REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 2

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF REGN4461, A LEPTIN RECEPTOR AGONIST ANTIBODY, IN PATIENTS WITH GENERALIZED LIPODYSTROPHY

Compound	REGN4461
Protocol Number	R4461-GLD-1875
Clinical Phase	Phase 2
Sponsor	Regeneron Pharmaceuticals, Inc.
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Version / Date	V 2.0 / August 22, 2022

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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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ARH	Autoregressive heterogeneous
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the curve
CI	Confidence interval
CMQ	Company MedDRA queries
CRF	Case report form (electronic or paper)
CV	Cardiovascular
DBTP	Double-blind treatment period
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EOT	End of treatment
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GLD	Generalized lipodystrophy
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HLGT	High level group term
HLT	High level term
HRQoL	health-related quality of life
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IV	Intravenously
ITT	Insulin-tolerance test
IVRS	Interactive voice response system

LSM	Least squares mean
LDL-C	Low-density lipoprotein cholesterol
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model with repeated measures
MMTT	Mixed meal tolerance test
MRI	Magnetic resonance imaging
NAS	Non-alcoholic fatty liver disease activity score
OLTP	Open label treatment period
PCS	Physical component summary
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PDFF	Proton Density Fat Fraction
PedsQL™	The Pediatric Quality of Life Inventory
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PRO	Patient reported outcomes
PT	Preferred term
QW	Every week
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
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
SMT	Safety Monitoring Team
SMQ	Standard MedDRA queries
SOC	System organ class

TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
ULN	Upper limit of normal
WBC	White blood cell
WHO-DD	WHO Drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) Version 2 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 for R4461-GLD-1875 study. The content of this SAP is inclusive of all analyses, specifically the interim, first-step and final analyses.

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 blinded data review, and a final plan will be issued prior to the first database lock.

1.1. Background/Rationale

REGN4461, a leptin receptor (LEPR) agonist, is a fully human monoclonal antibody (mAb) that is being investigated for the treatment of conditions associated with leptin deficiency, including lipodystrophy. Generalized lipodystrophy (GLD) is an ultra-rare condition characterized by near-complete loss of adipose tissue (lipoatrophy). Adipose tissue functions to store energy and signal the status of energy stores by secreting hormones (adipokines) such as leptin, which regulates energy intake, energy expenditure, and reproductive function. Severe lipoatrophy and leptin deficiency in GLD manifest as hyperphagia, insulin resistance, diabetes, hypertriglyceridemia, pancreatitis, infertility, and hepatic steatosis (progressing to non-alcoholic steatohepatitis [NASH] and advanced liver disease).

REGN4461 binds and activates leptin receptors (LEPR) signaling. REGN4461 is not related to endogenous leptin, and therefore should not have elevated risks of anti-drug antibodies cross-reacting with endogenous leptin. Once-weekly administration of REGN4461 improved glycemic control, insulin sensitivity, hypertriglyceridemia, food intake, body weight, hepatic mass, and steatosis in lipodystrophic humanized LEPR mice. In toxicology studies (a non-GLP single- and repeated-dose pilot study and a GLP 13-week toxicology study in monkeys), REGN4461 administration resulted in either reduction in body weight gain or body weight loss. These effects are consistent with a role of leptin in regulation of body weight. No adverse reactions of treatment have been identified to date. A first-in-human (FIH), double-blind, placebo-controlled study of REGN4461 in healthy volunteers (R4461-HV-1794) is completed. [redacted] There were no safety signals identified from the TEAEs observed in the REGN4461-treated groups compared to placebo group in either part of the study.

The primary purpose of this current study is to demonstrate the efficacy, safety, and tolerability of REGN4461 in patients with GLD. 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 of the study are to:

- Estimate the effects of REGN4461 on glycemic parameters in the subset of patients with elevated baseline hemoglobin A1c levels (HbA1c ≥7%)
- Estimate the effects of REGN4461 on fasting triglyceride levels in the subset of patients with elevated baseline fasting triglycerides (TG ≥250 mg/dL)

1.2.2. Secondary Objectives

The secondary objectives are to:

- Estimate the effects of REGN4461 on a composite endpoint of changes in either HbA1c or fasting TG for all patients
- Estimate the effects of 3 dose levels of REGN4461 on glycemic parameters and fasting TG
- Estimate the effects of REGN4461 on insulin sensitivity
- Evaluate the safety and tolerability of REGN4461
- Evaluate the pharmacokinetics (PK) and immunogenicity of REGN4461

1.2.3. Exploratory Objectives

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-GLD-1875 Amendment 3 with the following exceptions:

- In general, nominal p-values will not be provided unless otherwise specified in Section 5.7.
- The FAS analysis set definition has been updated to "The full analysis set (FAS) includes all randomized patients who received any study drug." The change to this definition is the deletion of the criteria "have at least 1 post-baseline assessment", so as to bring the FAS definition into alignment with regulatory guidance.
- The following analysis will not be performed since the non-informative prior will not provide additional information than is already planned for the primary analysis: "In addition, posterior probability that the improvement in each of the primary endpoints is greater than zero will be computed at week 8 separately for patients receiving REGN4461. Non-informative prior will be used for the posterior probability. The posterior probability will also be used to assess the treatment effect of REGN4461".
- For the primary efficacy analysis of Fasting TG, the statistical method of MMRM planned in the protocol will be replaced with a robust regression analysis. The robust regression method will be able to better address the lack of normality in the TG distribution.

