) / Opposition to use of data /biological samples | Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.<br>Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent. |

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## Protocol summary

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| Protocol number | CMBL949A12201 |
| Full Title | 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 |
| Brief title | Study to assess safety, tolerability and efficacy of SC administered MBL949 in obese participants with or without T2DM |
| Sponsor and Clinical Phase | Novartis, Phase II |
| Investigation type | Drug |
| Study type | Interventional |
| Purpose and rationale | This Phase II study is designed to assess the safety, tolerability, and efficacy for body weight reduction of different MBL949 regimens in obese participants with or without T2DM. Data from this study will support the future development of MBL949 for these disorders. |
| Primary Objective(s) | To evaluate the safety and tolerability of MBL949 in obese participants with or without T2DM by monitoring safety endpoints including adverse events and SAEs.<br>To evaluate the efficacy for body weight reduction of MBL949 in obese participants with or without T2DM. |
| Study design | The study comprises a screening/baseline period of up to 35 days (5 weeks), a 14-week treatment period in which participants will receive 8 doses of MBL949 or placebo at bi-weekly intervals starting on Day 1 and a 10 week follow-up period.<br>Commercially Confidential Information<br>Each participant will be randomized to 1 of 5 MBL949 arms or placebo and will receive eight dose administrations biweekly over 14 weeks. Refer to Section 4.2 for dosing rationale.<br>MBL949 Arm 1: Commercially Confidential Information<br>MBL949 Arm 2: Commercially Confidential Information<br>MBL949 Arm 3: Commercially Confidential Information<br>MBL949 Arm 4: Commercially Confidential Information<br>MBL949 Arm 5: Commercially Confidential Information<br>The enrollment flow is described in Figure 3-2. First, participants will be enrolled into MBL949 arm 1, MBL949 arm 2, and placebo arm with a 1:1:1 ratio in each randomization stratum. Upon completion, each arm will have 12 participants who complete week 16 weight assessment. After successful enrollment of MBL949 arm 1, MBL949 arm 2, and placebo, participants will be enrolled into MBL949 arm 3, MBL949 arm 4 and placebo arm with a 1:1:1 |

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|---|---|
| | ratio in each stratum. MBL949 arm 3 and MBL949 arm 4 will each have 12 participants who complete week 16 weight assessment; and an additional 12 participants will be added to placebo arm. MBL949 dosing arm 5 will be triggered if MBL949 dosing arm 1 is tolerated (i.e., 7 treated participants complete week 8). Participants will be enrolled into MBL949 arm 5 and placebo arm independently with a ratio of 2:1 in each stratum. MBL949 arm 5 will have 12 participants and 6 participants added in the placebo arm. Decisions on whether the study enrollment will be continued or discontinued will be based on ongoing safety and tolerability assessments throughout the study. |
| Study population | The study population will be comprised of obese (BMI ≥ 32 kg/m$^2$) adult males and females between 18 and 60 years old with or without T2DM. Commercially Confidential Information approximately 106 participants will be randomized based on an estimated dropout rate of 15% in order to achieve 90 total completers. |
| Key Inclusion criteria | **ALL participants:**<br>Participants must be between 18 to 60 years of age inclusive<br>• At screening participants must have:<br>• Body mass index (BMI) ≥ 32 kg/m$^2$, BMI = body weight (kg) / [Height (m)]$^2$<br>• Weight ≥ 77 kg, stable weight i.e., less than 1.5 kg self-reported change within 90 days and/or 3 kg self-reported weight loss within 6 months before screening<br>**Participants with T2DM**<br>• Diagnosed diabetes duration less than 10 years<br>• Hemoglobin A1C below ≤9%<br>• C-peptide ≥ 0.2 ng/ml<br>• If treated for T2DM, treatment may be limited to diet and exercise. In addition, treatment with one of the following anti-diabetic agents is permitted (stable for approximately 3 months prior to randomization):<br>• Metformin<br>• SGLT2 inhibitors (if prescribed as the first line i.e. single agent)<br>• DPP4 inhibitors<br>• Acarbose |
| Key Exclusion criteria | **ALL participants**:<br>Participants with:<br>• Systolic blood pressure less than 95 mmHg or greater than 155 mm Hg<br>• Diastolic blood pressure less than 60 mgHg or greater than 95 mg Hg<br>• Pulse rate less than 56 bpm or greater than 110 bpm<br>• History or presence of symptomatic cardiovascular disease such as angina pectoris, prior ASCVD events (including stroke, myocardial infarction, heart failure, claudication), or prior coronary revascularization<br>Commercially Confidential Information |

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|---|---|
| | Commercially Confidential Information<br>• Participation in an organized weight reduction program (e.g. Weight Watchers, NutriSystem) or any investigational weight loss trial within 6 months before screening<br>Commercially Confidential Information |
| Study treatment | • MBL949<br>• Placebo |
| Treatment of interest | The randomized treatment (MBL949 or placebo) |
| Efficacy assessments | • Weight (kg) |
| Commercially Confidential Information | |
| Key safety assessments | • Adverse Events<br>• Serious Adverse Event |
| Commercially Confidential Information | |

| | |
|---|---|
| Data analysis | The primary endpoint for efficacy is change in weight from baseline to week 16. Primary endpoints for safety and tolerability include frequency and severity of adverse events.<br>Commercially Confidential Information |
| Key words | Phase 2 study, Obese participants with or without type 2 diabetes mellitus, MBL949 |

# 1 Introduction

## 1.1 Background

Excess weight poses increased risk for a number of substantial co-morbidities. The most significant is type 2 diabetes mellitus (T2DM). Additional co-morbidities include, but are not limited to, excess risk for all forms of cardiovascular disease, liver disease, cognitive decline and several malignancies including hepatocellular carcinoma. Risk increases with weight as individuals progress from an overweight body mass index to class I obesity (BMI 30 to ≤ 34.9) to class II obesity (BMI 35 to ≤ 39.9) and class III obesity (BMI ≥ 40).

Rates of obesity in the United States have risen dramatically over the past two decades. The 2020 Centers for Disease Control report on obesity shows that there are 99 million obese individuals in the United States of which 9 million have class III obesity. In parallel, rates of diabetes have risen and in the United States to an estimated 34.2 million individuals, 26.8 million diagnosed and 7.3 million undiagnosed (DeFronzo et al 2015). The risk of diabetes increases with increasing weight. (Narayan et al 2007). The worldwide estimate for obesity associated diabetes is 463 million individuals.

