REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

A RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF THE LEPR AGONIST ANTIBODY REGN4461 FOR THE TREATMENT OF METABOLIC ABNORMALITIES IN PATIENTS WITH FAMILIAL PARTIAL LIPODYSTROPHY

Compound	Mibavademab (REGN4461)
Protocol Number	R4461-PLD-20100
Clinical Phase	Phase 2
Sponsor	Regeneron Pharmaceuticals, Inc.
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Version / Date	V 1.0 / May 16, 2024

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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ADA	Anti-drug antibody
ADIPO-IR	Adipose Insulin Resistance
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ARH	Autoregressive heterogeneous
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
APLD	Acquired partial lipodystrophy
ApoC3	Apolipoprotein C3
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BMI	Body mass index
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMQ	Company MedDRA queries
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CV	Cardiovascular
DBTP	Double-blind treatment period
DLHQ	Daily Lipodystrophy Hunger Questionnaire
DNA	Deoxyribonucleic acid
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcomes Assessment
eDISH	Evaluation of drug-induced serious hepatotoxicity
ELISA	Enzyme Linked Immunosorbent Assay
EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FFA	Free fatty acids

FPLD	Familial partial lipodystrophy
HADS	Hospital anxiety and depression scale
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HLGT	High level group term
HLT	High level term
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HRQoL	health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IUO	Investigational use only
IV	Intravenously
IVRS	Interactive voice response system
LSM	Least squares mean
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LEPR	Leptin receptor
LIPO-IR	Lipoprotein Insulin Resistance Index
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model with repeated measures
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-derived proton density fat fraction
NAS	Non-alcoholic fatty liver disease activity score
NIH	National Institutes of Health
NODM	New onset of diabetes mellitus
PBO	Placebo run-in period
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamic

PDFF	Proton Density Fat Fraction
PGIS	Patient Global Impression of Severity
PHQ-8	8-item patient health questionnaire depression scale
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PLD	Partial lipodystrophy
PRO	Patient reported outcomes
PT	Preferred term
QoL	Quality of life
QW	Every week
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
rhLeptin	Recombinant human leptin
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36 survey
sLEPR	soluble form of the leptin receptor
SMQ	Standard MedDRA queries
SOC	System organ class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TF	Trunk fat %/leg fat %
TG	Triglyceride
TLR	Trunk to leg fat ratio
TP1	Treatment Period 1 for double-blind treatment period
TP2	Treatment Period 2 for single-blind treatment period
ULN	Upper limit of normal
WBC	White blood cell

WHO-DD	WHO Drug dictionary
WOCBP	Women of childbearing potential

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data collected in R4461-PLD-20100 study.

This plan may be revised during the study to accommodate protocol amendments and adapt to unexpected issues in study execution that may affect planned analyses. These revisions will be based on data review, and a final plan will be issued prior to the final database lock.

1.1. Background/Rationale

This Phase 2, randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy and safety of mibavademab (or REGN4461) in patients with familial partial lipodystrophy and metabolic abnormalities (elevated fasting TG with or without elevated HbA1c) who are not receiving rhLeptin (metreleptin) therapy. This study will compare the efficacy and safety of mibavademab to placebo.

Lipodystrophy is a rare condition in which the body is unable to produce or maintain adipose tissue. Partial lipodystrophy (PLD) is characterized by the selective loss of adipose tissue from various areas of the body. Partial lipodystrophy is a heterogeneous disease, and the extent of lipoatrophy varies significantly among patients. The reduced number of functional adipocytes can lead to relative leptin deficiency and associated metabolic abnormalities due to lipids being stored in other tissues, including muscle and liver. These metabolic abnormalities include hypertriglyceridemia, insulin resistance/diabetes, and nonalcoholic fatty liver disease. Partial lipodystrophy patients with diabetes are at increased risk for complications of diabetes, including nephropathy. In a large fraction of familial partial lipodystrophy (FPLD) patients (one-third to one-half, based on available data), lipoatrophy is extensive enough to result in reduced leptin levels (<8.0 ng/mL), which could drive severe hunger and insulin resistance.

The true incidence of PLD is unknown, with estimates of 2 to 3 clinical cases per million (Chiquette, 2017). Most cases of PLD are familial (FPLD), and often are associated with pathogenic mutations in genes important for adipocyte biology. However, due to a presentation that overlaps with the much more common metabolic syndrome, FPLD is clinically underdiagnosed. Recent data point to a higher prevalence of individuals with FPLD gene variants, as high as 160 per million (Gonzaga-Jauregui, 2020) .

Mibavademab is a human antibody that binds and activates the leptin receptor (LEPR) independent of leptin binding. Mibavademab is not related to endogenous leptin, and therefore should not have the risk of anti-drug antibodies (ADAs) cross-reacting with and neutralizing endogenous leptin.

Based on preclinical and clinical studies performed to-date, it is hypothesized that low-leptin familial PLD (FPLD) patients will benefit from treatment with mibavademab, and therefore FPLD patients with a range of lower leptin levels will be enrolled to explore the relationship between leptin levels and response to mibavademab in this study. The primary analysis of this study includes FPLD patients with leptin levels <8.0 ng/mL (Cohort A). A second cohort of FPLD patients with leptin levels of 8.0 ng/mL to ≤20.0 ng/mL (Cohort B) will also be assessed (separately) given analyses of individualized patient data from the National Institutes of Health (NIH), which indicated that patients with leptin ≤20.0 ng/mL had a better response to metreleptin

than did those with leptin >20.0 ng/mL. An analysis of the combined set of cohorts A plus B (also named as combined Cohort A+B that includes all patients in Cohort A and Cohort B) will also be performed to determine the effect of mibavademab on endpoints in patients with leptin levels within the broader range (≤20.0 ng/ml). An Investigational Use Only (IUO) leptin assay (ie, investigational human leptin assay) is being developed for stratification and patient selection purposes; study eligibility and cohort allocation will be determined using this leptin Enzyme Linked Immunosorbent Assay (ELISA) developed and validated under Clinical Laboratory Improvement Amendments (CLIA) guidelines.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objectives will be evaluated for patients in cohort A (leptin <8.0 ng/ml) only:

- To evaluate the effect of mibavademab on fasting TG in patients with baseline leptin <8.0 ng/mL and with elevated baseline fasting TG (>200 mg/dL)
- To evaluate the effect of mibavademab on hyperglycemia in patients with baseline leptin <8.0 ng/mL and with elevated baseline HbA1c (>7.0%)

1.2.2. Secondary Objectives

The following secondary objectives of the study will be evaluated for cohort B and for the combined set of cohorts A plus B:

- To evaluate the effect of mibavademab on fasting TG levels in patients with hypertriglyceridemia (screening fasting TG >200 mg/dL)
- To evaluate the effect of mibavademab on glycemic control in patients with hyperglycemia (screening HbA1c >7.0%)

The following secondary objectives of the study will be evaluated for cohorts A and B separately, and for the combined set of cohorts A plus B:

- To evaluate the effect of mibavademab on liver fat in patients with hepatic steatosis (baseline Hepatic Fat Fraction [Magnetic resonance imaging-derived proton density fat fraction, MRI-PDFF] ≥8.5%)
- To evaluate the effect of mibavademab on hunger
- To evaluate safety and tolerability of mibavademab
- To characterize the concentration profile of mibavademab over time
- To assess immunogenicity to mibavademab

1.2.3. Exploratory Objectives

The exploratory objectives of the study, will be evaluated for cohorts A and B separately, and for the combined set of cohorts A plus B:

- To evaluate the effect of mibavademab on insulin sensitivity
- To evaluate the effect of mibavademab on pain
- To evaluate the effect of mibavademab on depression
- To evaluate the effect of mibavademab on anxiety
- To evaluate the effect of mibavademab on body weight
- To evaluate the effect of mibavademab on regional body composition
- To evaluate the effect of mibavademab on Quality of Life (QoL)
- To study the activity of mibavademab (including biomarker discovery related to safety and efficacy of mibavademab), the leptin pathway and FPLD (including insulin resistance, hepatic steatosis, and hypertriglyceridemia)
- To determine if bioimpedance measurements can be used as adequate surrogates for dual-energy X-ray absorptiometry (DXA) to measure regional body composition in patients with FPLD

1.2.4. Modifications from the Statistical Section in the Final Protocol

The content of this SAP reflects the content of the statistical section of Protocol R4461-PLD-20100 Amendment 1 with the following exceptions:

- Protocol Section 4. Endpoints: The definitions of endpoints are clarified in SAP Section 5.7 by replacing:
  - "elevated baseline fasting TG" into "screening TG"
  - "elevated baseline HbA1c" for defining subgroup into "screening HbA1c" to match HbA1c strata (screening HbA1c ≤7.0%, >7.0%)
  - "baseline leptin" for defining Cohort into "screening leptin"
- Protocol Section 11.3.2. Safety Analysis Set: Safety analysis set (SAF) is replaced with DB SAF and SB SAF as follows in SAP Section 3.2:
  - DB SAF includes all randomized patients who received any double-blind study drug.
  - SB SAF includes all the patients in the double-blind SAF who also received at least 1 study drug in the single-blind treatment period.
- Protocol Section 11.4.5.4. Treatment Compliance: Compliance % calculation is replaced with study treatment administration interval compliance in SAP Section 5.8.8.
- Protocol Section 11.4.3. Efficacy Analyses: The randomization strata per IVRS in the analysis models (eg, MMRM) are replaced with actual strata in SAP Section 5.7 to reflect the actual disease characteristic for statistical modeling.
- Protocol Section 11.4.3. Efficacy Analyses: Due to the early termination of the study and subsequent limited number of participants enrolled, only descriptive summaries

and line plots for fasting TG, HbA1c, fasting glucose, liver fat (MRI-PDFF), and Daily Lipodystrophy Hunger Questionnaire (DLHQ) over time will be provided by treatment group. Spaghetti plots for fasting TG, HbA1c, fasting glucose, liver fat (MRI-PDFF), and DLHQ will be provided for individual patient data across visits for the endpoints by treatment group if applicable.

- SAP Section 7 Timing of Statistical Analyses: First Step Analysis and Second Step Analysis will not be performed.

1.2.5. Revision History for Statistical Analysis Plan Version 1

This is the original version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

The study consists of the following 5 periods (Figure 1):

- A screening period up to 10-weeks
- A placebo run-in period (PBO) for 4 weeks
- A randomized double-blind placebo-controlled treatment period (TP1 or DBTP) for 12 weeks
- A single-blind treatment period (TP2 or SBTP) during which all patients receive mibavademab for 12 weeks
- An off-drug safety follow-up period for 16 weeks

Figure 1: Study Flow Diagram

Patients 18 years of age or older with a clinical diagnosis of FPLD will undergo screening, including measurement of HbA1c, fasting TG, and leptin levels. A diagnosis of FPLD requires either a documented ClinVar pathogenic or likely pathogenic variant in a known FPLD gene or pathognomonic regional lipoatrophy by DXA. In addition, patients must have metabolic abnormalities (elevated fasting TG with or without elevated HbA1c) and leptin level ≤20.0 ng/mL to be included.

After the screening period of up to 10 weeks, eligible patients will be assigned to one of the following two leptin cohorts based on the mean screening leptin levels:

- Cohort A: FPLD patients with serum leptin <8.0 ng/mL
- Cohort B: FPLD patients with serum leptin 8.0 to ≤20.0 ng/mL

Then, these patients will begin the single-blind 4-week placebo run-in period.

On Day 1 after the placebo run-in period, each cohort of patients will be centrally randomized via interactive voice response system (IVRS) in a 1:1 ratio to Arm 1 or Arm 2:

- Arm 1: placebo
- Arm 2: mibavademab

Subjects will be stratified based on screening HbA1c (HbA1c ≤7% or HbA1c >7%) to ensure equal representation of patients with elevated HbA1c in each study arm. Schedules of study treatments and follow-up periods are summarized in Table 1.

Table 1: Summary of Study Arms

		Arm 1	Arm 2
Double-blind Treatment Period (DBTP)	Day 1 (IV loading dose based on weight)	Placebo IV	[redacted] mg/kg mibavademab IV
	Day 8 onwards (for 11 weekly maintenance doses)	Placebo SC QW	[redacted] mg mibavademab SC QW
Single-blind Treatment Period (SBTP)	Day 85 (IV loading dose based on weight)	[redacted] mg/kg mibavademab IV followed by Placebo SC	Placebo IV followed by [redacted] mg mibavademab SC
	Day 92 (for 11 weekly doses)	[redacted] mg mibavademab SC QW	
	Day 169 until week 40	Off-Drug Safety Follow-up	

The study event table is presented in Appendix 10.7.

2.2. Justification of Sample Size

The size of the study is determined by feasibility assessments. Due to the limited number of identified FPLD patients with low leptin and moderate metabolic abnormalities, up to 40 patients will be enrolled.

With a total of 40 patients (20 per cohort, randomized in the ratio of 1:1 into Arm 1 and Arm 2), the primary analysis will be carried out on the 20 patients in the lower leptin Cohort A in DBTP. The fact that it is unlikely that all of the patients will have HbA1c >7.0%, ie, not all of the patients will be assessed for the HbA1c endpoint, has also been accounted for. From the feasibility work, it is estimated that 78% of the patients will have elevated screening HbA1c. With 20 patients in Cohort A (10 patients per study arm; Table 2), the half-width of the 90% confidence interval of the difference in change from baseline to week 12 between Arm 1 and Arm 2 for HbA1c is 1.4 percentage points, assuming a SD of 1.81%. For TG, the half-width of the 90% confidence interval

in logarithm-transformed geometric mean ratio (GMR) (mibavademab week12/baseline divided by placebo week12/baseline) is 0.67, assuming the SD for logarithm-transformed fasting TG is 0.87. The SD estimates are from the FPLD subset samples of the extracted NIH study data (Diker-Cohen. 2015).

Table 2: Half-Width of the 90% Confidence Interval for Primary Endpoints

Endpoint	Number of Patients per Group in the Subset	Half of the 90% confidence interval**
HbA1c*	7	1.72%
	8	1.59%
HbA1c†	10	1.4%
Fasting TG†		0.67

*Assuming 78% of the patients have elevated screening HbA1c.
**The estimates of treatment effects of drug at the end of the DBTP (week 12) are -1.18% for HbA1c, and -52% for fasting TG. After adjusting for placebo effect, the between-group treatment effect estimates are -0.98% for HbA1c, and -47% for fasting TG. SD for HbA1c is assumed to be 1.81%, and for logarithm-transformed fasting TG is assumed to be 0.87 (SD estimates extracted from NIH study data).
†Assuming all patients have baseline HbA1c >7.0% and TG >200 mg/dL.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), below are the patient populations defined for statistical analysis. The efficacy analysis population is the full analysis set. Additional patient populations include safety analysis sets, pharmacokinetic analysis set, immunogenicity analysis set, and clinical outcome assessment set. For the purposes of the definitions below, a patient is considered randomized to study treatment when they have been screened and received a randomization number and are recorded in the IVRS/IWRS database.