1.2.5. Revision History for Statistical Analysis Plan Version 2

This is the second version of Statistical Analysis Plan (SAP). The following changes have been made to the SAP since Version 1.

- Addition of descriptive statistical analyses for OLTP 5, per Protocol R4461-GLD-1875 Amendment 3.
- Section 4.8.1. Adverse Events Variables – the post-treatment period definition has been clarified.
- Section 4.9 and 5.9. Other variables – total sLEPR has been moved from the PK section.
- Section 4.9. Other variables – DXA analysis variables are not limited to the Appendix 10.6.
- Appendix 10.7. Calculation for efficacy variables – calculated total glucose infusion rate formula has been updated to "(M * 20) / (body mass * 6)" in step 2, correcting a typo.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of REGN4461 in patients with GLD who are not receiving recombinant methionyl human leptin (rhLeptin, metreleptin) therapy.

After a screening period of up to 4 weeks, eligible patients will begin the single-blind placebo run-in period. After baseline testing, patients will be centrally randomized via interactive voice response system (IVRS) in a 1:1 ratio to Treatment Arm A or Treatment Arm B and treated double-blind for 24 weeks to receive:

Treatment Arm A:

[redacted]

Treatment Arm B:

[redacted]

[redacted]

Subjects will be stratified based on screening HbA1c (HbA1c ≤8% or HbA1c >8%) to ensure equal representation of patients with very elevated HbA1c in each study arm.

2.2. Sample Size and Power Considerations

The size of the study is determined by feasibility assessments. Due to the limited number of GLD patients not being treated with metreleptin in the world, up to 26 patients will be enrolled for the study, with approximately a 20% dropout rate. The primary objective is estimating the treatment effect of REGN4461 on glycemic and lipids parameters.

Metreleptin demonstrated a 2% absolute drop in HbA1c (standard deviation [SD]=1.5%) and a 50% relative drop in fasting TG (SD=40%) from baseline to month 4 (Myalepta, 2018) (FDA, 2013). As a conservative treatment effect estimation for 8 weeks, the anticipated drop in HbA1c is 1.5%, because HbA1C will not have fully re-equilibrated by week 8; full equilibration would be expected at approximately 12 weeks. The change in fasting TG is expected to be the same at week 8 as at week 16. With 20 patients completing the study (10 patients per study arm,

assuming approximately a 20% dropout rate from 26 patients), the minimal detectable change (MDC) and power for the study are provided in Table 1 as below, for a 2-sided alpha of 0.05 test.

Note: Ultimately, study enrollment was terminated on December 2, 2021, with a total of 16 patients randomized and treated.

Table 1: Minimal Detectable Change and Power for HbA1c, Fasting Glucose, WMG, and Fasting TG Separately (N=20, 10 Treated vs. 10 Placebo, Assuming Approximately 20% Dropout Rate from 26 Patients)

	Number of Treated Patients	Within-Group	Between-Group	Within-Group	Between-Group
		MDC (half of the confidence interval), alpha=0.05		Power for a 1.5% reduction in HbA1c, 60 mg/dL reduction in fasting glucose/MWG, and 50% reduction in fasting TG	
HbA1c*	10	1%	1.4%	80%	56%
Fasting Glucose*	10	53 mg/dL	70 mg/dL	60%	38%
WMG[&]	10	40 mg/dL	53 mg/dL	84%	60%
Fasting TG*	10	28%	37%	93%	75%

*Assuming SD for HbA1c is 1.5%, fasting glucose is 76 mg/dL, and fasting TG is 40% (FDA, 2013).
[&] SD for WMG is 75% of SD for fasting glucose (57 mg/dL).
A total of 16 patients were randomized and treated.

If the glycemic and lipid subsets for the primary analysis have fewer patients with abnormal TGs or fasting glucose values, the table below (Table 2) provides minimal detectable change and power for the subset analysis.

Table 2: Minimal Detectable Change and Power for HbA1c, Fasting Glucose, WMG, and Fasting TG Separately (N=20, 10 Treated vs. 10 Placebo, Assuming Approximately 20% Dropout Rate from 26 Patients)

	Number of Treated Patients in the Subset*	Within-Group	Between-Group	Within-Group	Between-Group
		MDC (half of the confidence interval), alpha=0.05		Power for a 1.5% reduction in HbA1c, 60 mg/dL reduction in fasting glucose/WMG and 50% reduction in fasting TG	
HbA1c[$]	5	1.7%	2.1%	40%	28%
Fasting Glucose[$]	5	88 mg/dL	107 mg/dL	27%	19%
WMG[$]	5	66 mg/dL	80 mg/dL	43%	31%
Fasting TG[$]	9	30%	39%	90%	70%

*Assuming 50% of the patients have elevated baseline HbA1c and 90% of the patients have elevated baseline TG.
[$]Assuming SD for HbA1c is 1.5%, fasting glucose is 76 mg/dL, and fasting TG is 40% (FDA, 2013). SD for WMG is 75% of SD for fasting glucose (57 mg/dL).
A total of 16 patients were randomized and treated.