Weight loss ameliorates the complications of obesity and can lead to complete remission and in some cases reversal of some of the comorbidities, including T2DM and non-alcoholic fatty liver disease (Gadde et al 2018). Short term calorie restriction leads to rapid improvements in insulin sensitivity (Kirk et al 2009). In individuals with diabetes, significant improvements are seen with weight loss in fasting glucose, insulin and hemoglobin HbA1c, are noted after 5% weight loss and improve as weight loss increases (Petersen et al 2005) (Wing et al 2011). Weight loss, especially of 15 kilograms and above can lead to remission of T2DM (Zhang et al 2018, Lean et al 2019), regardless of whether weight loss is achieved through surgery, diet or pharmacologic intervention.

Multiple classes of medications aimed at achieving weight loss are available, however generally efficacy is limited (Khera et al 2016). Surgical approaches such as bariatric surgery are effective in achieving significant and durable weight loss and remission of T2DM (le Roux and Heneghan 2018, Zhang et al 2018). Eligibility is reserved for individuals with a BMI of 40 kg/m$^2$ or greater or 35 kg/m$^2$ in the case of a co-morbidity. This leaves a substantial unmet medical need for a more effective pharmacotherapy for those who do not meet the criteria or do not want surgery. In addition, pharmacotherapy may benefit those with other obesity-associated disorders such as heart failure with preserved ejection fraction (HFpEF).

The paucity of effective weight lowering agents that could be used for the potential remission of T2DM led to substantial interest in the discovery that growth differentiation factor 15 (GDF15/MIC1) was elevated in conditions of significant weight loss and loss of appetite. Furthermore, in pre-clinical studies, treatment with a long acting analogue of GDF15 associated with reduction in weight. (Tsai et al 2014, Tsai et al 2016). The nature of this pathway remained elusive until the receptor – designated GFRAL, a member of the glial cell derived neurotrophic factor family, was identified and found to be expressed in the central nervous system. This discovery was soon followed by reports that the GFRAL receptor was required for the action of GDF15 defining the central nervous system as a site of GDF15 action (Emmerson et al 2017, Hsu et al 2017, Mullican et al 2017, Yang et al 2017).

## 1.2 Purpose

The purpose of this study is to assess the safety, tolerability, efficacy, CCI of subcutaneous (SC) MBL949 in obese participants with or without T2DM on weight loss. Data from this study will be used to inform the future development plans for MBL949 to reduce weight in obesity-associated disorders such as T2DM.

# 2 Objectives and endpoints

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for 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)** | **Endpoint(s) for exploratory objective(s)** |

| **Objective(s)** | **Endpoint(s)** |
|---|---|
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# 3 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.

Approximately106 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 the 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

Enrollment into MBL949 dose arms will be staggered as described below under Enrollment Flow and in Figure 3-2.

Participants will be evaluated for safety, tolerability, efficacy, CCI during the treatment and follow-up period as described below and shown in the assessment schedule (Table 8-1).

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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 (see inclusion/exclusion criteria Section 5). 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 as defined in Section 8 (Assessment Schedule). To facilitate study conduct, participants may come to the clinic on multiple days to complete the required assessments prior to Day 1, Commercially Confidential Information

### 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 as defined in Assessment schedule Table 8-1 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.

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Participants may be discharged from the site when the Investigator judges them to be medically stable, in general good health, and not needing further observation.

### 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 The specific assessments for each visit are detailed in Table 8-1 (Assessment Schedule). Participants in consultation with the Investigator may elect to have selected visits throughout the study, as specified on the Assessment Schedule, 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, CCI The specific assessments for the follow-up and end of study visits are detailed in Table 8-1.

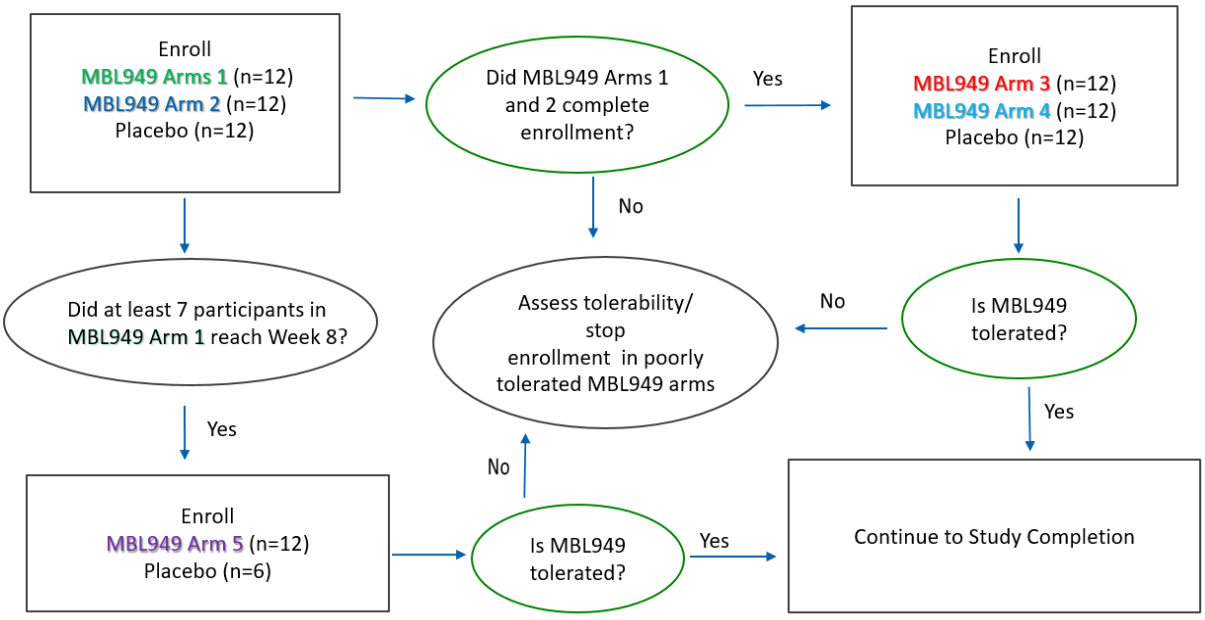
### Enrollment Flow

The enrollment flow is described in Figure 3-2 . First, participants will be enrolled into MBL949 arm 1, MBL949 arm 2, and placebo arm with a 1:1:1 ratio in each randomization stratum. Upon completion, each arm will have 12 participants who complete week 16 weight assessment. After successful enrollment of MBL949 arm 1, MBL949 arm 2, and placebo, participants will be enrolled into MBL949 arm 3, MBL949 arm 4 and placebo arm with a 1:1:1 ratio in each stratum. MBL949 arm 3 and MBL949 arm 4 will each have 12 participants who complete week 16 weight assessment; and an additional 12 participants will be added to placebo arm. MBL949

dosing arm 5 will be triggered if MBL949 dosing arm 1 is tolerated (i.e., 7 treated participants complete week 8). Participants will be enrolled into MBL949 arm 5 and placebo arm independently with a ratio of 2:1 in each stratum. MBL949 arm 5 will have 12 participants and 6 participants added to the placebo arm. Decisions on whether the study enrollment will be continued or discontinued will be based on ongoing safety and tolerability assessments throughout the study.