3.1. Efficacy Analysis Sets

3.1.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients who received any study drug in DBTP and have at least 1 post-baseline assessment. Patients in the FAS population will be analyzed according to the treatment group allocated by randomization (as-randomized). Efficacy endpoints will be analyzed using the FAS.

3.2. Safety Analysis Sets (SAF)

3.2.1. Double-Blind Safety Analysis Set

The double-blind safety analysis set (DB SAF) includes all randomized patients who received any double-blind study drug. Patients will be analyzed according to the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the double-blind SAF.

In addition:

- Randomized patients for whom it is unclear whether they took the study drug will be included in the DB SAF as randomized.
- For randomized patients receiving both mibavademab and placebo study treatment in the DBTP, the treatment group allocation for as-treated analysis will be mibavademab.

3.2.2. Single-Blind Safety Analysis Set

The single-blind safety analysis set (SB SAF) includes all randomized patients who received any single-blind study drug.

3.3. Pharmacokinetic (PK) Analysis Set

The PK analysis set is defined as all randomized patients who received any study drug and have at least 1 non-missing measurement of mibavademab concentration following the first dose of study drug. Treatment assignments for DBTP are based on the actual treatment received (as treated).

3.4. Immunogenicity Analysis Set

The ADA analysis set includes all treated patients who received any amount of study drug (active or placebo) and had at least one non-missing anti-drug antibody result following the first dose of study drug. The ADA analysis set is based on the actual treatment received (as treated).

3.5. Clinical Outcome Assessment

The analyses for Clinical Outcome Assessments (COA) will be performed on all randomized patients who received any study treatment. Patients will be analyzed according to the treatment received (as treated). Further for each scale:

- For the daily lipodystrophy hunger questionnaire, patients will be included when a baseline and at least one-week post-baseline scores are available.
- For the remaining COA item (eg, quality-of-life questionnaire, etc.), patients will be included when a baseline and at least one post-baseline score is available.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

For each patient, demographic and baseline characteristics will be obtained from the last available value up to the date of the first double blind study treatment administration (ie, baseline definition).

All baseline safety and efficacy parameters (apart from those listed below) will be presented along with the summary statistics in the safety and efficacy sections. The following variables will be summarized:

Demographic Characteristics

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other, Pacific Islander, Not Reported, Other)
- Age in years (quantitative and qualitative variable: ≥18 to <45, ≥45 to <65, ≥65 to <75, and ≥75 years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)

Baseline Characteristics

- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) in kg/m² (quantitative and qualitative variable defined as <30, ≥30)
- Leptin by sex (leptin in male, leptin in female)
- Strata on leptin
  - Randomization strata as reported in the IVRS, leptin (≤ 8mg/dL or 8 mg/dL to 20 mg/dL)
  - Actual strata as reported in the clinical database, leptin (≤ 8mg/dL or 8 mg/dL to 20 mg/dL)
- ***Baseline Disease Characteristics***
- Fasting TG in mg/dL quantitative variable and qualitative variable defined as: >200 to ≤450, and >450)
- HbA1c (quantitative variable)
- Strata on screening HbA1c
  - Randomization strata as reported in the IVRS, screening HbA1c (≤7% or >7%)
  - Actual strata as reported in the clinical database, screening HbA1c (≤7% or >7%)
- Fasting glucose
- Liver volume from MRI and liver fat content from MRI-PDFF
- Insulin (quantitative variable and qualitative variable defined as: Yes/No)
- Lipid Panel
  - Low density lipoprotein cholesterol (LDL-C)
  - High-density lipoprotein cholesterol (HDL-C)
  - Total Cholesterol (TC)
  - Apolipoprotein B

- Biomarker-Lipoprotein NMR Analysis (Note: List of data fields reported in the biomarker-lipoprotein NMR are listed in Appendix 10.5.)
- Body Composition from DXA
  - Total lean mass
  - Total fat mass
  - Trunk fat mass
  - Percentage of body fat
  - Trunk/leg fat ratio (TLR; trunk fat %/leg fat %)

4.2. Medical History

As applicable, patient medical history will be dictionary coded by primary system organ class, high level term, and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), specifically the latest MedDRA version at the time of the first database lock.

FPLD disease history will be assessed by the following variables:

- FPLD related medical history (Yes/No)
- Time from diagnosis to study treatment randomization (years)
- FPLD type
- Genetic variant known (Yes/No): if yes, then list.
- Pathogenic variant as determined by ClinVar (Yes/No)
- Method of diagnosis of FPLD

4.3. Prior and Concomitant Medications

All medications taken from the time of informed consent to the final study visit, including medications that were started before the study and are ongoing during the study, will be reported in Concomitant Medications CRF.

All medications will be dictionary coded using the World Health Organization-Drug Dictionary (WHO-DD) to both an anatomic category and a therapeutic category, with the latest version at the time of the first database lock. Drug names will be matched to respective Anatomical-Therapeutic-Chemical (ATC) classification, although a drug can be matched to more than one ATC classification (ie, patients can be counted in several categories for the same medication).

Prior medications, concomitant medications, and post-treatment medications are defined below and will be applied in the respective treatment periods (DBTP and SBTP).

- Prior medications are defined as medications for which the stop date is before the date of the first DBTP study treatment administration.

- Concomitant medications are defined as medications that are administered to the patients during the respective double-blind and single-blind study treatment periods. Specifically:
  - Start date of the concomitant medication is on or after the first study treatment administration in respective study treatment periods (≥ Day 1 for DBTP, or ≥ Day of the first single-blind study treatment administration for SBTP); **or**
  - Start date of the concomitant medication is before the first study treatment administration in respective study treatment periods and is "Ongoing" during the treatment emergent period; **or**
  - Start date of the concomitant medication is before the first study treatment administration in respective study treatment periods, and the end date is on or after the first study treatment administration in respective study treatment periods (≥ Day 1 for DBTP, or ≥ Day of the first single-blind study treatment administration for SBTP).

  The concomitant medication treatment emergent periods are defined as:
  - For concomitant medications in DBTP, the double-blind treatment emergent period is defined from the day of the first double-blind study treatment administration to (1) the last day of double-blind study treatment + 112 days (for patients who do not continue into the SBTP); (2) to the day of the first single-blind study treatment administration (for patients who enter the SBTP).
  - For concomitant medications in SBTP, the single-blind treatment emergent period is defined from the day of the first single-blind study treatment administration to the last day of single-blind study treatment administration + 112 days.

  Note: In the case that the medication start day is before first study treatment administration and both ongoing status and stop date are missing, the medication will be assumed to be concomitant.
- Post-treatment medications are defined as medications for which the start date is after last date of study treatment administration + 112 days (≥ last study treatment +112 days).

4.4. Prohibited Medications and Procedures During Study

The definitions of prohibited medications and procedures are described in the Section 8.10.1 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

4.5. Patient Disposition

Patient disposition will include the description of patient status at major milestone decisions in the study, as well as the patient analysis populations.

For patient study status, patient milestone categories for the DBTP are defined below. As applicable, percentages will be calculated using the number of randomized patients in the

denominator, with two exceptions. Specifically, the two exceptions will be for the screened and non-randomized categories, which will not have associated percentages shown.

- The total number of screened patients defined as having signed ICF.
- The total number of screen failure (SF) patients.
- The total number of randomized patients, defined as all screened patients with a double-blind treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used.
- The total number of patients randomized but not receiving study treatment.
- The total number of patients randomized and receiving study treatment.
- The total number of patients who completed the DBTP, defined as at least 11 weeks of study treatment administration and week 12 visit performed.
- The total number of patients who prematurely discontinued study treatment during the DBTP and the reasons for discontinuation collected on the study completion eCRF.
- The total number of patients who do not proceed into SBTP and complete the last study follow-up visit (ie, 16-week follow-up period).

Patient SBTP milestone categories are defined below. As applicable, percentages will be calculated using a denominator of the number of patients administered single-blind study treatment.

- The total number of patients receiving study treatment in single-blind treatment period
- The total number of patients ongoing in SBTP (applicable for first-step analysis)
- The total number of patients who completed the SBTP, defined as at least 23 weeks of study treatment administration and week 24 visit performed.
- The total number of patients who prematurely discontinued study treatment during the SBTP, and the reasons for discontinuation collected on the study completion eCRF.
- The total number of patients from SBTP who complete the last study follow-up visit (ie, 16-week follow-up period).

The following patient populations for analyses are defined in Section 3:

- Efficacy population: Full analysis set (FAS)
- Double-blind safety analysis set (DB SAF)
- Single-blind safety analysis set (SB SAF)
- Pharmacokinetic (PK) Analysis Set
- Immunogenicity (ADA) Analysis Set

The following patient listings will provide the details from the patient disposition table.

- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patient prematurely discontinued from treatment, along with reasons for discontinuation

4.6. Study Treatment Exposure and Compliance Variables

Study treatment exposure variables for study drug administered during the DBTP are listed below with associated definitions:

- Patient duration of DBTP SC study treatment exposure in weeks defined as: (last double-blind SC study treatment administration date – first double-blind SC study treatment administration date+7)/7. Values will be rounded to one decimal place.
- The total number of DBTP SC study treatment injections by patient.
- The following categories will be used for DBTP SC treatment exposure at 1-week intervals: ≥1 day and <1 week, ≥1 week and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, …, ≥10 weeks and <11 weeks, ≥11 weeks.
- The total number of DBTP IV study treatment administrations by patient.

Study treatment exposure variables for study drug administered during the SBTP are listed below with associated definitions:

- Patient duration of SBTP SC study treatment exposure in weeks defined as: (last single-blind SC treatm.ent administration date – first single-blind SC treatment administration date+7)/7. Values will be rounded to one decimal place.
- The total number of SBTP SC study treatment injections by patient.
- The following categories will be used for SBTP SC treatment exposure at 1-week intervals: ≥1 day and <1 weeks, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, …, ≥22weeks and <23 weeks, ≥23 weeks.
- The total number of SBTP IV study treatment administrations by patient.

Cumulative study treatment exposure variables combining DBTP and SBTP are listed below for all patients who received mibavademab in the DBTP:

- Cumulative patient duration of SC study treatment exposure in weeks defined as: DBTP SC treatment exposure + SBTP SC exposure.
- Cumulative total number of SC treatment administration by patient defined as: DBTP SC injections + SBTP SC injections.
- The following categories will be used for cumulative patient mibavademab treatment exposure in the study at 1-week intervals: ≥1 day and <1 weeks, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, …, ≥22 weeks and <23 weeks, ≥23 weeks.
- The total number of DBTP and SBTP IV study treatment administrations by patient.

With respect to patient treatment administration compliance, because the study treatment is administered either during the investigative site visits or by a visiting nurse, study compliance will be accessed by frequency for study drug administration for respective treatment periods (DBTP, SBTP), specifically:

- The administration frequency for DBTP SC study treatment administration will be defined for each patient as the average number of days between 2 consecutive SC study drug administration during DBTP: (last double-blind SC administration date – first double-blind SC administration date) / (number of SC administrations during DBTP), for patients receiving at least 2 SC administrations during DBTP.
- The administration frequency for SBTP SC study treatment administration will be defined for each patient as the average number of days between 2 consecutive SC study drug administration during SBTP: (last single-blind SC administration date – first single-blind SC administration date) / (number of SC administrations during SBTP), for patients receiving at least 2 SC administrations during SBTP.

In the DBTP, all important and minor protocol deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, as well as other deviations, will be collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Plan (PDP). Both monitoring collected and programmatically derived deviations are listed and defined in the PDP.

4.7. Efficacy Variables

Efficacy will be assessed through the following parameters: fasting TG, HbA1c, fasting glucose, liver fat content as measured by MRI-PDFF, and lipodystrophy hunger questionnaire outcomes.

4.7.1. Primary Efficacy Variables

The two primary endpoints of the study are:

- Percent change in fasting serum TG from baseline to week 12.
- Absolute change in HbA1c from baseline to week 12.

4.7.2. Secondary Efficacy Variables

The secondary endpoints include:

- Percent change in fasting serum TG from baseline to week 24.
- Absolute change in HbA1c from baseline to week 24.
- Change in fasting glucose from baseline to week 12.
- Change in fasting glucose from baseline to week 24.
- Percent change in liver fat (MRI-PDFF) from baseline to week 12.
- Percent change in liver fat (MRI-PDFF) from baseline to week 24.
- Change on the daily lipodystrophy hunger questionnaire from baseline to week 12.
- Change on the daily lipodystrophy hunger questionnaire from baseline to week 24.

4.7.3. SBTP-specific Secondary Efficacy Variables

SBTP-specific secondary efficacy endpoints include:

- Percent change in fasting serum TG from week 12 to week 24.
- Absolute change in HbA1c from week 12 to week 24.
- Change in fasting glucose from week 12 to week 24.
- Percent change in liver fat (MRI-PDFF) from week 12 to week 24.

4.8. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, physical examination, and ECG. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of double-blind study treatment.

4.8.1. Adverse Events Variables

The period of safety observation starts from the time when the patient gives informed consent and continues into the following periods:

- The pre-treatment period is defined from the day the ICF is signed to the time of the first dose of double-blind study treatment administration.
- The double-blind treatment-emergent adverse event (DB TEAE) period is defined from the time of the first dose of double-blind study treatment administration to the day of the last dose of double-blind study treatment administration + 112 days (16 weeks) for those patients not proceeding into SBTP, or up to the time of the first dose of SBTP study treatment administration for those patients proceeding into the SBTP.
- The single-blind treatment-emergent adverse event (SB TEAE) period is defined from the time of the first single-blind study treatment administration to the day of the last single-blind study treatment administration + 112 days (16 weeks).
- The post-treatment period is defined from the day after the end of the respective TEAE period to the last study visit.

4.8.1.1. Adverse Events and Serious Adverse Events

Adverse events (including serious adverse events (SAE), AEs causing permanent treatment discontinuation, deaths, and AEs of special interest) are recorded from the time of signed informed consent until the end of study. All AEs diagnosed by the Investigator will be reported and described.