2.3. Study Plan

The study comprises a 4-week screening period, [redacted]

Patients who are ≥12 years of age, (or lower limit of age approved by Health Authority, EC, and IRB) at the screening visit with a clinical diagnosis of GLD, will undergo screening, including measurement of HbA1c and fasting TG. Eligible patients will then begin the single-blind placebo run-in period within 4-weeks of screening. The [redacted] consists of two study treatment sequence arms, with each sequence containing three treatment periods (see diagram Figure 1 below).

As described in Protocol R4461-GLD-1875 Section 6.1, Study Description and Duration, the following DBTP R4461 IV loading doses and SC weekly doses are defined.

- IV [redacted]
- REGN4461 low-dose: [redacted]
- REGN4461 high-dose: [redacted]

The detailed dosing schedule for each treatment arm sequence (Treatment Arm A and Treatment Arm B) and body weight are provided in the Protocol Section 8.1, Table 2.

[redacted]

Figure 1: Study Flow Diagram

[redacted]

2.3.1. Sub-studies

[redacted]

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 primary efficacy analysis population is the FAS for the subgroup of patients with a baseline HbA1C ≥ 7% (glycemic analysis set) and the subgroup of patients with a baseline TG ≥ 250 mg/dL (triglyceride analysis set). Additional patient populations included for safety are anti-drug (REGN4461) anti-body (ADA), pharmacokinetic (PK), quality of life and [redacted], etc. 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 recorded in the IVRS/IWRS database.

3.1. Efficacy Analysis Set

3.1.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients in the DBTP who received any study drug. Patients in the FAS population will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group). Efficacy endpoints will be analyzed using the FAS.

3.2. Double-blind Safety Analysis Set

The double-blind safety analysis set (SAF) includes all randomized patients who received any double-blind study drug. Patients will be analyzed according to the treatment received. 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 double-blind SAF as randomized.
- For randomized patients receiving both REGN4461 and placebo study treatment in the DBTP1, the treatment group allocation for as-treated analysis will be REGN4461.
- For randomized patients receiving both low-dose REGN4461 and high-dose REGN4461 study treatment in the DBTP2, the treatment group allocation for as-treated analysis will be the most frequently administered REGN4461 dose.

3.3. OLTP Safety Analysis Set

The OLTP safety analysis set for Period 4 (OLTP 4 SAF) will be the randomized patients who received any open-label treatment period 4 study drug.

The OLTP safety analysis set for Period 5 (OLTP 5 SAF) will be the randomized patients who received any open-label treatment period 5 study drug.

The OLTP pooled safety analysis set (OLTP Pooled SAF) will be the randomized patients who received any open-label treatment period 4 study drug.

3.4. 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 post-baseline measurement of mibavademab concentration. Treatment assignments for the DBTP are based on the treatment received (placebo or mibavademab).

3.5. The Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all treated patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing anti-drug antibody

result following the first dose of study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

3.6. Glycemic Analysis Set

The glycemic analysis set includes all patients who are in the FAS and have elevated baseline HbA1c (HbA1c ≥7%). Primary efficacy endpoints for glycemic parameters will be analyzed using the glycemic analysis set. Patients will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group).

3.7. Triglyceride Analysis Set

The triglyceride analysis set includes all patients who are in the FAS and have elevated baseline fasting TG (TG ≥250 mg/dL). Primary efficacy endpoints for triglycerides will be analyzed using the triglyceride analysis set. Patients will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group).

3.8. MRI Analysis Set

The MRI analysis set includes all patients who are in the FAS and eligible for the MRI test (some patients are not eligible for the MRI due to MRI contraindications or some sites do not have the technical capability to perform liver MRI). Patients will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group).

3.9. Clamp Analysis Set

The clamp analysis set includes all patients who are in the FAS and eligible for the clamp test (some patients are at the sites where there is no clamp capability). Patients will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group).

3.10. Clamp Glycemic Analysis Set

The clamp glycemic analysis set includes all patients who are in the clamp analysis set and have elevated baseline HbA1c (HbA1c ≥7%).

3.11. Insulin-Tolerance Test Analysis Set

The insulin-tolerance test analysis test includes all patients who are in the FAS, are not eligible for the clamp test, and are eligible for the qualified insulin-tolerance test (some patients are at the sites without clamp capability, but which have qualified insulin-tolerance test). Patients will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group).

3.12. Insulin-Tolerance Test Glycemic Analysis Set

The insulin-tolerance test glycemic analysis set includes all patients who are in the insulin-tolerance test analysis set and have elevated baseline HbA1c (HbA1c ≥7%). Patients will be analyzed according to the treatment group allocated by randomization (i.e., as-randomized group).

3.13. Quality-of-life Analysis Set

The analyses for quality of life will be performed on all patients in the FAS. Further for the SF-36 and the PedsQL:

- For Short-Form (SF-36) analysis set: patients will be included when a baseline and at least 1 matching post-baseline component summary score (physical or mental) are available.
- For Pediatric Quality of Life Inventory (PedsQL) analysis set: patients will be included when a baseline and at least one post-baseline total scale score are available.