The ratio of obese only to obese T2DM individuals will be examined and consideration given to expanding enrollment to include additional participants with T2DM.

**Figure 3-2 Enrollment Flow**

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# 4 Rationale

## 4.1 Rationale for study design

**Table 4-1 Rationale for study design**

| Study Design Aspect | Rationale |
|---|---|
| ***Overall*** | This is a randomized, placebo-controlled, participant-and investigator-blinded, sponsor open-label study to evaluate the safety, tolerability, and efficacy of different MBL949 dosing regimens in obese participants with or without T2DM. In this study, a subcutaneous injection of MBL949 or placebo is planned at biweekly dosing intervals for 14 weeks to study the effect of MBL949 on weight loss. The design (5 different MBL949 treatment arms and placebo) allows assessment of the safety, tolerability and efficacy of different up titration regimens modelled to reach three different steady state plasma concentrations. This will help determine the optimal dosing regimen for MBL949. The randomized and blinded study design was chosen to minimize bias. |
| ***Randomization*** | Commercially Confidential Information<br><br>The randomization strategy as defined in Section 3 will maximize the statistical power for detecting differences in each strata while avoiding allocation bias. |
| ***Blinding*** | Blinding of participants and the investigator allows for an unbiased assessment of study endpoints, particularly for participant readouts such as adverse events and patient-reported outcomes. The blinding table, as detailed in Table 6-3 and will improve the accuracy of safety-related decisions during trial conduct, if needed. |
| ***Duration of study periods*** | Participants will be treated over a period of 14 weeks. The treatment period of 14 weeks followed by a 10 week evaluation period will allow adequate safety and efficacy data to be collected to assess the future potential of MBL949 in obesity-related disorders. This trial duration is comparable to the early assessment of weight loss efficacy identified in studies of weight loss agents. CCI |

| Study Design Aspect | Rationale |
|---|---|
| ***Placebo comparator*** | The use of placebo as a comparator is to provide a comparison group for the collection and assessment of safety, tolerability, and efficacy data while avoiding historical comparisons and helps to distinguish time-effects from drug effects. |

## 4.2 Rationale for dose/regimen and duration of treatment

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All 5 proposed dosing arms consist of a total of 8 bi-weekly SC injections over 14 weeks, followed by a 10 week follow-up period with primary endpoint evaluation at week 16.

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## 4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The use of a placebo comparator allows for a comparison group of safety CCI effects. An excipient matched placebo will be used to evaluate the benefit of MBL949 beyond any potential physiologic effect of the excipients, Commercially Confidential Information

## 4.4 Purpose and timing of interim analyses/design adaptations

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## 4.5 Risks and benefits

There may be a benefit of weight loss and improvement in metabolic parameters for participants in this study. Commercially Confidential Information

It is hoped that this study will benefit individuals with obesity through weight loss and thereby lead to a new therapeutic approach to treat obesity related comorbidities.

Risks to participants are minimized by the appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific guidelines for dosing holidays as well as stopping rules, and are included in this protocol.

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### 4.5.6 Injection site reaction

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### 4.5.7 Hypoglycemia

The risk of hypoglycemia in participants with T2DM in this study is low. Weight loss itself is not associated with hypoglycemia. Medications that increase the risk of hypoglycemia with weight loss are those that induce insulin secretion such as sulfonylureas and insulin. These are excluded in this study.

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### 4.5.9 Blood sample volume

The total volume of blood collected over a period of approximately 27 weeks is smaller than the volume of a typical blood donation. This sampling will be performed in each participant of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule Table 8-1.

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See the Section 8.5.3.1 on the potential use of residual samples.

### 4.5.10 Potential risk associated with the COVID-19 pandemic

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the COVID-19 pandemic, including COVID-19 testing of participants if applicable. The Novartis clinical trial team will review the situation in each participating country and work with investigators to continue to ensure the safety of participants during the conduct of the trial. A benefit/risk assessment has been made and has been determined to be positive for the participants to be enrolled. As the COVID-19 situation evolves, investigators must use their best judgement to minimize risk to participants during the conduct of the study. Study specific details of vaccination of COVID-19 is provided in Section 8.1.1.3 of the protocol.

MBL949 is not an immunosuppressive agent, and is not expected to compromise participants' immune systems.

### 4.5.11 New diagnosis of T2DM

Per standard of care, typically individuals with a new diagnosis of T2DM receive counseling on diet and exercise through their health care provide and dietitian. Evaluation of diet and exercise usually proceeds for 3-4 months after which initiation of an anti-diabetes drug is typically prescribed if diet and exercise therapy are ineffective. Thus enrollment in the study would not materially change or delay T2DM management.

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## 4.7 Rationale for Public Health Emergency mitigation

In Commercially Confidential Information the event of a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, additional mitigation procedures to ensure participant safety and trial integrity may be implemented. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or additional visits by OHPs to the participant´s home, can replace onsite study visits (in addition to the already planned off-site visits), for the duration of the disruption until it is safe for the participant to visit the site again.

Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

# 5 Study Population

The study population will include obese (BMI >/= 32 kg/$m^2$) men and women between 18 and 60 years of age with or without T2DM. To account for 15% drop out rate, approximately 106 participants are planned to be randomized to achieve 90 total completers. The Investigator must ensure that all participants being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the Investigator, in order that the study population will be representative of all eligible participants. Participant selection is to be established by checking through all eligibility criteria at both screening, baseline, and prior to randomization as applicable. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the site. Deviation from any entry criterion excludes a participant from enrollment into the study.

## 5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

### ALL PARTICIPANTS

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. At screening, men and women must be between 18 and 60 years of age inclusive
4. At screening, participants must have a body mass index: ≥ 32 kg/m$^2$, weight ≥ 77 kg, stable body weight i.e., less than 1.5 kg self-reported change within 90 days and/or 3 kg self-reported change within 6 months prior to screening [BMI = Weight (kg) / [Height (m)]$^2$

### PARTICIPANTS WITH T2DM

5. Diagnosed T2DM as documented by medical history and confirmed by Investigator and with diagnosed duration < 10 yrs, HbA1c ≤ 9%, and fasting C-peptide ≥ 0.2 ng/ml
6. If treated for T2DM, treatment must be limited to diet and exercise and treatment with **one** of the following anti-diabetic agents is permitted (stable for 90 days prior to randomization):
   - Metformin
   - SGLT2i inhibitors (if prescribed as the first line, i.e. single agent)
   - DPP4 inhibitors
   - Acarbose

## 5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

### ALL PARTICIPANTS

1. At screening, vital signs (blood pressure and pulse rate) will be assessed in the sitting position (see Table 8-2 for detailed description on vital signs methodology). The sitting vital signs defined below are exclusionary:
   - systolic blood pressure less than 95 mm Hg or greater than 155 mm Hg
   - diastolic blood pressure less than 60 mg Hg or greater than 95 mm Hg
   - pulse rate less than 56 or greater than 110 bpm

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2. History of bariatric surgery, Roux-en-Y Gastric Bypass, Sleeve Gastrectomy, gastric banding, and any other intra abdominal procedures designed for weight loss at screening

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3. Commercially Confidential Information

4. History of myocardial infarction within 2 years of screening
5. Commercially Confidential Information

6.
7.