All AEs will be dictionary coded by “lowest level term (LLT)”, “preferred term (PT)”, “high level term (HLT)”, “high level group term (HLGT)” and associated primary “system organ class (SOC)” using the latest version of MedDRA at the time of the first database lock.

Adverse Event Observation Period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.

- TEAEs are AEs that developed or worsened or became serious during the respective TEAE period.
- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

4.8.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner. AESIs will be recorded on the adverse event e-CRF using dedicated tick boxes, and/or identified using standard MedDRA queries (SMQ), company MedDRA queries (CMQ), MedDRA terms, and/or applicable laboratory assessments. Appendix 10.3 contains the definitions used to identify AESIs:

The AESIs include:

- Hypoglycemia, defined as blood glucose <54 mg/dL (eCRF, lab data)
- New onset diabetes mellitus (NODM) (eCRF, lab data)
- For patients with no diabetes at baseline, NODM is defined using the following lab parameters:
  a. Two values of fasting (≥8 hours) plasma glucose ≥126 mg/dL (7.0 mmol) during the treatment period
  OR
  b. Two values of HbA1c ≥6.5% (48 mmol/mol) during the treatment period
- Hyperglycemia requiring treatment (eCRF, lab data), defined using the following lab parameter:
  a. HbA1c ≥10.5% AND at the same visit an increase in HbA1c of ≥1.5% from baseline value
  OR
  b. Fasting glucose ≥250 mg/dL on 2 occasions including symptoms consistent with hyperglycemia AND increase in fasting glucose >50 mg/dL above baseline
- Development of new or worsening of autoimmune disease (eCRF)
- Moderate or severe hypersensitivity reactions (CMQ, eCRF)
- Moderate or severe infusion reactions (eCRF)

4.8.1.3. Adverse Events of Interest

Adverse events of interest are AE's for which additional documentation is collected. Adverse events of interest include:

- Injection site reaction, collected from the eCRF
- Mild infusion reaction collected from the eCRF
- Mild hypersensitivity reactions from the eCRF

4.8.1.4. Events Causing Death

The observation periods for patient deaths are per the observation periods defined above.

- Death on-treatment: deaths occurring during the respective TEAE period.
- Death post-treatment: deaths occurring during the post-treatment period.

4.8.2. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology, clinical chemistry and other) and urinalysis. Clinical laboratory values will be converted and analyzed in international units and US conventional units, with associated normal ranges provided by the central laboratory. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see Appendix 10.4 for PCSV definitions). For those laboratory tests that do not have PCSV ranges, central laboratory normal ranges will be applied to identify out-of-range values. All laboratory samples will be collected before study treatment administration during the protocol scheduled visits, unless otherwise indicated.

Unless otherwise specified below, blood samples for clinical laboratories will be collected at the protocol scheduled visits, and visits will be assigned to the Global Analysis Windows (See Appendix 10.2). The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

Hematology:

- Red blood cells and platelets: hemoglobin, hematocrit, erythrocytes count, platelets count, red blood indices
- White blood cells: white blood cells, neutrophils, lymphocytes, monocytes, basophils, eosinophils

Clinical chemistry:

- Electrolytes: sodium, potassium, chloride, carbon dioxide, calcium
- Metabolism: fasting glucose, total protein, albumin, Creatine phosphokinase
- Renal function: creatinine, blood urea nitrogen (BUN), uric acid
- Liver function: Alanine aminotransferase (ALT), aspartate aminotransferases (AST), alkaline phosphatase (ALP), total bilirubin, LDH, Gamma-glutamyl transferase (GGT)

Fasting Lipid Panel

- HDL-C, LDL-C, TC, Apo B, TG, NMR lipoprotein analysis

Urinalysis

- Color, clarity, pH, specific gravity, ketones, protein, glucose, blood, bilirubin, leukocyte esterase, nitrite, WBC, RBC

Other

- Fasting Leptin, Pregnancy test (serum/urine), Fasting Free Fatty Acids, Hepatitis B surface antigen (sAg), HIV (Ab), HbA1c, Fasting Apolipoprotein C3, Fructosamine, Hepatitis C (Ab), Fasting ANGPTL3, Urine albumin and creatinine

4.8.3. Vital Signs

Vital signs parameters will include weight (kg), height (cm), BMI (kg/m^2), respiratory rate (breaths/min), temperature (C), systolic and diastolic blood pressures (mmHg), and pulse (bpm) after the patient has been sitting or in the supine position. Both actual values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries, and visits will be assigned to the Global Analysis windows (see Appendix 10.2). Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.4 for PCSV definitions).

4.8.4. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at specified time points according to Appendix 10.7. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT and QTcF intervals will be recorded. Electrocardiogram assessments will be described as normal or abnormal, and visits will be assigned to the Global Analysis Windows (see Appendix 10.2). Potentially clinically significant values (PCSV) ranges will be applied to the selected ECG parameter values as applicable (see Appendix 10.4 for PCSV definitions).

4.8.5. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits (See Appendix 10.7 for schedule of event). The result is an outcome of normal, abnormal, and if abnormal then clinically significant (Yes/No, not examined), and visits will be assigned to the Global Analysis Windows (see Appendix 10.2).

4.9. Other Variables

Other assessment endpoints are listed and defined below. Protocol schedule visits will be assigned to Analysis Windows (See Appendix 10.2).

- Change from baseline in body composition (including absolute and percent lean mass and fat mass) using DXA at weeks 12 and 24 (only at sites with whole body DXA capability). DXA analysis will occur on variables included but not limited to those listed in Appendix 10.6.
- Change from baseline [redacted]
- Change from baseline [redacted]
- Change from baseline [redacted]
- Change from baseline [redacted]
- Change from baseline [redacted]

4.10. Pharmacokinetic Variables

Pharmacokinetic (PK) variables include concentrations of total drug and time as specified in the protocol.

4.11. Immunogenicity Variables

The immunogenicity variables include anti-drug antibody (ADA) status, and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.7.

4.12. Clinical Outcomes Assessment

4.12.1. Hunger

Daily Lipodystrophy Hunger Questionnaire

The daily lipodystrophy hunger questionnaire was developed to assess hunger related behaviors among patients with lipodystrophy. Patients will complete the PRO assessments daily. The Hunger questionnaire is self-administered and contains 4 items: highest level of hunger, lowest level of hunger, how much time felt hungry, and frequency of fullness after eating meals or snacks. Each item is furnished with 5 response categories; and a numerical value is assigned to each response category as follows:

	Value Assigned to Each Category				
Item	0	1	2	3	4
1. How would you rate your highest level of hunger you felt today?	Not hungry at all	A little hungry	Moderately hungry	Quite hungry	Extremely hungry
2. How would you rate the lowest level of hunger you felt today?	Not hungry at all	A little hungry	Moderately hungry	Quite hungry	Extremely hungry
3. How much time did you feel hungry today?	None of the time	A little of time	Some of the time	Most of the time	All of the time
4. How often did you feel full after eating meals or snacks today?	Every time	Most of the time	Some of the time	A little of the time	None of the time

Patient Global Impression of Severity-Hunger

The Patient Global Impression of Severity (PGI-S) – Hunger is an anchor-based assessment used to interpret meaningful change of the Hunger PRO. PGI-S–Hunger endpoints consists of the number and percentage of responses for each category at baseline and weeks 12 and 24 as well as categorical shift responses from baseline to week 12 and 24.

Patient Global Impression of Change- Hunger

The Patient Global Impression of Change (PGI-C) – Hunger is an anchor-based assessment used to interpret meaningful overall change of the Hunger PRO. PGI-C–Hunger endpoints consists of the number and percentage of responses for each category at weeks 12 and 24.

4.12.2. Pain

Brief Pain Inventory – Short Form Questionnaire

The BPI-SF measures pain and its interference with daily lives. It is a self-administered measure which consists of 9 items including:

- 1 historical pain item: "Have you had pain other than these every- day kinds of pain today?" (Yes = 1 / No = 0). The proportion of "Yes" will be used as a measure of historical pain status.
- 1 pain-location item that identifies the body area that hurts the most on a diagram.
- 4 pain-severity items, measured on a 0 to 10 scale, where 0 is "no pain" and 10 is the "pain as bad as you can imagine." The arithmetic mean for each of the 4 severity items will be used as the measure of the pain severity for the item.
- 2 pain-relief items:
  - "What treatments or medications are you receiving for your pain?"
  - "In the last 24 hours, how much relief have pain treatments or medications provided?" This question is measured on a 0% to 100% scale, where 0% is "no relief" and 100% is the "complete relief."
- 1 pain-interference item that includes 7 sub questions, where 0 is "does not interfere" and 10 is "completely interferes." The arithmetic mean of the 7 interference items will be used as a measure of pain interference.

Patient Global Impression of Severity- Pain

The Patient Global Impression of Severity (PGI-S) – Pain is a self-administered PRO assessing the patient's perception of their overall severity of pain. The PGI-S–Pain is an anchor-based assessment used to interpret meaningful change of the BPI-SF. PGI-S–Pain endpoints consists of the number and percentage of responses for each category at baseline and weeks 12 and 24 as well as categorical shift responses from baseline to week 12 and 24.

Patient Global Impression of Change- Pain

The Patient Global Impression of Change (PGI-C) – Pain is a self-administered PRO assessing the patient's perception of their overall change in pain since the beginning of the study. The PGI-C–Pain is an anchor-based assessment used to interpret meaningful change of the pain via the BPI-SF. PGI-C–Pain endpoints consists of the number and percentage of responses for each category at weeks 12 and 24.

4.12.3. Anxiety and Depression

Patient Health Questionnaire-8

The 8-item PHQ-8 is a self-administered instrument to measure depression. The PHQ-8 consists of 8 items each of which is scored 0 to 3, providing a 0 to 24 severity score. Scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe, and severe depression, respectively.

If a patient scores between 10 to 14 on the PHQ-8, s/he should be referred to a mental health professional – if a referral is not deemed necessary, then the investigator must document why.

A referral is mandatory if the PHQ-8 ≥15 or is deemed necessary by the investigator.

Hospital Anxiety and Depression Scale Questionnaire

The Hospital Anxiety and Depression Scale (HADS) questionnaire is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state over time (Zigmond, 1983; Herrmann, 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended: 0 to 7 normal, 8 to 10 borderline abnormal, 11 to 21 abnormal. For this study, only the 7 anxiety questions will be scored.

4.12.4. Quality of Life

Short Form – 36

The Short Form – 36 Survey (SF-36) is a 36-item self-administered PRO measure assessing health-related quality of life (HRQoL) concepts relevant across age, disease, and treatment group. The SF-36 assesses physical functioning, limitations due to physical health bodily pain, general health, vitality, social functioning, limitations due to emotional problems, and mental health. Patients answer questions assessing these concepts over the previous week using 3-, 5-, or 6-point Likert scales; scores range from 0 to 100, with higher scores indicating better health. These eight scales can be aggregated into two summary measures: Physical (PCS) and Mental (MCS) Component Summary scores. The SF-36 endpoints include change from baseline in PCS and MCS at weeks 12 and 24.

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized twice, specifically by study treatment and overall for the study in the DBTP, and again in the SBTP by DB treatment group and overall for the study, unless otherwise noted.

DBTP summaries will be descriptively presented containing all patients in the DB SAF by treatment group and overall for the study, as well as by treatment group and overall for the study within each of the stratification factors (Cohort [A or B] and screening HbA1c [≤7% or >7%]).

Continuous data will be summarized using the number of patients, mean, SD, median, minimum, and maximum for each treatment group and for each of the strata. First quartile (Q1) and third quartile (Q3) will be also provided for baseline fasting triglyceride. Categorical and ordinal data will be summarized using the number and percentage of patients in each group.

As applicable, other safety baseline data not listed in Section 4.1 will be presented collectively in the descriptive statistics summary tables containing respective post-baseline data.

SBTP summaries will be descriptively presented containing all patients in the SB SAF by DB treatment group (mibavademab, placebo) and overall for the study, unless otherwise noted. Parameters listed in Section 4.1 will be summarized in SBTP as described for the DBTP summaries.

5.2. Medical History

Medical history will be descriptively summarized twice, specifically by study treatment and overall for the study in the DBTP, and again in the SBTP by DB treatment group and overall for the study, unless otherwise noted. DBTP summaries will be presented containing all patients in the DB SAF, and SBTP summaries will be presented with patients in the SB SAF.

All reported patient medical history will be presented by PT, primary SOC and HLT. The tables will be presented by SOC sorted alphabetically and in decreasing patient frequency of HLT based on the incidence in the study.

Patient disease characteristics as described in Section 4.2 will be summarized in the DB SAF.

5.3. Prior and Concomitant Medications

All prior medications, dictionary coded by WHO-DD, will be descriptively summarized by study treatment and overall for the study, in the DBTP for patients in the DB SAF. Summaries will present patient counts (and percentages) for all prior medications, by decreasing frequency of the overall incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication but may be counted several times for the same medication.

For patients in the DB SAF, all concomitant medications during the DBTP, dictionary coded by WHO-DD, will be descriptively summarized by study treatment in the DBTP for patients in the DB SAF. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, by decreasing frequency of the incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication.

For the SBTP, concomitant medications will be dictionary coded by WHO-DD and will be descriptively summarized as described for the DBTP. For patient in the SB SAF, medications will be summarized by DB treatment group (ie, mibavademab, placebo) and overall for the SBTP.

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the safety analysis set for the DBTP and respective SBTP. Prohibited medications are listed in the protocol and identified through medical review.

5.5. Patient Disposition

Patient disposition includes the description of patient status at major milestone decisions in the study as described in Section 4.5, as well as the patient analysis populations. Patient disposition and analysis populations will be summarized two times, specifically by study treatment group and overall (including screened patients and screen failures) for the patients in the DBTP, and again in the SBTP by DB treatment group and all patients receiving single-blind study treatment, unless otherwise noted. Exception listings will be generated for any patient treated but not randomized, randomized but not treated, and treated differently than randomized.

5.6. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and compliance for the DBTP described in Section 4.6 will be assessed and summarized by treatment group, for patients in the DB SAF. The extent of study treatment exposure for the SBTP described in Section 4.6 will be assessed and summarized for all patients and by DB treatment group for patients in the SB SAF.