3.14. Clinical Outcome Assessment

The analyses for Clinical Outcome Assessments will be performed on all patients in the FAS. Further for each scale:

- For the hunger and eating behaviors questionnaire, patients will be included when a baseline and at least one-week post-baseline scores are available.
- For the sensation of Body Temperature PRO, patients will be included when a baseline and at least one post-baseline score is available.

3.15. [redacted]

[redacted]

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 (i.e. baseline definition). For patients randomized and not treated in R4461-GLD-1875, the baseline value is defined as the last available measurement prior to the date of randomization.

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: ≥12 to <18, ≥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)
- Randomization strata as reported in the IVRS
  - HbA1c (≤8% or >8%)
- Randomization strata as reported in the clinical database.
  - HbA1c (≤8% or >8%)

Baseline Disease Characteristics

- Fasting glucose
- HbA1C both quantitative variable and qualitative variable defined as: <7%, ≥7%
- WMG
- Glucose AUC_{0-4} during MMTT
- Glucose infusion rate per Kg body mass
- Glucose infusion rate normalized for fat free mass
- Glucose clearance rate (k_{ITT}) during ITT
- Fasting TG both quantitative variable and qualitative variable defined as: <250 mg/dL and ≥250 mg/dL
- Low density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (HDL-C)
- Total Cholesterol (TC)
- NMR Lipoprotein analysis (Note: List of data fields reported in the Lipoprotein NMR are listed in Appendix 10.5.)
- Apo-B
- Leptin

4.2. Medical History

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

GLD disease history will be assessed by the following variables:

- Time from diagnosis to study treatment randomization (years)

- GLD type (genetic or acquired, per CRF)
- Congenital Generalized Lipodystrophy Gene type (genetic)
- Method of diagnosis of GLD (genetically, clinical diagnosis, imaging or other)
- Frequency of hospitalization of acute pancreatitis in the last three months, 6 months, and 12 months.
- Metreleptin taken less than 30 days prior to informed consent (Yes/No)
  - If no, select >1month, >3months, >1year

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 (i.e. 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 OLTP).

- 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 open-label study treatment periods. Specifically:
  - Start date of the concomitant medication is on or after the first study treatment administration in respective study treatment periods [redacted]; **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 [redacted].

The concomitant medication treatment emergent periods are defined as:

- For concomitant medications in the DBTP, the treatment emergent period is defined from the first day of double-blind study treatment administration to the last day of double blind study treatment + 112 days (for patients who do not continue into the

OLTP) or to the day before the first open-label study treatment administration (for patients who enter the OLTP).

- For concomitant medications in the OLTP, the treatment emergent period is defined from the first day of open-label study treatment administration to the last day of open-label study treatment administration + 112 days.

Note: In the case the start date 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 8.7.1 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 who have 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 23 weeks of study treatment administration and week 24 visit performed.
- The total number of patients ongoing in DBTP (interim analysis).
- 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 OLTP and complete the last study follow-up visit (i.e. 16-week follow-up period).

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

- The total number of patients receiving study treatment in open-label treatment period 4.
- The total number of patients ongoing in OLTP 4 (applicable for interim analysis)
- The total number of patients who completed the OLTP 4, [redacted]
- The number of patients who received [redacted] of treatment.
- The total number of patients who prematurely discontinued study treatment during the OLTP 4, and the reasons for discontinuation collected on the study completion eCRF.
- The total number of patients receiving study treatment in open-label treatment period 5.
- The total number of patients ongoing in OLTP 5.
- The total number of patients who completed the OLTP 5, defined as at least OLTP 5 [redacted]
- The total number of patients who prematurely discontinued study treatment during the OLTP 5, and the reasons for discontinuation collected on the study completion eCRF.
- The total number of patients from OLTP 5 who complete the last study follow-up visit (i.e. 16-week follow-up period).

The following patient populations for analyses are defined below:

- Efficacy population: Full analysis set (FAS)
- Safety analysis set (Double-blind SAF, OLTP 4 SAF, OLTP 5 SAF, Pooled OLTP SAF)
- Glycemic analysis set
- Triglyceride analysis set
- MRI analysis set
- Clamp analysis set
- Insulin–Tolerance Test 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 DBTP1 are listed below with associated definitions:

- Patient duration of DBTP1 SC study treatment exposure in weeks defined as: (last double-blind study treatment administration date in DBTP1 – first double-blind SC study treatment administration date in DBTP1 + 7)/7. Values will be rounded to one decimal place.
- The total number of DBTP1 SC study treatment administrations by patient.
- The following categories will be used for DBTP1 SC treatment exposure at 1 week intervals: ≥1 day and <1 week, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks.
- The total number of DBTP1 IV study treatment administrations by patient.

Study treatment exposure variables for study drug administered during the DBTP2 are listed below with associated definitions:

- Patient duration of DBTP2 SC study treatment exposure in weeks defined as: (last double-blind study treatment administration date in DBTP2 – first double-blind SC study treatment administration date in DBTP2 + 7)/7. Values will be rounded to one decimal place.
- The total number of DBTP2 SC study treatment administrations by patient.
- The following categories will be used for DBTP2 SC treatment exposure at 1 week intervals: ≥1 day and <1 week, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks and <8 weeks and ≥8 weeks.
- The total number of DBTP2 IV study treatment administrations by patient.