8.

9. Diet attempts using herbal supplements or over-the-counter medications within 90 days before screening
10. Participation in an organized weight reduction program (e.g. WeightWatchers, NutriSystem) or any investigational weight loss trial within 6 months before screening
11. Commercially Confidential Information

12.

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20. Commercially Confidential Information

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Commercially Confidential Information

28.

**PARTICIPANTS WITH T2DM**

29. Commercially Confidential Information

30.

31.

# 6 Treatment

## 6.1 Study treatment

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

### 6.1.1 Investigational and control drugs

**Table 6-1 Investigational and control drug**

| Investigational/ Control Drug (Name and Strength) | Pharmaceutical Dosage Form | Route of Administration | Supply Type | Sponsor (global or local) |
|---|---|---|---|---|
| MBL949 10 mg/mL | Solution for injection | Subcutaneous Use | Open label; bulk supplies | Sponsor (global) |
| Placebo 0 mg/mL | Solution for injection | Subcutaneous Use | Open label; bulk supplies | Sponsor (global) |

The investigational drug, MBL949 10 mg/mL and placebo, will be prepared by Novartis and supplied to the Investigator as an open labeled medication to be dispensed by the unblinded pharmacist or designated staff at the investigator site according to the randomization schedule. Study medication will be administered by an unblinded staff at the site.

MBL949 drug product is formulated for subcutaneous injection as 10 mg/mL liquid in vial. Details of the dose administration can be found in the Pharmacy Manual.

Each vial of MBL949 contains 10 mg of drug product formulated as a solution for injection. In addition to the active substance, each vial contains the following excipients: CCI

A 20% overfill is provided to allow the withdrawal of the designated amount of 10 mg/mL MBL949 upon administration.

MBL949 10 mg solution for injection is packaged in glass vials with coated rubber stoppers sealed with aluminum caps with plastic flip-off disks, which are in common use for packaging of parenteral products.

### 6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

### 6.1.3 Treatment arms/group

Participants will be assigned to one of five arms in this study; MBL949 dosing arms 1-5 and placebo arm. MBL949 Arm 1, MBL949 arm 2 and placebo to be enrolled in a 1:1:1 ratio in each randomization stratum. MBL949 arm 3 and MBL949 arm 4 and placebo will be enrolled in a 1:1:1 ratio in each randomization stratum. If triggered, MBL949 dosing arm 5 will be randomized in a 2:1 ratio of MBL949 or placebo. Refer to Section 3 for study design in Figure 3-1 and enrollment flow Figure 3-2.

Study treatments are defined as:

- Once every other week SC injection of MBL949 mg, for dosing details refer to Section 4.2
- Once every other week SC injection of Placebo 0 mg

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## 6.2 Other treatment(s)

### 6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is

already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Medications allowed in the study as chronic therapy:

- Oral anti-diabetic therapy (limited to metformin and/or DPP4 inhibitor or acarbose), with stable treatment for 90 days prior to randomization, for diabetes management during the trial.
- Treatment with SGLT2i (permitted if first line agent)

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### 6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed per the prohibition period below.

**Table 6-2 Prohibited medication**

| Medication | Prohibition period | Action taken |
|---|---|---|
| Over the counter anti-obesity medications, nutritional supplements, dietary interventions particularly chromium picolinate and sodium vanadate (other than described in protocol) or over the counter products of weight loss | Within 90 days prior to randomization and through duration of study | Discontinue study treatment |
| Prescription anti obesity agents and GLP1 receptor agonists such as (e.g., semaglutide, exenatide, liraglutide, lixisenitide, albiglutide, dulaglutide) Refer to Section 5.2<br>Sulfonylureas or thiazolidinediones<br>Insulin | Within 6 months prior to randomization and through duration of study | Discontinue study treatment |

### 6.2.3 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

## 6.3 Participant numbering, treatment assignment, randomization

### 6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

### 6.3.2 Treatment assignment, randomization

Randomization for this study will be managed by Novartis Interactive Response Technology (IRT). The randomization numbers will be generated using the following procedure to ensure

that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

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

## 6.4 Treatment blinding

This is a participant-and investigator-blinded, sponsor open-label study. Participants and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

### Site staff

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

- Designated unblinded site staff, CCI for dose administration: required due to the range of different dose levels and to maintain the investigator and site staff blinding.
- Unblinded pharmacist who is independent of the study team will be required in order to manage drug product supplied in bulk and prepare doses.

  This unblinded pharmacist will receive a randomization assignments via IRT. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff, with the exception of the designated unblinded site staff who will administer the dose.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via the IRT system.

### 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
- Commercially Confidential Information

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 participants. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist. The names of the unblinded monitor(s) are detailed in the monitoring plan.

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.

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The study statistician will be able to access the randomization list at any time throughout the study and is allowed to share unblinded information with the rest of the clinical team including an unblinded study lead and Trial Medical Expert as appropriate for internal decision purposes, as outlined in Table 6-3. Commercially Confidential Information

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 6-3 Blinding levels**

| Role | Time or Event | | | |
|---|---|---|---|---|
| | Randomization list generated | Treatment allocation & dosing | Safety event (single subject unblinded) | CCI dose escalation |
| **Subjects/Patients** | 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 | UI | UI | UI |
| **All other sponsor staff not identified above** | B | UI | UI | UI |

B Remains blinded

UI Allowed to be unblinded on individual patient level

## 6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments or modifications are not permitted.
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## 6.6 Additional treatment guidance

### 6.6.1 Treatment compliance

MBL949 will be administered by clinical personnel at the site CCI under delegation of the Investigator following the procedures outlined in the Pharmacy manual.

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### 6.6.2 Recommended treatment of adverse events

This is the first study of MBL949 in obese participants with or without T2DM receiving repeat doses of MBL949, therefore, careful management of potential adverse events is essential.
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All medications required or recommended to manage adverse events associated with study drug should be recorded. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

#### Management of injection site reactions

If a participant experiences mild injection site discomfort, the Investigator may attempt applying a cold compress.