5.6.1. Exposure to Investigational Product

Study treatment SC exposure in the DBTP and SBTP will be descriptively summarized for treatment duration and total number of injections as described in Section 4.6. Treatment duration and total number of injections will be summarized using the number of patients with data, mean, SD, median, minimum, and maximum. Additionally, the frequency of patients receiving study treatments at each weekly protocol scheduled visit will be summarized by number of patients (%).

For study treatment IV administration in the DBTP and SBTP, total number of infusions will be summarized using the number of patients with data, mean, SD, median, minimum, and maximum.

Additionally, mibavademab dosing SC exposure will be summarized cumulatively across the study, combining DBTP and SBTP for patients who received mibavademab in the DBTP.

5.6.2. Study Treatment Compliance

The SC treatment compliance will be assessed by SC administration frequency for a treatment period (DBTP, SBTP), which is defined for each patient as the average number of days between 2 consecutive SC administrations during the treatment period: (last SC administration date – first SC administration date) / (total number of SC administrations during the treatment period - 1), for participants receiving at least 2 SC administrations during the treatment period.

Descriptive statistics of the SC administration frequency will be summarized separately for DBTP and SBTP by mean, SD, median, minimum, and maximum. Further, study treatment injection interruptions and incomplete injections with reason will be provided in a patient listing for those patients with incomplete injections.

Important protocol deviations will be summarized. Both monitored and derived protocol deviations will be summarized for important deviation categories by count (percentage), and again by type of important deviation (patient count and percentage).

5.7. Analyses of Efficacy Variables

For statistics where international and conventional units do not impact the results (eg, means and least square (LS) means for percent changes from baseline, statistical testing for both percent and absolute changes from baseline, rates of patients below a threshold), derivations will be calculated and statistical models will be run using conventional units. For other statistics (eg, descriptive statistics at baseline and over time, absolute changes from baseline), derivations will be presented in both international and conventional units.

All efficacy assessment values obtained during the study (scheduled or unscheduled) can be used to provide a value for the efficacy endpoints as appropriate.

All efficacy measurements will be assigned to Efficacy Analysis Windows defined in Appendix 10.2, with the intent to provide an assessment for week 1 to 24 time points. For all visits post-baseline, the value used for the analyses at a given time point (eg, at week 12) is the value obtained within the corresponding efficacy analysis window. If multiple values exist for an analysis window, the value obtained closest to the targeted time of the window will be used as appropriate. Unless otherwise specified, the baseline value is defined as the last available measurement before the first double-blind study treatment administration. For patients randomized and not treated, the baseline value is defined as the last available value prior to the date of randomization.

Statistical analyses for the primary efficacy endpoints will be completed during the first step efficacy analysis (Section 7). Remaining descriptive efficacy analyses will be completed during the second step analyses.

5.7.1. Analysis of Primary Efficacy Variables

For the two primary efficacy variables, the primary analyses will be conducted in Cohort A (screening baseline leptin <8.0) for the following patient subgroups:

- Fasting serum TG percent change from baseline to week 12: patients with screening fasting TG >200 mg/dL
- HbA1c absolute change from baseline to week 12: patients with screening HbA1c >7.0%

5.7.1.1. Percent Change in Fasting TG from Baseline to Week 12

Percent change from baseline to week 12 in fasting serum TG, will be analyzed in the FAS population for the Cohort A patients with elevated baseline fasting TG >200 mg/dL by using a mixed-effect model with repeated measures (MMRM) approach. The MMRM model will include the following effects: fixed categorical treatment groups (Placebo versus mibavademab), time points (weeks 2, 4, 6, 8, 10, 11, and 12), actual strata (screening HbA1c ≤7.0%, >7.0%), strata-by-time-point interaction, and treatment-group-by-time-point interaction, as well as the continuous fixed covariates of baseline TG value and baseline value-by-time point interaction. Logarithm transformation will be performed to normalize the fasting TG.

Post-baseline data available up to and including the week 12 efficacy analysis window for fasting TG (Table 11 in Appendix 10.2) will be used and missing data are accounted for by the MMRM. Measurements on not-fasting patients will be excluded. Contrast and estimate statements will be used to assess baseline adjusted least-squares (LS) means estimates at week 12 for each treatment group with their corresponding 95% confidence intervals. The LS means at week 12 will be back-transformed into the geometric means to ease clinical interpretation of the result. The difference between the two study treatment groups (mibavademab, placebo) in geometric means will be provided along with its corresponding 95% confidence interval, and nominal p-value.

To support interpretation of the TG results at week 12, descriptive summaries will be provided at each protocol specified DBTP visit. Median percent changes (with Q1 and Q3 bars) will be plotted across visits by treatment group. A spaghetti plot will be provided for individual patient data across visits by treatment group.

Sensitivity Analysis

- A non-parametric approach will be performed on the primary efficacy endpoint for comparing the mibavademab and placebo. Specifically, the percent change in fasting serum TG from baseline to week 12 will be ranked for an analysis of covariance (ranked ANCOVA). For the case >5% missing data at week 12, missing data will be imputed using multiple imputation based on other observed measurements. The ranked ANCOVA model will be able to provide significance of the treatment effect as compared to placebo. Nominal p-values will be provided as a measure of the strength of evidence. Median treatment difference and its 95% confidence interval can be derived from the Hodges-Lehmann estimation and Moses distribution free confidence interval respectively.
- To assess the impact of a systemic dosing error on the primary efficacy endpoint, the primary efficacy analysis will be performed excluding affected patients. Patients known to be under dosed at the time of database lock will be identified for this analysis before database lock. Any additional patients determined to be affected post-database lock will be separately identified.

5.7.1.2. Change in HbA1c from Baseline to Week 12

Absolute change from baseline to week 12 in HbA1c, will be analyzed in the FAS population for the Cohort A patients using a mixed-effect model with repeated measures (MMRM) approach. The MMRM model will include the following effects: fixed categorical treatment groups (Placebo, mibavademab), time points (weeks 4, 6, 10, and 12), actual strata (screening HbA1c ≤7.0%, >7.0%), strata-by-time-point interaction, and treatment-group-by-time-point interaction, as well as the continuous fixed covariates of baseline HbA1c value and baseline value-by-time point interaction. An unstructured covariance matrix will be used to model the within patient errors. In the case that the unstructured covariance matrix does not converge, then a structured covariance matrix such as autoregressive heterogeneous [ARH] will be assessed.

Post-baseline data available up to and including the week 12 efficacy analysis window for HbA1c (Table 12 in Appendix 10.2) will be used and missing data are accounted for by the MMRM. Contrast and estimate statements will be used to assess baseline adjusted least-squares

(LS) means estimates at week 12 in the actual strata of screening HbA1c>7.0% for each treatment subgroup with their corresponding standard errors and 95% confidence intervals. The difference of the study treatment HbA1c mean changes from baseline to week 12 for patients with screening HbA1c>7.0% will be provided along with its corresponding 95% confidence interval, and nominal p-value.

To support interpretation of the HbA1c results at week 12, descriptive summaries will be provided at each protocol specified DBTP visit. Mean changes (±SE) will be plotted across visits by treatment group. A spaghetti plot will be provided for individual patient data across visits by treatment group.

5.7.2. Analysis of Secondary Efficacy Variables

Statistical analyses for the secondary efficacy endpoints (defined in Section 4.7.2) and SBTP-specific secondary efficacy endpoints (described in Section 4.7.3) will be performed in the FAS population.

All measurements, scheduled or unscheduled, will be assigned to efficacy analysis windows defined in Appendix 10.2 in order to provide an assessment for these time points. For fasting TG, measurements on not-fasting patients will be excluded; the median percent changes (with Q1 and Q3 bars) will be plotted across visits by treatment group.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (example: absolute change in HbA1c) and continuous measurements expected to have a non-normal distribution (example: TG).

The following patient groups are also used for analyzing secondary efficacy variables:

- Combined Cohort A+B include all patients in Cohort A and Cohort B as defined in Section 2.1.
- DBTP-stable patient is defined as a patient who meets both of the following two stability criteria:
  - Absolute change in HbA1c from baseline to week 12 $\leq$ 0.5%
  - Percent change in fasting serum TG from baseline to week 12 $\leq$ 25%

5.7.2.1. Continuous Endpoints Anticipated to have a Normal Distribution

Continuous secondary variables defined in Section 4.7.2 and Section 4.7.3 anticipated to have a normal distribution (including HbA1c, fasting glucose, and liver fat) will be analyzed using a similar MMRM model as described for the primary endpoint in HbA1c.

Daily lipodystrophy hunger questionnaire (DLHQ) will be descriptively summarized from baseline to week 12 and again from baseline to week 24. Mean changes in monthly averaged DLHQ scores (±SE) will be plotted across visits by treatment group; a spaghetti plot will be provided for individual patient data across visits by treatment group. Monthly averaging windows of the DLHQ scores are defined in the Efficacy Analysis Windows for Daily Lipodystrophy Questionnaire (See Appendix 10.2). If a participant reported less than 10 scores

within a monthly averaging window for a DLHQ item, the averaged score will be assigned a missing value.

The statistical estimates, comparisons, and descriptive statistics for these secondary efficacy variables are summarized in Table 3, Table 4, Table 5, and Table 6.

Table 3. Summary of Statistical Estimates and Comparisons in Normally-distributed Secondary Endpoints

Endpoint	Cohort for Modeling	Analysis Method / Estimates	Comparisons
• Absolute change in HbA1c from baseline to week 12.	• Separately for Cohort B and Cohort A+B	MMRM / Least-squares (LS) means with their corresponding standard errors and 95% confidence intervals. Note: Strata level = HbA1c>7.0%. Note: Post baseline visits to include in the model are weeks 4, 6, 10, and 12.	REGN4461 versus Placebo with nominal p-value.
• Change in fasting glucose from baseline to week 12.	• Separately for Cohort A, Cohort B, and Cohort A+B	MMRM / Least-squares (LS) means with their corresponding standard errors and 95% confidence intervals. Note: Strata level = HbA1c>7.0%. Note: Post baseline visits to include in the model are weeks 2, 4, 6, 8, 10, 11, and 12.	REGN4461 versus Placebo with nominal p-value.
• Percent change in liver fat (MRI-PDFF) from baseline to week 12	• Separately for Cohort A, Cohort B, and Cohort A+B	MMRM / Least-squares (LS) means with their corresponding standard errors and 95% confidence intervals. Note: patient subgroup = baseline MRI-PDFF ≥8.5% Note: Post baseline visit at week 12.	REGN4461 versus Placebo with nominal p-value.

Table 4. Summary of Descriptive Statistics for Patients Randomized to REGN4461 in Normally-distributed Secondary Endpoints for the combined DBTP and SBTP Analysis

NOTE: These descriptive statistics will be presented three times, specifically in Cohort A, Cohort B, and Cohort A+B.

Endpoint	Descriptive Statistics
• Absolute change in HbA1c from baseline to week 24	For Arm 2, descriptive summaries will be provided at each protocol specified visit up to week 24; mean changes (±SE) will be plotted across visits by treatment group; a spaghetti plot will be provided for individual patient data across visits by treatment group. These descriptive statistics will be provided twice, specifically for patients with baseline HbA1c>7% and again for All Patients.
• Change in fasting glucose from baseline to week 24	For Arm 2, descriptive summaries will be provided at each protocol specified visit up to week 24; mean changes (±SE) will be plotted across visits by treatment group; a spaghetti plot will be provided for individual patient data across visits by treatment group. These descriptive statistics will be provided twice, specifically for patients with baseline HbA1c>7% and again for All Patients.
• Percent change in liver fat (MRI-PDFF) from baseline to week 24	For patients with hepatic steatosis (baseline MRI-PDFF ≥8.5%) in Arm 2, descriptive summaries will be provided at each protocol specified visit up to week 24; mean changes (±SE) will be plotted across visits by treatment group; a spaghetti plot will be provided for individual patient data across visits by treatment group.

Table 5. Summary of Descriptive Statistics in Normally Distributed Secondary Endpoints based on REGN4461 Exposure

NOTE: Efficacy data for study treatment arm 1 (placebo) and arm 2 (REGN4461) will be combined by re-aligning to the first REGN4461 treatment administration, specifically study day 1 for arm 2 and week 12 for arm 1 will become REGN4461 Day 1. These descriptive statistics will be presented three times, specifically in Cohort A, Cohort B, and Cohort A+B.

Endpoints	Descriptive Statistic
• Absolute change in HbA1c from baseline to week 12	• HbA1c mean changes from REGN4461 Day 1 to REGN4461 week 12 for combined DBTP-stable Arm 1 patients and Arm 2 patients will be provided along

• Absolute change in HbA1c from week 12 to week 24	with its corresponding 95% confidence interval.
• Change in fasting glucose from baseline to week 12 • Change in fasting glucose from week 12 to week 24	• Fasting glucose mean changes from REGN4461 Day 1 to REGN4461 week 12 for combined Arm 1 and Arm 2 patients will be provided along with its corresponding 95% confidence interval.
• Percent change in liver fat (MRI-PDFF) from baseline to week 12 • Percent change in liver fat (MRI-PDFF) from week 12 to week 24	• Liver fat (MRI-PDFF) mean changes from REGN4461 Day 1 to REGN4461 week 12 for combined Arm 1 and Arm 2 in patients with hepatic steatosis (baseline MRI-PDFF ≥8.5%) will be provided along with its corresponding 95% confidence interval.

Table 6. Summary of Statistics for Patients Randomized to Placebo in Normally distributed Secondary Endpoints

NOTE: These statistical estimates and descriptive statistics will be presented three times, specifically in Cohort A, Cohort B, and Cohort A+B.