Study treatment exposure variables for study drug administered during the DBTP3 are listed below with associated definitions:

- Patient duration of DBTP3 SC study treatment exposure in weeks defined as: (last double-blind study treatment administration date in DBTP3 – first double-blind study treatment administration date in DBTP3 + 7)/7. Values will be rounded to one decimal place.
- The total number of DBTP3 SC study treatment administrations by patient.
- The following categories will be used for DBTP3 SC treatment exposure at 1week intervals: ≥1 day and <1 week, ≥1 week and <2 weeks, ≥2 weeks and <3 weeks, ≥3

weeks and <4 weeks, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks and <8 weeks and ≥8 weeks.

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

- Patient duration of all DBTP SC study treatment exposure in weeks defined as: (last double-blind 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 administration by patient.
- The following categories will be used for DBTP 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, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks and <8 weeks, ≥8 weeks and <9, ≥9 weeks and <10, ≥10weeks and <11, ≥11 weeks and <12 weeks, ≥12 weeks and <13 weeks, ≥13 weeks and <14 weeks, ≥14 weeks and <15 weeks, ≥15 weeks and <16 weeks, ≥16 weeks and <17 weeks, ≥17weeks and <18 weeks, ≥18 weeks and <19 weeks, ≥19 weeks and <20 weeks, ≥20weeks and <21 weeks, ≥21 weeks and <22 weeks, ≥22 weeks and <23 weeks, ≥23 weeks and <24 weeks and ≥24 weeks.

REGN4461 treatment exposure variables for study drug administered during the OLTP 4 are listed below with associated definitions:

- Patient duration of OLTP 4 SC study treatment exposure in weeks defined as: (the last OLTP 4 REGN4461 treatment administration date – first OLTP 4 REGN4461 treatment administration date + 7)/7. Values will be rounded to one decimal place.
- The total number of OLTP 4 REGN4461 treatment SC injections by patient.
- The following categories will be used for OLTP 4 REGN4461 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, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks and <8 weeks, ≥8 weeks and <9, ≥9 weeks and <10, ≥10weeks and <11, ≥11 weeks and <12 weeks, ≥12 weeks and <13 weeks, ≥13 weeks and <14 weeks, ≥14 weeks and <15 weeks, ≥15 weeks and <16 weeks, ≥16 weeks and <17 weeks, ≥17weeks and <18 weeks, ≥18 weeks and <19 weeks, ≥19 weeks and <20 weeks, ≥20weeks and <21 weeks, ≥21 weeks and <22 weeks, ≥22 weeks and <23 weeks, ≥23 weeks and <24 weeks, ≥24 weeks and <25 weeks, ≥25 weeks and <26, ≥26 weeks and <27, ≥27weeks and <28 weeks, ≥28 weeks.

REGN4461 treatment exposure variables for study drug administered during the OLTP 5 are listed below with associated definitions:

- Patient duration of OLTP 5 SC study treatment exposure in weeks defined as: (last OLTP 5 REGN4461 treatment administration date – first OLTP 5 REGN4461 treatment administration date + 7)/7. Values will be rounded to one decimal place.
- The total number of OLTP 5 REGN4461 treatment SC injections by patient.

- The following categories will be used for OLTP 5 REGN461 SC treatment exposure at 1 week intervals, e.g. ≥1 day and <1 weeks, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥51weeks and <52 weeks, ≥52 weeks.

Cumulative OLTP REGN4461 exposure variables combining the 2 open label treatment periods (ie. OLTP 4 + OLTP 5) regardless of REGN4461 dose are listed below:

- Cumulative OLTP patient duration of SC REGN4461 exposure in weeks defined as: Treatment arm A: OLTP 4 exposure + OLTP 5 treatment exposure. Treatment arm B: OLTP 4 + OLTP 5 treatment exposure
- Cumulative total number of OLTP REGN4461 SC treatment administration by patient defined as: Treatment arm A: OLTP 4 + OLTP 5 treatment injections. Treatment arm B: OLTP 4 + OLTP 5 treatment injections.
- The following categories will be used for cumulative OLTP patient REGN4461 treatment exposure at 4 week intervals, e.g. ≥1 day and <1 weeks, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks and <8 weeks … ≥79 weeks and <80 weeks, ≥80.

Cumulative REGN4461 total trial exposure variables combining DBTP and OLTP (regardless of treatment dose) are listed below:

- Cumulative patient duration of SC REGN4461 study exposure in weeks defined as: Treatment arm A: DBTP2 treatment exposure + DBTP3 treatment exposure + OLTP 4 exposure + OLTP 5 treatment exposure. Treatment arm B: DBTP1 treatment exposure + DBTP2 treatment exposure + DBTP3 treatment exposure + OLTP 4 treatment exposure + OLTP 5 treatment exposure.
- Cumulative total number in study of REGN4461 SC treatment administration by patient defined as: Treatment arm A: [redacted]
- The following categories will be used for cumulative patient REGN4461 treatment exposure in the study at 4 week intervals, e.g. ≥1 day and <1 weeks, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, ≥4 weeks and <5 weeks, ≥5 weeks and <6, ≥6 weeks and <7, ≥7weeks and <8 weeks… ≥103 weeks and <104 weeks, ≥104

With respect to patient treatment administration compliance in the DBTP, the study treatment is administered during the investigative site visits or by a visiting nurse. Therefore, study compliance will be accessed by frequency for SC study drug administration for respective treatment periods, specifically:

- The mean frequency for SC study treatment administration will be defined for each patient as the average number of days between 2 consecutive study drug

administration: (last double-blind dose date – first double-blind dose date) / (number of injections in DBTP), for patients receiving at least 2 injections.