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**Management of hypoglycemia**

1. In participants on anti-diabetic medication, the investigator should monitor glucose levels closely by recommending frequent blood glucose monitoring as per standard diabetes care guidelines.
2. If symptomatic hypoglycemia occurs:
    - The investigator should provide standard of care to maintain glucose balance. This may involve reducing or discontinuing anti-diabetic medication.

### 6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to unmanageable adverse events if deemed necessary by the site PI and Sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team 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 IRT at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

## 6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1). MBL949 will be administered to the participant via subcutaneous injection. Refer to the Pharmacy Manual for further details.

A unique medication number is printed on the study medication label.

Unblinded investigator staff will identify the treatment to dispense to the participant by contacting the IRT and obtaining the treatment assignment. As per the treatment assigned to the participant, unblinded investigator staff will select the study treatment to dispense to the participant and record the batch number on the accountability logs accordingly.

### 6.7.1 Handling of study treatment and additional treatment

#### 6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Study treatment must be prepared by an unblinded pharmacist to ensure treatment masking. Please refer to the Pharmacy Manual for complete preparation instructions.

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. If study treatment is administered off site, the unblinded OHP study personnel will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### 6.7.1.2 Handling of additional treatment

Not applicable.

### 6.7.2 Instruction for prescribing and taking study treatment

MBL949 or placebo will be administered to the participant via subcutaneous injection at the site Commercially Confidential Information . Please refer to the Pharmacy Manual for detailed instructions.

# 7 Informed consent procedures

Eligible participants may only be included in the study after providing (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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed 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 participant informed consent and should be discussed with the participant 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 participant.

The following informed consents are included in this study:

Main study consent, which also includes:

- Commercially Confidential Information
- 
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Commercially Confidential Information

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 requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

# 8 Visit schedule and assessments

The Assessment Schedule Table 8-1 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-1 or as close to the designated day/time as possible as per described visit window. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue from study treatment are to return for an end of treatment (EoT) visit (Day 99), as soon as possible and if able, attend the follow up visits on days 100, 103, 108, 112, 140 and 169 week visits for safety.

Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time the assessments listed for the final visit should be performed. At this final visit the adverse event and concomitant medications not previously report must be recorded on the CRF.

If unable to complete the final visit, the participant will be asked to have the following assessments performed. See details on study discontinuation in Section 9.1.1

- Physical exam
- ECG

- Vitals
- Weight
- Safety labs

The “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

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**Table 8-1 Assessment Schedule**

| Period | Screening | | Treatment | | | | | | | | | | | | Post-Treatment Follow-Up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Baseline** | **Day 1** | **Day 2[2]** | **Day 5[2]** | **Day 7[2]** | **Day 10[2]** | **Day 15 / Week 2[2]** | **Day 29 / Week 4[2]** | **Day 43 / Week 6[2]** | **Day 57 / Week 8[2]** | **Day 71 / Week 10[2]** | **Day 85 / Week 12[2]** | **Day 99/Week 14[2]** | **Day 100[2]** | **Day 103[2]** | **Day 105[2]** | **Day 108[2]** | **Day 112/Week 16[2]** | **Day 140/Week 20[2]** | **Day 169/Week 24/ EOS[2]** |
| **Visit Numbers[1]** | **1** | **20** | **100** | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** | **210** | **220** | **230** | **240** | **250** | **260** | **270** | **1999** |
| **Days** | **-35 to -15** | **-14 to -1** | **1** | **2** | **5** | **7** | **10** | **15** | **29** | **43** | **57 ±1** | **71** | **85** | **99** | **100** | **103** | **105** | **108** | **112 ±1** | **140** | **169** |
| **Time (post-dose)** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144h ±2** | **216h ±2** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144 h ±2** | **216h ±2** | **312h ±2** | **984h ±6** | **1680 ±6** |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |
| Inclusion / Exclusion criteria | X | X | X[3] | | | | | | | | | | | | | | | | | | |
| IRT | X | | X | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | |
| Alcohol Test and Drug Screen | S | | | | | | | | | | | | | | | | | | | | |
| HIV screen | S | | | | | | | | | | | | | | | | | | | | |
| Hepatitis screen | S | | | | | | | | | | | | | | | | | | | | |
| COVID-19 testing[4] | S | As required per COVID-19 at the site and per local regulations | | | | | | | | | | | | | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |
| Psychological evaluation | X | | | | | | | | X | | | | | | | | | | | | X |

| **Period** | **Screening** | | **Treatment** | | | | | | | | | | | | **Post-Treatment Follow-Up** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Baseline** | **Day 1** | **Day 2[2]** | **Day 5[2]** | **Day 7[2]** | **Day 10[2]** | **Day 15 / Week 2[2]** | **Day 29 / Week 4[2]** | **Day 43 / Week 6[2]** | **Day 57 / Week 8[2]** | **Day 71 / Week 10[2]** | **Day 85 / Week 12[2]** | **Day 99/Week 14[2]** | **Day 100[2]** | **Day 103[2]** | **Day 105[2]** | **Day 108[2]** | **Day 112/Week 16[2]** | **Day 140/Week 20[2]** | **Day 169/Week 24/ EOS[2]** |
| **Visit Numbers[1]** | **1** | **20** | **100** | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** | **210** | **220** | **230** | **240** | **250** | **260** | **270** | **1999** |
| **Days** | **-35 to -15** | **-14 to -1** | **1** | **2** | **5** | **7** | **10** | **15** | **29** | **43** | **57 ±1** | **71** | **85** | **99** | **100** | **103** | **105** | **108** | **112 ±1** | **140** | **169** |
| **Time (post-dose)** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144h ±2** | **216h ±2** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144 h ±2** | **216h ±2** | **312h ±2** | **984h ±6** | **1680 ±6** |
| Pregnancy and assessments of fertility | S | | S | | | | | | S | | S | | S | | | | | | | | S |
| Medical history/current medical conditions | X | As Required | | | | | | | | | | | | | | | | | | | |
| Concomitant therapies | X | As Required | | | | | | | | | | | | | | | | | | | |
| Physical Examination | S[5] | S | S | | | | | | S | | | | S | | | | | | S | | S |
| Body Height | X | | | | | | | | | | | | | | | | | | | | |
| Body Weight | X | X | X | X | X | | X | X | X | X | X | X | X | X | | | | | X | X | X |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |
| Vital Signs | X | X | | | | | | | | | | | | | | | | | | | |
| Electrocardiogram (ECG) | X | X | X | | | | | | X | | X | | X | | | | | | X | | X |
| Hematology | X | X | X[6] | | | | X | X | X | X | X | X | X | X | | | | | X | X | X |
| Clinical Chemistry | X | X | X[6] | | | | X | X | X | X | X | X | X | X | | | | | X | X | X |
| Urinalysis | X | X | X | | | | | | X | | X | | X | | | | | | | | X |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |

| Period | Screening | | Treatment | | | | | | | | | | | | Post-Treatment Follow-Up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Baseline** | **Day 1** | **Day 2[2]** | **Day 5[2]** | **Day 7[2]** | **Day 10[2]** | **Day 15 / Week 2[2]** | **Day 29 / Week 4[2]** | **Day 43 / Week 6[2]** | **Day 57 / Week 8[2]** | **Day 71 / Week 10[2]** | **Day 85 / Week 12[2]** | **Day 99/Week 14[2]** | **Day 100[2]** | **Day 103[2]** | **Day 105[2]** | **Day 108[2]** | **Day 112/Week 16[2]** | **Day 140/Week 20[2]** | **Day 169/Week 24/ EOS[2]** |
| **Visit Numbers**[1] | **1** | **20** | **100** | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** | **210** | **220** | **230** | **240** | **250** | **260** | **270** | **1999** |
| **Days** | **-35 to -15** | **-14 to -1** | **1** | **2** | **5** | **7** | **10** | **15** | **29** | **43** | **57 ±1** | **71** | **85** | **99** | **100** | **103** | **105** | **108** | **112 ±1** | **140** | **169** |
| **Time (post-dose)** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144h ±2** | **216h ±2** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144 h ±2** | **216h ±2** | **312h ±2** | **984h ±6** | **1680 ±6** |
| Study drug administration | | | X | | | | | X | X | X | X | X | X | X | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |
| HbA1C | X | | | | | | | | | | | | | | | | | | | | |

| Period | Screening | | Treatment | | | | | | | | | | | | Post-Treatment Follow-Up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Baseline** | **Day 1** | **Day 2[2]** | **Day 5[2]** | **Day 7[2]** | **Day 10[2]** | **Day 15 / Week 2[2]** | **Day 29 / Week 4[2]** | **Day 43 / Week 6[2]** | **Day 57 / Week 8[2]** | **Day 71 / Week 10[2]** | **Day 85 / Week 12[2]** | **Day 99/Week 14[2]** | **Day 100[2]** | **Day 103[2]** | **Day 105[2]** | **Day 108[2]** | **Day 112/Week 16[2]** | **Day 140/Week 20[2]** | **Day 169/Week 24/ EOS[2]** |
| **Visit Numbers[1]** | **1** | **20** | **100** | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** | **210** | **220** | **230** | **240** | **250** | **260** | **270** | **1999** |
| **Days** | **-35 to -15** | **-14 to -1** | **1** | **2** | **5** | **7** | **10** | **15** | **29** | **43** | **57 ±1** | **71** | **85** | **99** | **100** | **103** | **105** | **108** | **112 ±1** | **140** | **169** |
| **Time (post-dose)** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144h ±2** | **216h ±2** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **24h ±2** | **96h ±2** | **144 h ±2** | **216h ±2** | **312h ±2** | **984h ±6** | **1680 ±6** |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |
| Adverse Events | | As Required | | | | | | | | | | | | | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | | | | | | | | | | |
| Study completion information | | | | | | | | | | | | | | | | | | | | | X |

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Commercially Confidential Information

| Period | Screening | | Treatment | | | | | | | | | | | | Post-Treatment Follow-Up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Day 1 | Day 2[2] | Day 5[2] | Day 7[2] | Day 10[2] | Day 15 / Week 2[2] | Day 29 / Week 4[2] | Day 43 / Week 6[2] | Day 57 / Week 8[2] | Day 71 / Week 10[2] | Day 85 / Week 12[2] | Day 99/Week 14[2] | Day 100[2] | Day 103[2] | Day 105[2] | Day 108[2] | Day 112/Week 16[2] | Day 140/Week 20[2] | Day 169/Week 24/ EOS[2] |
| Visit Numbers[1] | 1 | 20 | 100 | 110 | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 | 210 | 220 | 230 | 240 | 250 | 260 | 270 | 1999 |
| Days | -35 to -15 | -14 to -1 | 1 | 2 | 5 | 7 | 10 | 15 | 29 | 43 | 57 ±1 | 71 | 85 | 99 | 100 | 103 | 105 | 108 | 112 ±1 | 140 | 169 |
| Time (post-dose) | - | - | - | 24h ±2 | 96h ±2 | 144h ±2 | 216h ±2 | - | - | - | - | - | - | - | 24h ±2 | 96h ±2 | 144 h ±2 | 216h ±2 | 312h ±2 | 984h ±6 | 1680 ±6 |

[3] Final review of all eligibility criteria prior to dosing
[4] As required per COVID-19 protocols at the site and local regulations
[5] Complete Physical examination to be done. All other PEs will be abbreviated.
[6] To be collected pre dose
[7] Commercially Confidential Information
[8]
[9]
[10]
[11]
[12]
[13]
[14]
[15] To be administered fasting, before lunch, before dinner, and before bedtime

## 8.1 Screening

### Screening

It is permissible to re-screen a participant if s/he fails the initial screening and reason for screen fail is reasonably expected to have resolved; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

### 8.1.1 Eligibility screening

#### 8.1.1.1 Diagnosis of T2DM at Screening

If diagnosed with diabetes at screening, enrolling in the study versus receiving medical care from participant's healthcare provider should be discussed (see Section 4.5.11).

#### 8.1.1.2 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg) and, if standard local practice, Hepatitis B core antigen (HBcAg). Screening for Hepatitis C will be based in HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site e.g. Western blot. Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

#### 8.1.1.3 COVID-19

COVID-19 testing and frequency of testing in this study will follow the local guidance and COVID-19 protocols according to the study site and/or OHP.

COVID-19 vaccination (single dose vaccine or two dose vaccine) is recommended prior to enrollment and at least 2 weeks before dosing and evidence of minimal side effects. At screening unvaccinated individuals will be encouraged to receive a COVID vaccine. Vaccination during the trial is permitted and careful review of potential side effects of vaccination that may include nausea and vomiting that may mimic AEs will require documentation. Novartis has adopted for this reason the MHRA guidelines last updated on 16th March 2021 on how to manage clinical trials during Coronavirus pandemic which includes recommendations on risk assessment and reporting of an SAE in relation to the vaccine during the trial period.

#### 8.1.1.4 Alcohol test, Drug screen

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

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### 8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information and informed consent pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE Section 10.1.2 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

## 8.2 Participant demographics/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 need to 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. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

## 8.3 Efficacy

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Efficacy will be assessed by changes in Commercially Confidential Information weight from Baseline and Day 112.