Endpoints	Estimates	Comparison
• Absolute change in HbA1c from baseline to week 12 • Absolute change in HbA1c from week 12 to week 24	• For Arm 1, baseline adjusted least-squares (LS) mean estimate at week 12 and week 12 adjusted least-squares (LS) mean estimate at week 24 will be provided along with the corresponding standard errors and 95% confidence intervals. MMRM / Least-squares (LS) means with their corresponding standard errors and 95% confidence intervals. Note: Treatment Group = Arm 1; Strata level = HbA1c>7.0%. • Note: Post baseline visits to include in the model are	• For Arm 1, difference between the HbA1c mean changes from week 12 to week 24 and from baseline to week 12 will be provided along with its corresponding 95% confidence interval, and nominal p-value when appropriate. • • REGN4461 in Arm 1 SBTP

	weeks 4, 6, 10, 12, 16, 18, 22, and 24.	versus Placebo Arm 1 DBTP
• Change in fasting glucose from baseline to week 12 • Change in fasting glucose from week 12 to week 24	• For Arm 1, baseline adjusted least-squares (LS) means estimates at week 12 and week 12 adjusted least-squares (LS) means estimates at week 24 will be provided along with the corresponding standard errors and 95% confidence intervals.	• Within Arm 1 patients, difference between the fasting glucose mean changes from week 12 to week 24 and from baseline to week 12 will be provided along with its corresponding 95% confidence interval, and nominal p-value.
• Percent change in liver fat (MRI-PDFF) from baseline to week 12 • Percent change in liver fat (MRI-PDFF) from week 12 to week 24	• For Arm 1 patients with hepatic steatosis (baseline MRI-PDFF ≥8.5%), baseline adjusted least-squares (LS) means estimates at week 12 and week 12 adjusted least-squares (LS) means estimates at week 24 will be provided along with their corresponding standard errors and 95% confidence intervals.	• Difference between the liver fat percent mean changes from week 12 to week 24 and from baseline to week 12 will be provided along with its corresponding 95% confidence interval, and nominal p-value.

5.7.2.2. Continuous Endpoints Anticipated to have a Non-normal Distribution

Continuous secondary efficacy variables defined in Section 4.7.2 and Section 4.7.3 anticipated to have a non-normal distribution (ie, TG) will be analyzed using the same MMRM model as described for the primary endpoint in TG.

For comparisons that defined on the DBTP-stable Arm 1 patients, the MMRM model will be fitted again to exclude the Arm 1 patients who do not meet the DBTP-stability criteria. The LS means will be back-transformed into the geometric means to ease clinical interpretation of the result. Table 7 summarizes the statistical analysis methods that will be performed for the secondary efficacy variables in fasting TG.

Table 7. Summary of Statistical Estimates, Comparisons, and Descriptive Statistics in Fasting-TG Secondary Endpoints

Endpoints	Cohort	Estimates	Statistics
• Percent change in fasting TG from baseline to week 12.	• Separately for Cohort B and Cohort A+B	Baseline adjusted least-squares (LS) means estimates at week 12 for each treatment subgroup with their corresponding standard errors and 95% confidence intervals. The LS means at week 12 will be back-transformed into the geometric means.	Difference of the study treatment TG geometric mean changes from baseline to week 12 will be provided along with its corresponding 95% confidence interval, and nominal p-value.
• Percent change in fasting TG from baseline to week 24	• Separately for Cohort A, Cohort B, and Cohort A+B	N/A	For Arm 2 patients, descriptive summaries will be provided at each protocol specified visit up to week 24; median percent changes with Q1 and Q3 bars will be plotted across visits; a spaghetti plot will be provided for individual patient data across visits.

• Percent change in fasting TG from baseline to week 12 • Percent change in fasting TG from week 12 to week 24	• Separately for Cohort A, Cohort B, and Cohort A+B	For Arm 1, baseline adjusted least-squares (LS) means estimates at week 12 and week 12 adjusted least-squares (LS) means estimates at week 24 will be provided with the corresponding standard errors and 95% confidence intervals. The LS means will be back-transformed into the geometric means.	For Arm 1, difference between the fasting TG geometric means from week 12 to week 24 and from baseline to week 12 will be provided along with its corresponding 95% confidence interval, and nominal p-value when appropriate.
• Percent change in fasting TG from baseline to week 12 • Percent change in fasting TG from week 12 to week 24	• Separately for Cohort A, Cohort B, and Cohort A+B	N/A	Fasting TG median change from REGN4461 Day 1 to REGN4461 week 12 for combined Arm 1 and Arm 2 patients will be provided along with Q1 and Q3 bars.

5.8. Analysis of Safety Data

The summary of safety results will be presented separately for the DBTP and SBTP, unless otherwise noted. Safety summaries for the DBTP will be presented by treatment group (ie, mibavademab, placebo) containing patients from the DB SAF. Safety summaries for the SBTP will be presented by all patients and by study treatment group in DBTP (ie, DB mibavademab, DB placebo), for patients in the SB SAF. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

General common rules

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety analysis sets (ie, exposed but not randomized) will be listed separately.
- Potentially Clinically Significant Values (PCSVs) or Potentially Clinically Significant Abnormalities (PCSAs) are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, ECG (PCSV version dated January 2009 [Appendix 10.4]).

- PCSV criteria will determine which patients had at least 1 PCSV during the respective TEAE period, taking into account all evaluations including unscheduled or repeated evaluations.
- The treatment-emergent PCSV denominator for a given parameter will be based on the number of patients assessed for that given parameter at least once during the respective TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to the Global Analysis Windows defined in Appendix 10.2 to provide an assessment for the screening visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.
- Unless otherwise specified, in the case of multiple assessments within an analysis window, the assessment closest to the protocol planned visit study day will be used in analysis.

5.8.1. Adverse Events

In general, the primary focus of AE reporting will be on TEAEs summarized in respective TEAE period, specifically the DBTP and SBTP.

If an AE onset date (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment or post-treatment status. Details on classification of AEs with missing or partial onset dates are provided in Section 6.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC and PT. In addition, incidence tables by SOC and PT will be provided for all TEAEs, serious TEAEs, and TEAEs leading to permanent treatment discontinuation. Multiple occurrences of the same event in the same patient will be counted only once in the tables. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event. The denominator for computation of percentages is the respective safety analysis set within each treatment group.

AE incidence tables will present data by SOC and PT and summarize the number (n) and percentage (%) of patients experiencing an AE.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with:
  - Any TEAE
  - Serious TEAE
  - TEAEs related to study treatment

  - TEAE leading to death
  - TEAE leading to treatment discontinuation
- All TEAEs by primary SOC and PT
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC and PT (PT incidence ≥ 2 patients in any treatment group)
- All TEAEs causality relationship (related/not related) to study treatment, presented by SOC and PT
- All TEAEs by maximum severity (ie, mild, moderate, or severe), presented by SOC and PT

Analysis of all treatment emergent serious adverse event(s)

- All Serious TEAEs by primary SOC and PT

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to permanent treatment discontinuation, by primary SOC and PT

Patient Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (TEAE) and reason for death
- TEAEs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by SOC and PT

5.8.2. Analysis of Adverse Events of Special Interest

Treatment-emergent adverse events of special interest (AESI), as listed in Section 4.8.1.2, will be presented by SOC and PT as applicable. AESI are defined by SMQ, CMQ, lab data, and/or dedicated e-CRF are summarized by frequency (%) as described in Appendix 10.3.

5.8.3. Adverse Events of Interest

Treatment emergent adverse events for mild infusion reactions, mild hypersensitivity reactions, and injection site reactions (ISR) as defined in Section 4.8.1.3 will be summarized by patient frequency (%) by SOC and PT.

Treatment emergent adverse events for infusion reactions and hypersensitivity reactions will also be summarized regardless of severity by SOC and PT.

5.8.4. Clinical Laboratory Measurements

General clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit (collected up to the day of last dose of study treatment + 14 days). These parameters will be presented by the biological functions defined in Section 4.8.2.

Individual patient laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.4), specifically identifying patients with at least one post-baseline

measurement that meets the PCSV criteria within the respective TEAE period. These laboratory parameters will be presented by the biological functions defined in Section 4.8.2. The incidence of PCSVs at any time during the respective TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria

Patient listings of laboratory measurements that meet PCSV criteria will be provided for the report appendix. For those laboratory parameters that don't have an associated PCSV criteria, similar summary tables can be provided based on measurements outside the central laboratory normal ranges, if applicable.

5.8.5. Analysis of Vital Signs

The vital sign actual values and change from baseline values obtained will be descriptively summarized at baseline and each post-baseline visit, collected up until the day of the last dose of study treatment + 14 days.

Individual patient vital sign measurements (regardless of sitting position) will be additionally evaluated by PCSV criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria within the TEAE period. The incidence of PCSVs at any time during the respective TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria

Patient listings of vital sign measurements that meet PCSV criteria will be provided for the report appendix.

5.8.6. Analysis of 12-Lead ECG

ECG results will be presented through an overall interpretation of ECG status and by ECG parameters (HR, PR, QRS, QT and QTcF), collected up until the day of the last dose of study treatment + 14 days.

- ECG parameters will be summarized through an overall interpretation of ECG status, specifically normal or abnormal (includes clinically significant (Yes/No)). The count and percentage of patients with at least 1 abnormal post-baseline ECG during the respective TEAE period will also be summarized according to the following baseline status categories:
  - Normal/missing
- Abnormal
  - Individual patient ECG measurements will be additionally evaluated by PCSV criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria within the TEAE period. The incidence of PCSVs at any time during the respective TEAE period will be

summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria
  - Patient listings of ECG measurements that meet PCSV criteria will be provided for the report appendix.

5.8.7. Physical Exams

A list of patients with any clinically significant abnormality results will be generated.

5.8.8. Treatment Exposure and Treatment Compliance

The duration of exposure during each study part in weeks will be presented by treatment group and study period, calculated as:

(Date of last study drug injection in the specific study part – date of first study drug injection in the specific study part + 7 days)/7

Number (%) of patients exposed to study drug during the study will be presented for each treatment group and study period.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

A summary of the number of doses by treatment group and study period will be provided.

The compliance with study treatment will be calculated as follows:

$$Compliance\ \% = 100\% \times \frac{\#\ actual\ injections}{\#\ planned\ injections}$$

The treatment compliance will be presented by specific ranges for each treatment group and study period.

5.9. Analysis of Other Variables

All measurements, scheduled or unscheduled, will be assigned to the Analysis Windows (Appendix 10.2) in order to provide an assessment for all post-baseline visit.

Change from baseline liver volume and hepatic fat content by MRI will be descriptively summarized by treatment group (Arm 1, Arm 2) and cohort (Cohort A, Cohort B, and combined Cohort A+B) at weeks 12 and 24 for patient in the MRI analysis set. Mean difference between treatments with associated 95% CI will also be provided at week 12.

Change from baseline in body composition (including lean mass and fat mass) using DXA at weeks 12 and 24 will be descriptively summarized by treatment group (Arm 1, Arm 2) and cohort (Cohort A, Cohort B, combined Cohort A+B) in patients in FAS and have at least one post-baseline assessment.

Change from baseline in leptin level at weeks 12 and 24, will be descriptively summarized by treatment group (Arm 1, Arm 2) and cohort (Cohort A, Cohort B, combined Cohort A+B) in patients in FAS and have at least one post-baseline assessment.

[redacted]

Summary statistics will include the number of patients with data, mean, SD, median, minimum, maximum, Q1 and Q3.

5.10. Analysis of Pharmacokinetic Variables

Descriptive statistics for concentrations of total drug will be presented. Mean concentrations will be tabulated by visit and treatment group, with concentrations below the LLOQ set to zero. Plots of the mean concentrations (linear and log scales) will be presented by nominal sampling time. Plots of the individual concentrations (linear and log scales) will be presented by actual sampling time. In the linear-scaled plots, concentrations below the LLOQ will be set to zero; in the log-scaled plots, concentrations below the LLOQ will be imputed as LLOQ/2. Where appropriate, relationship between concentrations of total drug and other pharmacodynamic biomarkers including, but not limited to, changes in endpoints of interest (eg, HbA1c, glucose, and TG) may be evaluated descriptively.

5.11. Analysis of Immunogenicity Data

[redacted]

  - Transient - Not persistent or indeterminate, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

- The maximum titer category of each patient is classified as:
- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)
  - Samples that are positive in ADA assay may be assessed for the presence of neutralizing anti-drug antibodies (NAb) when NAb assay is available.
- The following will be summarized by treatment group and ADA titer level:
- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of patients with pre-existing ADA
- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients
  - Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent, and treatment-boosted ADA response.

5.11.1. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.1.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to mibavademab will be explored by treatment groups. Plots of individual mibavademab concentration time profiles may be provided to examine the potential impact of ADA by maximum titer on these profiles.

5.11.1.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety will be explored with a primary focus on adverse events during the TEAE period.

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])

  - Potential association between immunogenicity variables and efficacy endpoints may be explored (eg, scatter plot or spaghetti plot).The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category

5.12. Analysis of Clinical Outcome Assessment

The summary of results for clinical outcomes assessments will be presented by treatment groups (Arm 1, Arm 2) and by cohorts (Cohort A, Cohort B) containing patients from the full analysis set, unless otherwise specified.

The baseline value is defined as the last available measurement prior to the time of the first double-blind study treatment administration. All measurements, scheduled or unscheduled, will be assigned to the Global Analysis Windows (Appendix 10.2) to provide an assessment for all post-baseline visit.

For the SF-36, raw value and change from baseline will be summarized using mean, median, SD, min, max, Q1, Q3 for each post baseline visit among the SF-36 analysis set.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment is programmatically defined as the last available measurement prior to the time of the first double-blind study treatment administration. For patients randomized and not treated, the baseline value is defined as the last available value prior to the date of randomization.

6.2. Data Handling Convention for Efficacy Variables

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.7.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Date and Time of First/Last Study Treatment

The date and time of study drug administration are filled in e-CRF. No missing data is expected. Date of first/last administration is the first/last start date of study drug provided in e-CRF.

Adverse Event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

When the partial AE date/time information does not indicate that the AE started prior to study treatment or after the TEAE period, the AE will be classified as treatment-emergent.

Medication/Procedure

No imputation of medication/procedure start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure.

Potentially Clinically Significant Value (PCSV)

If a patient has a missing baseline value, this patient will be grouped in the category "normal/missing at baseline."

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing. For example, for eosinophils, the PCSV is >0.5 giga/L or >ULN if ULN ≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized nor included in the computation of PCSVs.

6.4. Visit Windows

Visit windows will be programmatically imposed on those efficacy and safety measures repeatedly collected over the course of the study. These visit windows are derived from the number of days in study, specifically assigning day ranges to represent the study assessment schedule provided in the protocol. Data analyzed by time point (including efficacy, laboratory safety data, vital signs, and ECG) will be summarized using the analysis windows given in Appendix 10.2. These analysis windows will be applicable for all efficacy and safety analyses, and they are defined to provide more homogeneous data for time point-specific analyses. If multiple valid values of a variable exist within an analysis window, the nearest from the targeted study day will be selected for analysis, unless otherwise specified. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within a same day, then the first value of the day will be selected when time is available, else the scheduled visit will be selected.