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 Variable

Efficacy will be assessed through the following parameters: HbA1c, fasting glucose, WMG, fasting TG, glucose $AUC_{0\text{-}4h}$ from MMTT, glucose infusion rate per kg body mass from clamp, and glucose clearance rate (k_{ITT}) from Insulin-tolerance Test, liver volume as measured by MRI, and liver fat content as measured by MRI-PDFF. All parameters will be collected over the course of the study and sent for centralized evaluation, including scheduled and unscheduled blood draws.

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

All efficacy measurements will be assigned to efficacy analysis windows defined in Appendix 10.2 of this SAP, with the intent to provide an assessment for 24 weeks of DBTP timepoints, 24 weeks of OLTP 4 timepoint, and 52 weeks of OLTP 5 timepoints. For all time points post-baseline, the value used for the analyses at a given time point (e.g. at week 8) is the value obtained within the corresponding efficacy analysis window. Unless otherwise specified, the baseline value is defined as the last available measurement prior to the date of the first double-blind study treatment administration (applicable to measurement derivations during both DBTP and OLTP). For patients randomized and not treated, the baseline value is defined as the last available value prior to the date of randomization.

4.7.1. Primary Efficacy Variable (s)

The primary endpoints of the study are:

- Change in HbA1C from baseline to week 8.
- Change in fasting glucose from baseline to week 8.
- Change in weighted mean glucose (WMG) from baseline to week 8. Note: Calculation for WMG is in Appendix 10.7.
- Percent change in fasting TG from baseline to week 8. Note: For Fasting TG, baseline is defined as the average of the last two measurements prior to first study administration. Fasting TG at week 8 is defined as the average of raw scores at week 7 and week 8.

4.7.2. Secondary Efficacy Variable(s)

The secondary endpoints of the study are:

- Change in HbA1C from baseline to [redacted]
- Change in fasting glucose from baseline to [redacted]
- Change in weighted mean glucose (WMG) from baseline to [redacted]
- Percent change in fasting TG from baseline to [redacted]. Note: For Fasting TG, baseline is defined as the average of the last two measurements prior to first study administration. Fasting TG at week 8 is defined as the average of raw scores at week 7 and week 8.
- Change from baseline in glucose AUC_{0-4} during an MMTT at weeks 8, 16, and 24. Note: Calculation for glucose AUC_{0-4} is in Appendix 10.7.
- Change from baseline in glucose infusion rate per kg body mass during hyperinsulinemia-euglycemic clamp at weeks 8 and 52. Note: Calculation for glucose infusion rate is in Appendix 10.7.
- Change from baseline in glucose clearance rate (k_{ITT}) during Insulin-tolerance Test at weeks 8 and 52. Note: Calculation for glucose infusion rate is in Appendix 10.7.
- Change from baseline to week 8 in composite endpoint comprising absolute change in either HbA1c or percent change in fasting TG. See composite endpoint details in the Protocol R4461-GLD-1875 section 11.4.3.2. Note: Fasting TG is defined as the average of the raw scores at [redacted] for each patient.

4.8. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, physical examination, tanner stages 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 day before the first dose of double-blind study treatment administration.
- The double-blind treatment-emergent adverse event (TEAE) period is defined from the day 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 the OLTP 4 (i.e. patients who prematurely discontinue study treatment), or up to the day before the first dose of OLTP 4 study treatment administration for those patients proceeding into the OLTP 4.

- The OLTP 4 treatment-emergent adverse event (TEAE) period is defined from the day of the first OLTP 4 study treatment administration to the day of the last OLTP 4 study treatment administration + 112 days (16 weeks) for those patients not proceeding into the OLTP 5 (i.e., patients who prematurely discontinue study treatment), or up to the day before the first dose of OLTP 5 study treatment administration for those patients proceeding into the OLTP 5.
- The OLTP 5 treatment-emergent adverse event (TEAE) period is defined from the day of the first OLTP 5 study treatment administration to the day of the last OLTP 5 study treatment administration + 112 days (16 weeks).
- Adverse events reported after the end of the respective TEAE periods will be provided in a patient listing.

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 after the end of the respective TEAE periods.

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)
- Hyperglycemia requiring treatment: this is defined as: (eCRF, lab, concomitant medication)

- Development of new or worsening of autoimmune disease (eCRF)
- Hypersensitivity reactions (CMQ, eCRF [moderate and severe only])

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
- Infusion reaction collected 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 using the 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. 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:

- Metabolism: total protein, albumin, creatine phosphokinase
- Electrolytes: sodium, potassium, chloride, calcium, bicarbonate
- Renal function: creatinine, blood urea nitrogen (BUN), uric acid

- Liver function: Alanine aminotransferase (ALT), aspartate aminotransferases (AST), alkaline phosphatase (ALP), total bilirubin, LDH

Non-Efficacy Lipid Panel

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

Urinalysis

Urinalysis will include the following parameters: color, clarity, pH, specific gravity, ketones, protein, glucose, blood, bilirubin, leukocyte esterase, nitrite, WBC, RBC, hyaline and other casts, bacteria, epithelial cells, crystals, and yeast.