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### 8.3.1 Appropriateness of efficacy assessments

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This repeat dose study will expand our understanding of the effect on weight, Commercially Confidential Information in obese participants with our without T2DM over a 14 week treatment period followed, a two week evaluation. Additional evaluations for safety will be monitored for 10 weeks after the last dose.

### 8.3.2 Body weight and central obesity

#### Weight

Weight will be measured to the nearest 0.1 kg at visits indicated in the Assessment Schedule Table 8-1 on a calibrated scale per site specific standards. The measurement will be performed with the study participant dressed in light clothing or hospital gown and without shoes. Participants must void prior to having their weight measured.

#### Height

Height will be measured in centimeters without shoes.

#### Body mass index (BMI)

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

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

Rounding should be done to the nearest whole number.

The Screening Visit height measurement will be used for BMI calculation.

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## 8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.1.

**Table 8-2 Safety Assessments**

| Assessment | Specification |
|---|---|
| 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, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams may be performed.<br>A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be performed at all visits starting from visit 3 except where a complete physical examination is required (see above).<br>Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. |
| Vital signs | Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements. |

| Assessment | Specification |
|---|---|
| | After the participant has been sitting for approximately 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g. OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.<br>If vital signs are out-of-range at screening (see Inclusion Criteria Section 5.1 of the protocol for details), two additional readings can be obtained, so that up to three consecutive assessments can be made, with the participant seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the participant to qualify.<br>Efforts should be made to allow for a quiet, relaxed environment for the participants to have vital sign measurements taken to avoid the "white coat syndrome".<br>In case of repeated vital assessments, the eCRF should contain the qualifying results.<br>Clinically notable vital signs are defined in Section 16.1of the protocol. |
| Psychological Evaluation | Assessment of mental health will be conducted by the Investigator or qualified health professional to determine the participant's ability to participate in the study at Screening and as specified on the Assessment Schedule. |

### 8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Clinically notable laboratory findings are defined in Section 16.1 (Appendix 1). Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

### 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.

**Table 8-3 Laboratory evaluations**

| Test Category | Test Name |
|---|---|
| Hematology | Hematocrit, Hemoglobin, Platelets, White blood cells, Red blood cells |
| Chemistry | Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (*non-fasting unless specified otherwise)* |
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| Urinalysis | Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) |
| | CCI |
| Coagulation | International normalized ratio [INR]), Partial thromboplastin time (PTT) |
| Hepatitis markers | HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR (baseline) |
| Pregnancy Test | Serum (refer to Pregnancy and assessments of fertility Section 10.1.4) |
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### 8.4.2 Electrocardiogram (ECG)

ECGs must be recorded approximately after 10 minutes rest in the supine position to ensure a stable baseline. In the case of a series of assessments, ECG should be first assessment obtained while participant is at rest.

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

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 according to the following formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Single 12-lead ECGs are collected and results are entered into the appropriate eCRF page. The original ECGs on on non-heat-sensitive paper, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, participant initials, participant number, date and time, and filed in the study site source documents. Investigator should document clinical evaluation in source. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

### 8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are capable of becoming pregnant and not surgically sterile will have regular pregnancy testing. Serum pregnancy testing will be done at Screening, on Day 1 prior to the first dose, every month while in study, and at the end of the study. Additional pregnancy testing might be performed if requested by local requirements.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. Refer to Section 4.7.

It is important that participants are instructed to perform the urine pregnancy test first and only if the rest result is negative proceed with administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., follow country-specific measures).

#### Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

### 8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

### 8.4.5 Injection/infusion site reaction

Any local tolerability symptoms/signs related to injection will be reported as adverse events and followed until resolution.

## 8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

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# 9 Study discontinuation and completion

## 9.1 Discontinuation and completion

### 9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which study participation might result in a safety risk to the participant
- If a liver or renal event occurs, follow guidelines outlined in Section 16 regarding discontinuation of study treatment.
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant’s overall status, prevents the participant from continuing participation in the study
- Emergence of any medical or psychological issue in which in the PI assessment of the participant leads to the conclusion now has a risk of participating
- Following emergency unblinding

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up Section 9.1.3. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

### 9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason is not done.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table refer to Section 8.

### 9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

### 9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

## 9.2 Withdrawal of informed consent/Opposition to use data/biological samples

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

## 9.3 Study stopping rules

### Overall study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs:

- Two or more drug related-SAEs identified after Safety Review;
- Two or more participants experience hypersensitivity reactions or injection reactions of moderate to severe intensity;
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.

- The Sponsor unilaterally requests it.

If any of the above stopping rules are met, the Competent Authorities and Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of the temporary halt of study in accordance with local regulations. The study may resume following the safety review if the Sponsor and Lead Investigator agree it is safe to proceed and after approval to restart the study is obtained from the Competent Authorities and IRB/IECs.

## 9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes 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 (e.g., each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them). All attempts to contact the participant should be met.

# 10 Safety monitoring and reporting

## 10.1 Definition of adverse events and reporting requirements

### 10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

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

Adverse events must be recorded by the Investigator/site staff under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
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 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

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

- Dose not changed
- Dose increased/Dose reduced
- Drug interrupted/withdrawn

6. Its outcome (recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until the end of study visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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

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

Clinically significant abnormal laboratory values or test results must 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 participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

### 10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant 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 (please refer to the ICH-E2D Guidelines).

- 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 obesity-associated disorders
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - 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
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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 (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

### 10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

1. **Screen Failures:** SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. **Treated Participants**: SAEs collected between time participant signs ICF after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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 CMO & PS 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.

Any SAEs experienced after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

### 10.1.4 Pregnancy reporting

#### Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant 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.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the [study treatment] any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

### 10.1.5 Reporting of study treatment 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, participant 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.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

**Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse**

| Treatment error type | Document in Dosing CRF (Yes/No) | Document in AE eCRF | Complete SAE form |
|---|---|---|---|
| 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 the respective sections.

## 10.2 Additional Safety Monitoring

Not applicable.

# 11 Data Collection and Database management

## 11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

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

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

## 11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (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.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

## 11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDC or eCRFs) 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 field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & 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 participant 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 participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

# 12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

## 12.1 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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## 12.2 Participant demographics and other baseline characteristics

Baseline will be defined as the last non-missing assessment prior to the first dose of study drug, unless specified otherwise.

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for safety analysis set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

## 12.3 Treatments

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 for the FAS.

## 12.4 Analysis of the primary endpoint(s)/estimand(s)

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

### 12.4.1 Definition of primary endpoint(s)/estimand(s)

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

### 12.4.2 Statistical model, hypothesis, and method of analysis

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### 12.4.3 Safety endpoints

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

#### Adverse events

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

### Vital signs

All vital signs data will be listed by treatment group, 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.