6.5. Unscheduled Assessments

For efficacy, safety laboratory data, vital signs, and ECG, unscheduled visit measurements may be used to provide a measurement for a time point, including baseline, if appropriate according

to their definitions. The measurements may also be used to determine abnormal values, AESIs, and PCSVs.

6.6. Pooling of Centers for Statistical Analyses

Not applicable.

6.7. Statistical Technical Issues

Not applicable.

7. TIMING OF STATISTICAL ANALYSES

7.1. Interim Analysis

No formal interim analysis is planned. Periodic data reviews may be performed by selected unblinded Regeneron personnel with no direct involvement in the study conduct.

7.2. First Step Analysis

The first-step analysis will be conducted as soon as all patients have been randomized and all data through week 12 has been entered, cleaned, and locked. The first-step analysis will be conducted on all randomized patients who receive study treatment. These statistical analyses will include the primary and secondary endpoints collected during the double-blind period. All subsequent protocol work can be generated in an unblind-blind manner (study treatment assignments, primary efficacy variables, and applicable secondary efficacy variables), excluding the investigative sites.

7.3. Second Step Analysis

The second step analysis will be conducted as soon as all patients have been randomized and all data through week 24 has been entered, cleaned, and locked. The second-step analysis will be conducted on all randomized patients who receive study treatment. These statistical analyses will include the secondary endpoints collected during the single-blind period.

7.4. Final Analysis

The final analysis will be conducted at the end of the study, and will consist of the final analysis for efficacy, pharmacokinetic and safety measures.

7.5. Additional Rules

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for the first-step analysis:

- Any assessments within the Efficacy Analysis Windows (Appendix 10.2) up to the SBTP week 24 visit will be taken into account (may include few unscheduled lipid data soon after the cut-off date).

- Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date.
- Patients who did not complete the respective treatment period nor prematurely discontinued the study treatment at cut-off date will be:
  - Analyzed as "ongoing" in the disposition summary.
  - Their TEAE period and treatment period will end at the respective data cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last administration date.
  - Analyses of number of IP administrations, and mean IP administration frequency will be performed up to the last administration reported in the e-CRF up to the cut-off date.
  - AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.
  - Post-treatment period, and post-study period are not applicable for ongoing patients. Analyses of post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the data cut-off date.
  - Analysis of status at last study contact and proportion of patients with insufficient follow-up will be provided for patients who either completed or prematurely discontinued the treatment before or at the data cut-off date.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
• Change in HbA1c from baseline to week 12 in patients with elevated baseline HbA1c (ie, screening HbA1C > 7%).	Glycemic Analysis Set – Cohort A	MMRM		No	
• Percent change in fasting triglyceride (TG) from baseline to week 12 in patients with elevated screening baseline fasting TG (ie, fasting TG ≥ 200 mg/dL).	Triglyceride Analysis Set – Cohort A	MMRM	Ranked ANCOVA	No	

10.2. Windows for Analysis Time Points

Below are the definitions for the visit windows programmatically imposed on measures repeatedly collected over the course of the study. These visit windows reflect the study schedule of assessments as described in the protocol.

The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Below are the relevant definitions for the analysis visit windows:

1. Study day is defined as the number of days since the first study treatment administration +1. The first study treatment occurs on Day 1.

2. Single-blind study day is defined as the number of days since the first single-blind study treatment administration+1. Especially, Single-blind Study Day 1 (SB Day 1) is defined as the day for the first single-blind study treatment administration.
3. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1.
4. For randomized but not treated patients, Day 1 is the day of randomization.

Table 8: General Global Analysis Windows

Visit Label	Targeted DBTP Study Day	Targeted SBTP Study Day	Analysis Window in DBTP Study Days	Analysis Window in SBTP Study Days
Screening	< Day -28	N/A	Measurement obtained prior to 1st study trt, and not defined as baseline visit	N/A
Baseline	Day 1	N/A	Measurement obtained closest to 1st study trt, while remaining prior to 1st study trt.admin	N/A
Week 1	8	N/A	Day 2 to Day 15	N/A
Week 3	22	N/A	16 to 32	N/A
Week 6	43	N/A	33 to 50	N/A
Week 8	57	N/A	51 to 64	N/A
Week 10	71	N/A	65 to 78	N/A
Week 12	85	N/A	79 to SB Day 1	N/A
Week 13	N/A	SB Day 8	N/A	SB Day 2 to 15
Week 15	N/A	22	N/A	16 to 29
Week 17	N/A	36	N/A	30 to 39
Week 18	N/A	43	N/A	40 to 50
Week 20	N/A	57	N/A	51 to 64
Week 22	N/A	71	N/A	65 to 78
Week 24	N/A	85	N/A	79 to 92
FU- W5	Last study trt admin day + 35 days	Last study trt admin day +15 days TO last study trt admin day + 49 days		
FU-W9	Last study trt admin day + 63 days	Last study trt admin day + 50 days TO last study trt admin day + 77 days		
FU-W13	Last study trt admin day + 91 days	Last study trt admin day + 78 days TO last study trt admin day + 105 days		
FU-W17	Last study trt admin day + 119 days	Last study trt admin day + 106 days TO last study trt admin day + 126 days		

Table 9: Analysis Windows for Vital Sign

Visit Label	Targeted DBTP Study Day	Targeted SBTP Study Day	Analysis Window in DBTP Study Days	Analysis Window in SBTP Study Days
Screening	< Day 1	N/A	Measurement obtained prior to 1st study trt, and not defined as baseline visit	N/A
Baseline	Day 1	N/A	Measurement obtained closest to 1st study trt, while remaining prior to 1st study trt.admin	N/A
Week 1	8	N/A	Day 2 to Day 11	N/A
Week 2	15	N/A	12 to 18	N/A
Week 3	22	N/A	19 to 25	N/A
Week 4	29	N/A	26 to 32	N/A
Week 5	36	N/A	33 to 39	N/A
Week 6	43	N/A	40 to 46	N/A
Week 7	50	N/A	47 to 53	N/A
Week 8	57	N/A	54 to 60	N/A
Week 9	64	N/A	61 to 67	N/A
Week 10	71	N/A	68 to 74	N/A
Week 11	78	N/A	75 to 81	N/A
Week 12	85	N/A	82 to SB Day 1	N/A
Week 13	N/A	SB Day 8	N/A	SB Day 2 to 11
Week 14	N/A	15	N/A	12 to 18
Week 15	N/A	22	N/A	19 to 25
Week 16	N/A	29	N/A	26 to 32
Week 17	N/A	36	N/A	33 to 39
Week 18	N/A	43	N/A	40 to 46
Week 19	N/A	50	N/A	47 to 53
Week 20	N/A	57	N/A	54 to 60
Week 21	N/A	64	N/A	61 to 67
Week 22	N/A	71	N/A	68 to 74
Week 23	N/A	78	N/A	75 to 81
Week 24	N/A	85	N/A	82 to 92
FU- W5	Last study trt admin day + 35 days	Last study trt admin day +15 days TO last study trt admin day + 49 days		
FU-W9	Last study trt admin day + 63 days	Last study trt admin day + 50 days TO last study trt admin day + 77 days		

Visit Label	Targeted DBTP Study Day	Targeted SBTP Study Day	Analysis Window in DBTP Study Days	Analysis Window in SBTP Study Days
FU-W13	Last study trt admin day + 91 days	Last study trt admin day + 78 days TO last study trt admin day + 105 days		
FU-W17	Last study trt admin day + 119 days	Last study trt admin day + 106 days TO last study trt admin day + 126 days		

Table 10: Analysis Windows for Body Weight

Visit Label	Targeted DBTP Study Day	Targeted SBTP Study Day	Analysis Window in Study Days	SBTP Analysis Window in Study Days
Screening	< Day 1	N/A	Measurement obtained prior to 1st study trt, and not defined as baseline visit	N/A
Baseline	Day 1	N/A	Measurement obtained closest to 1st study trt	N/A
Week 1	8	N/A	Day 2 to 15	N/A
Week 3	22	N/A	16 to 29	N/A
Week 5	36	N/A	30 to 39	N/A
Week 6	43	N/A	40 to 50	N/A
Week 8	57	N/A	51 to 64	N/A
Week 10	71	N/A	65 to 78	N/A
Week 12	85	N/A	82 to SB Day 1	N/A
Week 14	N/A	SB Day 15	N/A	SB Day 2 to 22
Week 16	N/A	29	N/A	23 to 36
Week 18	N/A	43	N/A	37 to 50
Week 20	N/A	57	N/A	51 to 64
Week 22	N/A	71	N/A	65 to 78
Week 24	N/A	85	N/A	79 to 92
FU- W5	Last study trt admin day + 35 days	Last study trt admin day +15 days TO last study trt admin day + 49 days		
FU-W9	Last study trt admin day + 63 days	Last study trt admin day + 50 days TO last study trt admin day + 77 days		
FU-W13	Last study trt admin day + 91 days	Last study trt admin day + 78 days TO last study trt admin day + 105 days		
FU-W17	Last study trt admin day + 119 days	Last study trt admin day + 106 days TO last study trt admin day + 126 days		

Table 11: Efficacy Analysis Windows for Fasting Triglycerides and Fasting Glucose

Visit Label	Targeted DBTP Study Day	Targeted SBTP Study Day	Analysis Window in Study Days	SBTP Analysis Window in Study Days
Screening	< Day 1	N/A	Measurement obtained prior to 1st study trt, and not defined as baseline visit	N/A
Baseline	Day 1	N/A	Measurement obtained closest to 1st study trt while remaining prior to 1st study trt admin	N/A
Week 2	15	N/A	Day 2 to 22	N/A
Week 4	29	N/A	23 to 36	N/A
Week 6	43	N/A	37 to 50	N/A
Week 8	57	N/A	51 to 64	N/A
Week 10	71	N/A	65 to 74	N/A
Week 11	78	N/A	75 to 81	N/A
Week 12	85	N/A	82 to SB Day 1	N/A
Week 14	N/A	SB Day 15	N/A	SB Day 2 to 22
Week 16	N/A	29	N/A	23 to 36
Week 18	N/A	43	N/A	37 to 50
Week 20	N/A	57	N/A	51 to 64
Week 22	N/A	71	N/A	65 to 74
Week 23	N/A	78	N/A	75 to 81
Week 24	N/A	85	N/A	82 to 92
FU- W5	Last study trt admin day + 35 days		Last study trt admin day +15 days TO last study trt admin day + 49 days	
FU- W9	Last study trt admin day + 63 days		Last study trt admin day + 50 days TO last study trt admin day + 77 days	
FU- W13	Last study trt admin day + 91 days		Last study trt admin day + 78 days TO last study trt admin day + 105 days	
FU- W17	Last study trt admin day + 119 days		Last study trt admin day + 106 days TO last study trt admin day + 126 days	

Table 12: Efficacy Analysis Windows for HbA1c

Visit Label	Targeted Study DBTP Day	Targeted SBTP Study Day	Analysis Window in DBTP Study Days	Analysis Window in SBTP Study Days
Screening	< Day 1	N/A	Measurement obtained prior to 1st study trt, and not defined as baseline visit	N/A
Baseline	Day 1	N/A	Measurement obtained closest to 1st study trt while remaining prior to 1st study trt admin	N/A
Week 4	29	N/A	Day 2 to 36	N/A
Week 6	43	N/A	37 to 57	N/A
Week 10	71	N/A	58 to 78	N/A
Week 12	85	NA	79 to SB Day 1	N/A
Week 16	N/A	SB Day 29	N/A	SB Day 2 to 36
Week 18	N/A	43	N/A	37 to 57
Week 22	N/A	71	N/A	58 to 78
Week 24	N/A	85	N/A	79 to 92
FU- W5	Last study trt admin day + 35 days		Last study trt admin day +15 days TO last study trt admin day + 49 days	
FU- W9	Last study trt admin day + 63 days		Last study trt admin day + 50 days TO last study trt admin day + 77 days	
FU- W13	Last study trt admin day + 91 days		Last study trt admin day + 78 days TO last study trt admin day + 105 days	
FU- W17	Last study trt admin day + 119 days		Last study trt admin day + 106 days TO last study trt admin day + 126 days	

Table 13: Efficacy Analysis Windows for Daily Lipodystrophy Hunger Questionnaire

Visit Label	Analysis Window in DBTP Study Days	Analysis Window in SBTP Study Days
Baseline	Day -27 to Day 1 while remaining prior to 1st DB study trt admin	N/A
Week 4	Day 2 to 29	N/A
Week 8	30 to 57	N/A
Week 12	58 to SB Day 1 while remaining prior to 1st SB study trt admin or to last study trt admin day + 7 days if not entering SBTP	N/A
Week 16	N/A	SB Day 2 to 29
Week 20	N/A	30 to 57
Week 24	N/A	58 to Last study trt admin day + 7 days
FU- W5	Last study trt admin day +8 days TO last study trt admin day + 35 days	
FU- W9	Last study trt admin day + 36 days TO last study trt admin day + 63 days	
FU- W13	Last study trt admin day + 64 days TO last study trt admin day + 91 days	
FU- W17	Last study trt admin day + 92 days TO last study trt admin day + 119 days	

Table 14: Efficacy Analysis Windows for DXA, MRI, NMR Lipid, and Bioimpedance

Visit Label	Targeted Study DBTP Day	Targeted SBTP Study Day	Analysis Window in DBTP Study Days	Analysis Window in SBTP Study Days
Baseline	Day 1	N/A	Measurement obtained closest to 1st study trt while remaining prior to 1st study trt admin	N/A
Week 12	85	NA	Day 43 to SB Day 1 or to last DB trt admin day + 28 days if not entering SBTP	N/A
Week 24	N/A	SB Day 85	N/A	SB Day 43 to last SB trt admin day + 28 days
FU- W17	Last study trt admin day + 119 days		Last study trt admin day + 69 days TO last study trt admin day + 133 days	

Table 15: Double-blind treatment period – Period Windows

For those measurements that are collected over time (eg, IV and SC exposure), analyses performed within the 12-week double-blinded treatment period (DBTP) windows will use the following definitions to bin observations. Observations will be binned based on the start date of the measurement.

- The DBTP is defined as from the starting time of the first DBTP study drug administration to the day of the last DBTP study drug administration + 14 days for those patients not proceeding into the single-blinded treatment period (SBTP). For those patients proceeding into the SBTP, the DBTP ends at the starting time of the first SBTP study drug administration.
-

Table 16: Single-blind treatment period – Period Windows

For those measurements that are collected over time (eg, IV and SC exposure), analyses performed within the 12-week single-blinded treatment period (SBTP) windows will use the following definitions to bin observations. Observations will be binned based on the start date of the measurement.