Other

Sex hormones (luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone).

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 pressure (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. 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 Appendix10.9.The ventricular rate, heart rate (bpm), PR or PQ, QRS, RR, QTcF, and QT intervals will be recorded. Electrocardiogram assessments will be described as normal or abnormal. 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. Tanner stages

Tanner stage assessments will be performed at specified time points according to Appendix 10.9. Tanner stages (1, 2, 3, 4, 5) will be recorded based on sex.

4.8.6. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits (See Appendix 10.9 for schedule of event). The result is an outcome of normal, abnormal, and if abnormal then clinically significant (Yes/No, not examined).

4.9. Other Variables

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

- Change from baseline in liver volume as measured by MRI at [redacted] (only at sites with requisite capability)
- Change from baseline in hepatic fat content by MRI-PDFF at [redacted] (only at sites with requisite capability)
- Change from baseline in liver stiffness as assessed by VCTE at [redacted] (only at sites with VCTE capability).
- [redacted]
- Change from baseline in body composition (including absolute and percent lean mass and fat mass) using DXA at [redacted] (only at sites with whole body DXA capability). DXA analysis will occur on variables included but not limited to those listed in SAP Appendix 10.6.
- Change from baseline in total sLEPR at [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 10.9.

4.12. Quality of Life

- Change over time in patient-reported outcomes measuring quality of life (S F-36; PedsQL^{TM}), impacts on hunger and eating behaviors, and impacts on sensation of body temperature

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 will be completed by patients ages 18 years of age and older. The SF-36 assesses physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, 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 8, 16 and 24.

The Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales is a measure assessing HRQoL in children and adolescents. The PedsQL™ will be used to measure HRQoL in patients ages 12 to 17. The PedsQL™ is a 23-item measure that assesses physical functioning, emotional functioning, social functioning, and school/work/studies functioning. The instructions

for PedsQL™ ask how much of a problem each item has been over the past 7 days on a 5-point response scale, ranging from never a problem (0) to almost always a problem (4). The measure will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form). The items for each of the teen and child forms for patients are essentially identical, differing primarily in the use of developmentally appropriate language. Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate better HRQoL. The total scale score is computed as the sum of all the items over the number of items answered on individual scales.

The PedsQL endpoint include change from baseline in total scale score at weeks 8, 16 and 24.

4.13. Clinical Outcomes Assessment

Hunger and Eating Behaviors Questionnaire

The hunger and eating behaviors questionnaire is a novel daily PRO that measures hunger related to lipodystrophy. The PRO contains 4 daily 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 consists of 5 categories. The hunger and eating behaviors questionnaire include the below endpoints summarized at the weekly level for each patient.

For each item, a variable will be created for each response category representing the number of days in a week that a patient reports a response in that category and an additional variable will created for the number of days in a week with missing data.

Percentage of days in a week out of the number of non-missing days that a patient reports the following categories for each item:

- Highest level of hunger: “Quite hungry” or “Extremely hungry”
- Lowest level of hunger: “Not hungry at all” or “A little hungry”
- How much time felt hungry: “None of the time” or “A little of the time”
- Frequency of fullness after eating meals or snacks: “Most of the time” or “Every time”

In addition for each item of the hunger and eating behaviors questionnaire, weekly averages out of the number of non-missing will be calculated and change from baseline will be summarized at

each post-baseline week. Values will be assigned to each categorical response 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

Sensation of Body Temperature

The Sensation of Body Temperature PRO is a de novo PRO that measures aspects related to body temperature sensation, cold and hot. The PRO contains 2 items, each with 5 categories. The Sensation of Body Temperature PRO endpoints for each item consist of the number and percentage of responses for each category at baseline and weeks 8, 16 and 24 as well as categorical shift responses from baseline to week 8, 16, and 24.

PGI-S Hunger endpoints consists of the number and percentage of responses for each category at baseline and weeks 8, 16 and 24 as well as categorical shift responses from baseline to week 8, 16, and 24.

PGI-C Hunger endpoints consists of the number and percentage of responses for each category at weeks 8, 16 and 24.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, SD, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized three times, specifically by study treatment sequence in the DBTP, by double-blind treatment sequence and all patients in OLTP 4, and by all patients in OLTP 5, unless otherwise noted. Double-blind treatment period summaries will be presented containing all patients in the double-blind safety analysis set, and respective open-label treatment period summaries will be presented with patients from their respective open-label safety analysis set.

Definitions

For the analysis of safety data, the following definitions will be used to summarize data:

- Study treatment sequence A: Defined as patients receiving placebo followed by low-dose, followed by high-dose (Periods 1, 2 and 3 respectively)
- Study treatment sequence B: Defined as patients receiving low-dose, followed by high-dose followed by high-dose (Periods 1, 2 and 3 respectively)
- Study treatment dose groups: Defined as patients receiving placebo, low-dose, high-dose (all high dose periods, including study treatment sequence B Period 3), regardless of study treatment sequence.