### 12-lead ECG

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

Abnormal ECG, especially HR, will be flagged and listed by treatment group, participant and visit/time. Summary statistics of all ECG data will be provided by treatment and visit/time. Categorical analyses of QT/QTc, PR, QRS, QRS, RR intervals and HR data based on the number of participants meeting or exceeding predefined limits, in terms of absolute values or changes from baseline, will be presented. In addition, a listing of these participants will be produced by treatment group.

### Clinical laboratory evaluations

If normal ranges are available, abnormal laboratory data will be flagged and listed by treatment group, participant, and visit/time. Summary statistics of select laboratory parameters will be provided by treatment group and visit/time.

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### 12.4.5 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 analysis. Commercially Confidential Information

### 12.4.6 Sensitivity analyses for primary endpoint/estimand

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### 12.4.7 Supplementary analysis

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### 12.4.8 Supportive analyses

To evaluate the effect of intercurrent events on efficacy/safety results, primary analysis may be performed on FAS including/excluding some intercurrent events cases described in Section 12.4.4 as seen fit.

## 12.5 Analysis of secondary endpoints/estimands

None.

## 12.6 Analysis of exploratory endpoints

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Commercially Confidential Information

## 12.7 Interim analyses

Commercially Confidential Information

## 12.8 Sample size calculation

### 12.8.1 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 5 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 a 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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# 13 Ethical considerations and administrative procedures

## 13.1 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 CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 13.2 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, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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.

## 13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and

posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

## 13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

## 13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication

# 14 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 participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

## 14.1 Protocol amendments

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

Only amendments that are required for participant safety 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 participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

# 15 References

References are available upon request

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# 16 Appendices

## 16.1 Appendix 1: Clinically notable laboratory values and vital signs

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 than60 or greater than 95 mgHg
  - Pulse rate less than 56 or greater than 110 bpm

If these clinically notable vital signs are observed, investigators should initiate appropriate, guideline directed clinical care and inform the Sponsor.

## 16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

**Table 16-1 Liver event and laboratory trigger definitions**

| | **Definition/ threshold** |
|---|---|
| Liver laboratory triggers<br>If ALT, AST and total bilirubin normal at baseline: | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5<br>• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• Any adverse event potentially indicative of a liver toxicity* |
| If ALT or AST abnormal at baseline: | • ALT or AST > 2x baseline or > 300 U/L (whichever occurs first) |
| *These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal | |

**Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms**

| | **ALT** | **TBL** | **Liver Symptoms** | **Action** |
|---|---|---|---|---|
| **ALT increase without bilirubin increase:** | | | | |
| | **If normal at baseline:**<br>ALT > 3 x ULN | Normal<br>For patients with Gilbert's syndrome: No change in baseline TBL | None | • **No change to study treatment**<br>• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours.<br>• Follow-up for symptoms. |
| | **If elevated at baseline:**<br>ALT > 2 x baseline<br>or > 300 U/L (whichever occurs first) | | | |

| | ALT | TBL | Liver Symptoms | Action |
|---|---|---|---|---|
| | **If normal at baseline:**<br>ALT > 5 x ULN for more than two weeks | Normal<br>For patients with Gilbert's syndrome: No change in baseline TBL | None | • **Interrupt study drug**<br>• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours.<br>• Follow-up for symptoms.<br>• Initiate close monitoring and workup for competing etiologies.<br>• Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. |
| | **If elevated at baseline:**<br>ALT > 3 x baseline<br>or > 300 U/L (whichever occurs first) for more than two weeks | | | |
| | **If normal at baseline:**<br>ALT > 8 x ULN | Normal | None | |
| **ALT increase with bilirubin increase:** | | | | |
| | **If normal at baseline:**<br>ALT > 3 x ULN | TBL > 2 x ULN (or INR > 1.5)<br>For patients with Gilbert's syndrome: Doubling of direct bilirubin | None | |
| | **If elevated at baseline:**<br>ALT > 2 x baseline<br>or > 300 U/L (whichever occurs first) | | | |
| | **If normal at baseline:**<br>ALT > 3 x ULN | Normal or elevated | Severe fatigue, nausea, vomiting, right upper quadrant pain | |
| | **If elevated at baseline:**<br>ALT > 2 x baseline<br>or > 300 U/L (whichever occurs first) | | | |

**Table 16-3 Follow up requirements for liver laboratory triggers**

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| Total Bilirubin (isolated) | | |
| >1.5 – 3.0 ULN | • Maintain treatment<br>• Repeat LFTs within 48-72 hours | Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline |
| > 3 - 10 × ULN (in the absence of known Gilbert syndrome) | • Interrupt treatment<br>• Repeat LFT within 48-72 hours<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF | Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT)<br>Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) |
| > 10 x ULN | • Discontinue the study treatment immediately<br>• Hospitalize the participant<br>• Establish causality<br>• Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF | ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) |
| Any AE potentially indicative of a liver toxicity* | • Consider study treatment interruption or discontinuation<br>• Hospitalization if clinically appropriate<br>• Establish causality<br>• Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF | Investigator discretion |
| [a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN<br>[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. | | |

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

## 16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

**Table 16-4 Specific Renal Alert Criteria and Actions**

| | |
|---|---|
| Confirmed serum creatinine increase 25 – 49% | • Consider causes and possible interventions<br>• Follow up within 2-5 days |
| Serum creatinine increase ≥ 50%+ OR if <18 years old, eGFR < 35 mL/min/1.73 $m^2$ | • Consider causes and possible interventions<br>• Repeat assessment within 24-48h if possible<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected<br>• Consider patient hospitalization and specialized treatment |
| New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory) | • Consider causes and possible interventions<br>• Assess serum albumin & serum total protein<br>• Repeat assessment to confirm<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected |
| New onset hematuria ≥ 3+ on urine dipstick | **Assess & document:**<br>• Repeat assessment to confirm<br>• Distinguish hemoglobinuria from hematuria<br>• Urine sediment microscopy<br>• Assess sCr<br>• Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation<br>• Consider bleeding disorder |

+ Corresponds to KDIGO criteria for Acute Kidney Injury

### 16.3.1 Renal Event Follow-Up

**Table 16-5 Renal Event Follow-Up**

| |
|---|
| **Assess, document and record in CRF:**<br>• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells<br>• Blood pressure and body weight<br>• Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid<br>• Urine output |
| 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 |
| **Monitor patient regularly (frequency at investigator's discretion) until -**<br>• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or<br>• Event stabilization: sCr level with ±10% variability over last 6 months or proteincreatinine ratio stabilization at a new level with ±50% variability over last 6 months.<br>• Analysis of urine markers in samples collected over the course of the DIN event |