- The SBTP is defined from the time of the first SBTP study drug administration to the day of the last SBTP study drug administration + 14 days.
-

Table 17: Double-blind treatment-emergent adverse event period – Period Windows

- The double-blind treatment-emergent adverse event (TEAE) period is defined from the starting time of the first dose of double-blind study treatment administration to the day of the last dose of double-blind study treatment administration + 112 days (16 weeks) for those patients not proceeding into SBTP, or up to the starting time of the first dose of SBTP study treatment administration for those patients proceeding into the SBTP.
-

Table 18: Single-blind treatment-emergent adverse event period – Period Windows

- The single-blind treatment-emergent adverse event (TEAE) period is defined from the starting time of the first single-blind study treatment administration to the day of the last single-blind study treatment administration + 112 days (16 weeks).
-
-

10.3. List of AESIs with Data Sources and Definitions of SMQ/CMQ

Table 19: Summary of AESIs and the Methods of Data Collections and Derivations

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or Laboratory data criteria
Hypoglycemia	Yes	• Blood glucose <54 mg/dL
New onset diabetes mellitus (NODM)	Yes	For patients with no diabetes at baseline: • Two values of fasting (≥8 hr) plasma glucose ≥126 mg/dL (7.0 mmol) during treatment period OR • Two values of HbA1c ≥6.5% (48 mmol/mol) during treatment period Note: Patients who meet either of these criteria during the PBO run-in period will be considered to have diabetes at baseline.
Hyperglycemia requiring treatment	Yes	HbA1c ≥10.5% AND increase in HbA1c of ≥1.5% from baseline value OR b. Fasting glucose ≥250 mg/dL on 2 occasions AND increase in fasting glucose >50 mg/dL above baseline
Development of new or worsening of autoimmune disease	Yes	N/A
Moderate and severe Hypersensitivity reactions	Yes	• CMQ 'Hypersensitivity, which is defined as Hypersensitivity SMQ (narrow) excluding the following PTs:

		o Injection site dermatitis, o Injection site eczema, o Injection site hypersensitivity, o Injections site rash, o injection site reaction, o Injection site recall reaction, o Injection site urticaria, o Injection site vasculitis
Moderate and severe infusion reactions	Yes	N/A

^ *dedicated CRF for ISR captures event PT and associated symptoms*

10.4. Criteria for Potentially Clinically Significant Values (PCSV)

Table 20: Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical chemistry		
ALT	By distribution analysis: >2 ULN and baseline ≤ 2 ULN >3 ULN and baseline ≤ 3 ULN >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	
AST	By distribution analysis: >2 ULN and baseline ≤ 2 ULN >3 ULN and baseline ≤ 3 ULN >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	
Alkaline Phosphatase	> 1.5 ULN and baseline ≤ 1.5 ULN	
Total Bilirubin	> 1.5 ULN and baseline ≤ 1.5 ULN > 2 ULN and baseline ≤ 2 ULN	
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN and baseline ALT≤3 ULN or Total bilirubin ≤ 2 ULN	

Parameter	PCSV	Comments
CPK	> 3 ULN and ≤ 5 ULN and baseline ≤ 3ULN >5 ULN and ≤ 10 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN	
Creatinine	≥ 30% increase from baseline ≥ 60% increase from baseline	
Creatinine Clearance	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR)	
Uric Acid Hyperuricemia	>408 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride Hypochloremia: Hyperchloremia:	 <80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥ 150 mmol/L	Must also be outside the normal range.
Potassium	< 3 mmol/L ≥ 5.5 mmol/L	Must also be outside the normal range.
Total Cholesterol	≥6.20 mmol/L (Under 18 yrs) >7.74 mmol/L (18 yrs +)	Must also be outside the normal range.
Triglycerides	≥ 5.6 mmol/L if baseline < 5.6 mmol/L or >50% from baseline	Must also be outside the normal range.
Glucose	Hypoglycemia <3.9 mmol/L or 70 mg/dL Hyperglycemia Fasting glucose ≥250 mg/dL or 13.9mmol/L and Increase in fasting glucose >50 mg/dL or 2.8mmol/L above baseline	Must also be outside the normal range.

Parameter	PCSV	Comments
HbA1c	HbA1c ≥10.5% AND increase in HbA1c of ≥1.5% from baseline value	
Albumin	≤25 g/L	
Hematology		
WBC	< 3.0 Giga/L (3000/mm3) ≥ 16.0 Giga/L (18 yrs +)	Must also be outside the normal range.
Lymphocytes	>4.0 Giga/L <0.6 Giga/L	
Neutrophils	< 1.5 Giga/L (1,500/mm3)	Must also be outside the normal range.
Eosinophils	> 0.5 Giga/L (500/ mm_3) or > ULN if ULN ≥ 0.5 Giga/L	
Monocytes	>1.5 Giga/L	
Hemoglobin	≤115 g/L (Male 18 yrs +) ≤95 g/L (Female 18 yrs +) ≥185 g/L (Male 18 yrs +) ≥165 g/L (Female 18 yrs +) Decrease from Baseline ≥20 g/L (18 yrs +)	Must also be outside the normal range.
Platelets	< 100 Giga/L (100,000/mm^3) > 700 Giga/L (100,000/mm^3)	Must also be outside the normal range.
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	
Vital Signs		
HR	≤45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	
SBP	≤ 90 mmHg and decrease from baseline ≥ 20 mmHg (18 yrs +) ≥ 160 mmHg and increase from baseline ≥ 20 mmHg (18 yrs +)	

Parameter	PCSV	Comments
DBP	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg (18 yrs +) ≥ 110 mmHg and increase from baseline ≥ 10 mmHg (18 yrs +)	
Weight	≥ 10% decrease versus baseline	
ECG parameters		
HR	≤45 bpm and decrease from baseline ≥20 bpm (18 yrs +) ≥120 bpm and increase from baseline≥20 bpm (18 yrs +)	
PR	>220 ms and increase from baseline ≥20 ms (18 yrs +)	
QRS	>110 ms and increase from baseline ≥20% (18 yrs +) >120 ms and increase from baseline ≥20% (18 yrs +)	
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms (Male) 451-470 ms (Female) Prolonged*: >450 ms (Male) > 470 ms (Female) QTc ≥500 ms <u>Increase versus baseline (Males and Females)</u> Borderline 30-60 ms Prolonged*: >60 ms	To be applied to QTcF correction formulas

10.5. Biomarker-NMR Lipoprotein analysis

The following data fields are reported in the Biomarker-Lipoprotein NMR.

LP3 Data to be sent quarterly

Abbreviation	Parameter to be reported	Unit
VLDLCP3	VLDL & Chylomicron Particles (total) 1	nmol/L
VLCP3	Large VLDL & Chylomicrons Particles1	nmol/L
VMP3	Medium VLDL Particles1	nmol/L
VSP3	Small VLDL Particles1	nmol/L
LDLP3	LDL Particles (total) 1	nmol/L
IDLP3	IDL Particles1	nmol/L
LLP3	Large LDL Particles1	nmol/L
LSP3	Small LDL Particles (total) 1	nmol/L
HDLP3	HDL Particles (total) 1	µmol/L
HLP3	Large HDL Particles1	µmol/L
HMP3	Medium HDL Particles1	µmol/L
HSP3	Small HDL Particles1	µmol/L
VZ3	VLDL Size	nm
LZ3	LDL Size	nm
HZ3	HDL Size	nm
LP-IR	Lipoprotein Insulin Resistance Score	N/A

LP4 Data to be sent at the end of the study

Abbreviation	Analyte Description	Units
TRLP	Triglyceride rich lipoprotein (TRL) particles (Total chylomicron & VLDL particles)	nmol/L
VL_TRLP	Very large TRL particles	nmol/L
L_TRLP	Large TRL particles	nmol/L
M_TRLP	Medium TRL particles	nmol/L
S_TRLP	Small TRL particles	nmol/L
VS_TRLP	Very small TRL particles	nmol/L
LDLP	Total low density lipoprotein (LDL) particles	nmol/L
L_LDLP	Large LDL particles	nmol/L
M_LDLP	Medium LDL particles	nmol/L
S_LDLP	Small LDL particles	nmol/L
HDLP	Total high density lipoprotein (HDL) particles	µmol/L
L_HDLP	Large HDL particles	µmol/L
M_HDLP	Medium HDL particles	µmol/L
S_HDLP	Small HDL particles	µmol/L
H7P	H7 subspecies of HDL	µmol/L
H6P	H6 subspecies of HDL	µmol/L
H5P	H5 subspecies of HDL	µmol/L
H4P	H4 subspecies of HDL	µmol/L
H3P	H3 subspecies of HDL	µmol/L
H2P	H2 subspecies of HDL	µmol/L
H1P	H1 subspecies of HDL	µmol/L
TRLZ	Mean TRL size	nm
LDLZ	Mean LDL size	nm
HDLZ	Mean HDL size	nm
TRLTG	TRL triglycerides	mg/dL
TRLC	TRL cholesterol	mg/dL
LP-X	Lipoprotein X	mg/dL

LP-Z	Lipoprotein Z	nmol/L
ApoAI	Apolipoprotein A-I	mg/dL
BCAA	Total branched chain amino acids	µmol/L
Val	Valine	µmol/L
Leu	Leucine	µmol/L
Ileu	Isoleucine	µmol/L
Ala	Alanine	µmol/L

LP4 Derived Lipids

Abbreviation	Analyte Description	Units
TC	Total Cholesterol	mg/dL
HDLC	HDL Cholesterol	mg/dL
LDLC	LDL Cholesterol	mg/dL
TG	Total Triglycerides	mg/dL
ApoB	Apolipoprotein B	mg/dL

Inflammation Biomarker

Abbreviation	Analyte Description	Units
GlycA	GlycA	µmol/L

Ketone Bodies

Abbreviation	Analyte Description	Units
KetBod	Total Ketone Bodies	µmol/L
B-HB	β-hydroxybutyrate	µmol/L
AcAc	Acetoacetate	µmol/L
Acetone	Acetone	µmol/L

Small Molecule Metabolites

Abbreviation	Analyte Description	Units
Glu	Glucose	mg/dL
Ctr	Citrate	mg/dL

NMR Multimarker (score 1-100)

Abbreviation	Analyte Description
LP-IR	Lipoprotein Insulin Resistance Index
DRI	Diabetes Risk Index

10.6. DXA Variable List

LARM_AREA
LARM_BMC
LARM_BMD
LARM_FAT

LARM_LEAN
LARM_CR
RARM_AREA
RARM_BMC
RARM_BMD
RARM_FAT
RARM_LEAN
RARM_CR
LLEG_AREA
LLEG_BMC
LLEG_BMD
LLEG_FAT
LLEG_LEAN
LLEG_CR
RLEG_AREA
RLEG_BMC
RLEG_BMD
RLEG_FAT
RLEG_LEAN
RLEG_CR
TRUNK_FAT
TRUNK_LEAN
ANDRD_FAT
ANDRD_LEAN
GYND_FAT
GYND_LEAN
HEAD_AREA
HEAD_BMC
HEAD_BMD
HEAD_FAT
HEAD_LEAN
HEAD_CR
LEG_AREA
LEG_BMC
LEG_BMD
LEG_FAT
LEG_LEAN
LEG_CR
ARM_AREA
ARM_BMC
ARM_BMD
ARM_FAT

ARM_LEAN
ARM_CR
TOT_AREA
TOT_BMC
TOT_BMD
TOT_FAT
TOT_LEAN
TOT_PFAT
TOT_CR
TOT_ZSCORE
TOT_ZSCORE_CR
ADJTOT_AREA
ADJTOT_BMC
ADJTOT_BMD
ADJTOT_FAT
ADJTOT_LEAN
ADJTOT_PFAT
ADJTOT_CR
ADJTOT_ZSCORE
ADJTOT_ZSCORE_CR
VATMASS
VATVOL

10.7. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 21 and Table 22.

Table 21: Schedule of Events: Screening and Placebo Run-In

Study Period	Screening [1,2]			Placebo Run-In			
	Mandatory In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit 3		Mandatory In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit [3]		
Visit Number:	**1**	**2[4]**	**(3)[4]**	**4**	**5**	**6**	**7**
Day:	-98 to -63	-91 to -49	-77 to -49	-28	-21	-14	-7
±visit window (d):				±3	±3	±3	±3
Week:	week -14 to -9	week -13 to -7	week-11 to -7	week -4	week -3	week -2	week -1
Screening							
Informed Consent	X						
Inclusion/Exclusion	X			X			
Medical History [5]	X						
Demographics	X						
Confirm partial lipodystrophy diagnosis	X						
HIV serology and hepatitis testing (HBsAg, HCV)	X						
Treatment							
Placebo Administration for Run-In IV [1]				X			
Placebo Administration for Run-In SC					X	X	X
Concomitant Meds and Treatment	X	X	X	X	X	X	X
Monitoring/dose adjustments for antidiabetic and lipid lowering medication [6]				X	X	X	X
Safety [7]							
Vital Signs [8]	X			X	X	X	X
Height	X						
Weight [9]	X			X			X
Physical Examination	X			X			
Waist and hip circumference	X			X			
Electrocardiogram [10]	X						
Adverse Events	X	X	X	X	X	X	X
Menstrual history, pregnancy status reporting, and confirmation of contraception	X			X		X	
Laboratory Testing [11]							
Hematology	X			X		X	
Blood Chemistry	X			X		X	
Pregnancy Test (WOCBP)[12]	Serum			Urine		Urine	

Study Period	Screening [1,2]			Placebo Run-In			
	Mandatory In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit 3		Mandatory In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit [3]		
Visit Number:	**1**	**2[4]**	**(3)[4]**	**4**	**5**	**6**	**7**
Day:	-98 to -63	-91 to -49	-77 to -49	-28	-21	-14	-7
±visit window (d):				±3	±3	±3	±3
Week:	week -14 to -9	week -13 to -7	week-11 to -7	week -4	week -3	week -2	week -1
Urinalysis	X						
Leptin[13,14]	X	X	X		X		X
Efficacy[11]							
Lipid panel[14]				X			
Free Fatty Acids[14]				X		X	
Fasting Triglycerides[13,14]	X	X	X	X	X	X	X
Fasting Glucose [14]	X			X	X	X	X
HbA1c	X			X			
Fructosamine	X			X		X	
Insulin [14]				X		X	
NMR Lipid panel LDL-C, HDL-C, total-Cholesterol [14]				X			
Urine Creatinine and Albumin				X			
Patient eCOA Training[15]				X			
Daily Lipodystrophy Hunger questionnaire				← X →			
BPI-SF questionnaire				X			
PHQ-8 questionnaire				X			
SF-36 questionnaire				X			
HADS questionnaire				X			
Patient Global Impression of Severity- Hunger				X			
Patient Global Impression of Severity- Pain				X			
Bioimpedance	X			X			
DXA	X[16]			X[16]			
Liver volume (MRI) and liver fat content (MRI-PDFF)				X[16]			
Biomarkers Procedure/Samples							
Apolipoprotein C3 (ApoC3)[11,14]				X			
ANGPTL3[11,14]				X			

Study Period	Screening [1,2]			Placebo Run-In			
	Mandatory In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit 3		Mandatory In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit [3]		
Visit Number:	**1**	**2[4]**	**(3)[4]**	**4**	**5**	**6**	**7**
Day:	-98 to -63	-91 to -49	-77 to -49	-28	-21	-14	-7
±visit window (d):				±3	±3	±3	±3
Week:	week -14 to -9	week -13 to -7	week-11 to -7	week -4	week -3	week -2	week -1
Future biomedical research serum and plasma samples (Optional)				X			
Pharmacogenomics Sub-study (Optional)							
Blood sample for DNA isolation[17]	X						

Abbreviations: ANGPTL3=angiopoietin-like protein 3; BPI-SF=brief pain inventory – short form; DNA=deoxyribonucleic acid; DXA=dual-energy X-ray absorptiometry; eCOA=electronic clinical outcome assessment; HADS=hospital anxiety and depression scale; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; ; MRI=magnetic resonance imaging; MRI-PDFF=MRI-derived proton density fat fraction; NMR=nuclear magnetic resonance; PHQ-8=8-item patient health questionnaire depression scale; SC=subcutaneous; SF-36=short form 36; WOCBP=women of child-bearing potential; HDL-C=high density lipoprotein cholesterol; LEPR=soluble leptin receptor; l; IV=intravenous; LDL-C=low density lipoprotein cholesterol

10.7.1. Footnotes for the Schedule of Events Table 21: Screening and Placebo Run-in

1. Patients may be re-screened if they fail the screening for reasons related to incidental or transitory conditions (eg, medication use, concomitant illness, medical condition). If patients are re-screened within the original 10-week screening period, only screening test(s) (eg, an out-of-range lab value) that resulted in initial screen failure should be repeated. All patients will be monitored for 4 hours following IV placebo infusion to maintain study blinding. For those patients screened and found eligible under the original protocol, HbA1c and triglycerides assessments will be repeated to reconfirm eligibility of the patient if the screening window of 10 weeks has been exceeded by the time the relevant approvals for Protocol Amendment 1 are in place.
2. Procedures may be conducted on different days during the screening period, if needed. Blood draws for laboratory testing at the screening visit will be collected in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
3. Procedures may be conducted by trained study staff at a remote location (at home, work place, and/or school).
4. Visit 2 has to occur at least 7 days after visit 1. Visit 3 is conditional upon the results of results from visit 1 and visit 2. Visit 3 may not be required in all patients depending on the results from visit 1 and visit 2.

5. Medical history should include detailed lipodystrophy history including prior medication/IPs, genetic diagnosis (if known), and results of any previous anti-metreleptin antibody testing (if applicable).
6. Monitoring by qualified study personnel may be performed as a telephone contact or an in-clinic or inpatient assessment. A telephone contact may be converted to an in-person site visit if in the opinion of qualified study personnel that a direct, in-person assessment would aid assessment of safety or clarify concomitant medication use and adjustment. For diabetic patients, all monitoring assessments will include asking about symptoms of hypoglycemia (per local standards), a review of the patient's home glucometer readings (if applicable), and patient education regarding the importance of blood glucose monitoring and how to recognize symptoms of hypoglycemia (per local standards). Diabetic patients should be reminded to call the site if any signs or symptoms of hypoglycemia occur.
7. All safety assessment should be performed before study drug administration.
8. Vital signs should be recorded prior to IV study drug infusion, and approximately 120 minutes post-IV infusion or prior to SC study drug injection.
9. Body weight should be measured with patient in a gown after voiding (empty bladder) using a calibrated scale. Patients should empty pockets and remove shoes, belts, outer-layer clothing, or any other heavy wearable prior to being weighed.
10. The ECG can be performed up to 24 hours prior to study drug administration.
11. Blood (for safety, efficacy and biomarkers) and urine samples are to be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure.
12. If there is a positive urine pregnancy test, a confirmatory serum pregnancy test will be performed. Study treatment will not be administered until a negative serum pregnancy test is obtained. If the serum pregnancy test is negative the patient can continue in the study. A positive serum pregnancy test will result in permanent stopping of study drug administration.
13. Please refer to Appendix 1 in the study protocol for actions based on Hb1Ac, TG, and leptin results.
14. Patients must be in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
15. Patients must receive eCOA training at the time they receive the eCOA device.
16. Two DXA scans will be performed as follows: Screening DXA will be performed at either visit 1 or visit 2. The second DXA will be performed during the run-in period and can be performed from day -28 to day 1 prior to dosing of study drug. Two baseline liver volume and liver fat content MRI-PDFF scans will be obtained from day -28 to day 1 prior to dosing. These 2 MRI-PDFF scans must be performed on separate days at least 24 hours

apart and up to a maximum of 28 days apart. Patients may be required to fast at least 5 hours prior to the scans.

17. DNA should be collected at visit 1, but can be collected at any visit after obtaining consent.

Table 22: Schedule of Events: TP1, TP2, and Off-Drug Follow up

Study Period	Double Blind Treatment Period (TP1)												Single Blind Treatment Period (TP2)												EOT/ET[12]	Off-Drug Safety Follow up Period			EOS
	In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Patient Disposition																													
Randomization[1]	X																												
Treatment																													
Administer Study Drug (Mibavademab/Placebo)[2] (IV)	X												X																
Administer Study Drug (Mibavademab/Placebo)[2] (SC)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Concomitant Medications and Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Double Blind Treatment Period (TP1)												Single Blind Treatment Period (TP2)												EOT/ET[12]	Off-Drug Safety Follow up Period		EOS
	In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit			
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Monitoring dose adjustments for antidiabetic and lipid lowering medication [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety[4]																													
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[6]	X	X		X		X	X		X		X		X		X		X		X		X		X		X	X	X	X	X
Physical Examination	X												X												X		X		X
Waist and hip circumference	X												X												X		X		X
Electrocardiogram	X												X																X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Double Blind Treatment Period (TP1)**												**Single Blind Treatment Period (TP2)**												**EOT / ET[12]**	**Off-Drug Safety Follow up Period**			**EOS**
	In-Clinic Outpatient visit	**In-Clinic Outpatient visit or Remote visit**											**In-Clinic Outpatient visit**	**In-Clinic Outpatient visit or Remote visit**											**In-Clinic Outpatient visit**				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Menstrual history, pregnancy status reporting, and Confirmation of contraception	X	X		X		X		X		X		X	X		X		X		X		X		X		X	X	X	X	X
Laboratory Testing[7]																													
Hematology	X	X		X			X		X		X		X	X		X		X	X		X		X		X	X	X	X	X
Blood Chemistry	X	X		X			X		X		X		X	X		X		X	X		X		X		X	X	X	X	X
Pregnancy Test (WOCBP)[8]	X	X		X			X		X		X		X	X		X		X	X		X		X		X	X	X	X	X
Urinalysis	X	X		X			X		X		X		X			X			X		X		X		X	X	X	X	X
Leptin[9]	X						X						X						X						X				X
Efficacy[7]																													

Study Period	Double Blind Treatment Period (TP1)												Single Blind Treatment Period (TP2)												EOT/ET[12]	Off-Drug Safety Follow up Period			EOS
	In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Fasting Triglycerides[9]	X		X		X		X		X		X	X	X		X		X		X		X		X	X	X	X	X	X	X
Lipid Panel[9]	X						X						X						X				X		X	X	X	X	X
Fasting Glucose[9]	X		X		X		X		X		X	X	X		X		X		X		X		X	X	X	X	X	X	X
HbA1c	X				X		X				X		X				X		X				X		X	X	X	X	X
Fructosamine	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X	X
Insulin[9]	X		X		X		X				X		X				X		X				X		X	X	X	X	X
Free Fatty Acids[9]	X		X		X		X				X		X				X		X				X		X	X	X	X	X
NMR Lipid panel LDL-C, HDL-C, total-Cholesterol[9]	X												X												X				X
Urine Creatinine and Albumin	X						X						X						X						X				X

Study Period	**Double Blind Treatment Period (TP1)**												**Single Blind Treatment Period (TP2)**												**EOT / ET[12]**	**Off-Drug Safety Follow up Period**			**EOS**
	In-Clinic Outpatient visit	**In-Clinic Outpatient visit or Remote visit**											**In-Clinic Outpatient visit**	**In-Clinic Outpatient visit or Remote visit**											**In-Clinic Outpatient visit**				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Daily Lipodystrophy Hunger questionnaire	◄ X ►																												
BPI-SF questionnaire	X												X												X				X
SF-36 questionnaire	X												X												X				X
PHQ-8 questionnaire	X												X												X				X
HADS questionnaire	X												X												X				X
Patient Global Impression of Severity-Hunger	X												X												X				X
Patient Global Impression of Severity-Pain	X												X												X				X

Study Period	Double Blind Treatment Period (TP1)												Single Blind Treatment Period (TP2)												EOT/ET[12]	Off-Drug Safety Follow up Period			EOS
	In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Patient Global Impression of Change-Hunger													X												X				X
Patient Global Impression of Change-Pain													X												X				X
Bioimpedance	X												X												X				X
DXA[10]													X												X				
Liver volume (MRI) and liver fat content (MRI-PDFF)[10]													X												X				
PK/Drug Concentration and ADA Samples																													

Study Period	Double Blind Treatment Period (TP1)												Single Blind Treatment Period (TP2)												EOT/ET[12]	Off-Drug Safety Follow up Period			EOS
	In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
[redacted]																													
Biomarkers Procedure/Samples[7]																													
[redacted]																													

Abbreviations: ADA=antidrug antibodies; ANGPTL3=angiopoietin-like protein 3; BPI-SF=brief pain inventory – short form; DNA=deoxyribonucleic acid; DXA=dual-energy X-ray absorptiometry; EOS=end of study; EOT=end of treatment; ET=early termination; HADS=hospital anxiety and depression scale; HbA1c=hemoglobin A1c; HDL-C=high density lipoprotein cholesterol; IV=intravenous; LDL-C=low density lipoprotein cholesterol; MRI=magnetic resonance imaging; NMR=nuclear magnetic resonance; PK=pharmacokinetic; SC=subcutaneous; sLEPR=soluble leptin receptor; WOCBP=women of childbearing potential

10.7.2. Footnotes for the Schedule of Events Table 22: TP1, TP2 and Off-Drug Follow-Up

18. Randomization can occur within 24 hours prior to day 1 study drug administration if necessary.
19. All patients will be monitored for 4 hours following infusion on day 1 and day 85. For patients undergoing apheresis, study drug will be administered after the apheresis procedure.
20. Monitoring by qualified study personnel may be performed as a telephone contact or an in-clinic or inpatient assessment. A telephone contact may be converted to an in-person site visit if in the opinion of qualified study personnel a direct, in-person assessment would aid assessment of safety or clarify concomitant medication use and adjustment. For diabetic patients, all monitoring assessments will include asking about symptoms of hypoglycemia (per local standards), a review of the patient's home glucometer readings (if applicable), and patient education regarding the importance of blood glucose monitoring and how to recognize symptoms of hypoglycemia (per local standards). Diabetic patients should be reminded to call the site if any signs or symptoms of hypoglycemia occur.
21. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
22. Vital signs should be recorded prior to IV study drug infusion, and approximately 120 minutes post-IV infusion (on day 1 and day 85) and prior to SC study drug injection (on day 85).
23. Body weight should be measured after voiding (empty bladder) using a calibrated scale. Patients should empty pockets and remove shoes, belts, outer-layer clothing, or any other heavy wearable prior to being weighed.
24. Study assessments, urine, and blood (safety, efficacy and biomarkers) samples will be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments, urine, and blood samples will be collected immediately before the lipid-apheresis procedure.
25. If there is a positive urine pregnancy test, a confirmatory serum pregnancy test will be performed. Study treatment will not be administered until a negative serum pregnancy test is obtained. If the serum pregnancy test is negative, the patient can continue in the study. A positive serum pregnancy test will result in permanent stopping of study drug administration.
26. Patients must be in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
27. Liver volume (MRI) and liver fat content (MRI-PDFF) and whole body DXA scans may be performed up to14 days prior to visits 20 and 32. Patients may be required to fast at least 5 hours prior to the scans.

28. Collection of blood samples for drug concentration/sLEPR on days 1 and 85 will be pre-infusion and again at the end of infusion (0 to 15 mins after the end of the infusion). On other visits, drug concentration/sLEPR samples will be collected pre-dose.
29. Early termination (ET)/End of treatment (EOT) visit consists of the end of study assessments.

10.7.3. Early Termination Visit

Patients who withdraw from the study will be asked to return to the clinic for 2 visits: an EOT/ET visit and an end of study visit. The EOT/ET visit should take place within 5 days of treatment discontinuation, if possible. A final end of study visit should take place with assessments 17 weeks after the last dose of study drug as described in Table 22.

Patients who have discontinued study drug but who remain in the study will enter the off-drug follow-up period (Table 22) after completing the early termination visit. In the off-drug follow-up period, patients will continue with monthly visits until 17 weeks after last dose of study drug. Each of these monthly visits will consist of safety assessments, including laboratory tests.

Sexually active patients who discontinue the study prematurely should be reminded to maintain highly effective contraceptive measures for 17 weeks after the last dose of study drug.

10.7.4. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. An unscheduled visit may be performed as a remote visit or an outpatient in-clinic visit.

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Approval/eSignature	[redacted] 19-May-2024 12:11:18 GMT+0000
Approval/eSignature	[redacted] 19-May-2024 21:21:40 GMT+0000
Approval/eSignature	[redacted] 20-May-2024 01:34:11 GMT+0000
Approval/eSignature	[redacted] 20-May-2024 14:12:04 GMT+0000

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