5.2. Medical History

Medical history will be descriptively summarized by study treatment sequence in the DBTP for patients in the double-blind safety analysis set. All reported patient's medical history will be presented by PT, primary SOC and HLT. The tables will be presented by SOC sorted alphabetically and decreasing patient frequency of HLT based on the double-blind treatment incidence in the study.

Patient disease characteristics as described in section 4.2 will be summarized in the double-blind safety analysis set.

5.3. Prior and Concomitant Medications

All prior medications, dictionary coded by WHO-DD, will be descriptively summarized by study treatment sequence in the DBTP for patients in the double-blind safety analysis set. 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 safety analysis set, all concomitant medications during the DBTP, dictionary coded by WHO-DD, will be descriptively summarized by study treatment sequence in the DBTP for patients in the double-blind safety analysis set. 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 OLTP 4, concomitant medications will be dictionary coded by WHO-DD and will be descriptively summarized as described for the DBTP. For patient in the OLTP 4 safety analysis set, medications will be summarized by double-blind treatment sequence and all patients receiving open-label study treatment.

For the OLTP 5, concomitant medications will be dictionary coded by WHO-DD and will be descriptively summarized in the OLTP 5 safety analysis set, for all patients receiving open-label study treatment.

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the safety analysis set for the DBTP and respective OLTP. 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 three times, specifically by study treatment sequence in the DBTP, in OLTP 4 by double-blind treatment sequence and all patients receiving open-label study treatment, and in OLTP 5 for all patients, 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

Study treatment exposure will be summarized three times, specifically by study treatment sequence for period 1 and again by study treatment sequence for the whole DBTP, study treatment sequence by study treatment dose groups and combined doses (regardless of study treatment sequence) in the DBTP, in OLTP 4 by double-blind treatment sequence and all patients, and in OLTP 5 by all patients, unless otherwise noted. Double-blind treatment period safety summaries will be presented containing all patients in the double-blind safety analysis set, and open-label treatment period safety summaries will be presented with patients from the respective open-label safety analysis set.

5.6.1. Exposure to Investigational Product

Study treatment exposure in the respective treatment periods and for the overall DBTP will be descriptively summarized for SC treatment duration and total number of SC study drug administrations as described in Section 4.6. Treatment duration and total number of study drug administration will be summarized using the number of patients with data, mean, SD, etc.

Study treatment frequency in DBTP1 and DBTP2 will be descriptively summarized for IV treatment study drug administrations, specifically the number of infusions per patient.

REGN4461 dosing exposure will be summarized cumulatively for OLTP, combining OLTP 4 and OLTP 5 for all patients.

Additionally, REGN4461 dosing exposure will be summarized cumulatively across the study, combining DBTP and OLTP for patients who received REGN4461 in the DBTP regardless of dose.

5.6.2. Study Treatment Compliance

Descriptive statistics of the dosing intervals for SC study drug administration will be summarized. Further, study treatment infusion interruptions and incomplete infusions with reason will be provided in a patient listing for those patients with incomplete infusions.

Important protocol deviations will be summarized for the DBTP. 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

Efficacy results will be summarized three times, specifically by study treatment sequence and visit in the DBTP, by study treatment dose groups and combined doses (regardless of study treatment sequence) in the DBTP, in OLTP 4 by double-blind treatment sequence and all patients, and in OLTP 5 by all patients, unless otherwise noted. Double-blind treatment period efficacy summaries will be presented containing all patients in the double-blind FAS analysis set, open-label treatment period efficacy summaries will be presented with patients from respective open-label safety analysis set.

Note: Caution should be used when interpreting the results of the summary by study treatment dose groups and combined doses (regardless of study treatment sequence) in the DBTP. In this analysis the carry over effect from period to period is ignored since a washout period was not designed into this study between active study treatment periods.

Definitions

For the analysis of efficacy data, the following definitions will be used to summarize data:

- Study treatment sequence A: Defined as patients receiving placebo followed by low-dose, followed by high-dose (Periods 1, 2 and 3 respectively)
- Study treatment sequence B: Defined as patients receiving low-dose, followed by high-dose followed by high-dose (Periods 1, 2 and 3 respectively)
- Study treatment dose groups: Defined as patients receiving placebo, low-dose, high-dose (all high dose periods, including study treatment sequence B Period 3), regardless of study treatment sequence.

All efficacy endpoints will be analyzed using lab values in conventional units.

Comparisons between study treatment groups and within active treatment group comparisons to baseline in the DBTP will be provided with nominal p-values as appropriate. There will be no statistical hypothesis testing, so multiplicity adjustments do not apply.

5.7.1. Analysis of Primary Efficacy Variables

5.7.1.1. Analysis of the Primary Endpoints: Change in Fasting Glucose and HbA1C from Baseline

For primary glycemic endpoints, change from baseline to week 8 in fasting glucose and HbA1c, will be analyzed in the FAS population for the subgroup of patients with baseline HbA1C≥7% (Glycemic Analysis Set) using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 4 to week 8 efficacy analysis windows for HbA1C and within [redacted]fficacy analysis windows for fasting glucose will be used and missing data are accounted for by the MMRM model. Each model will include the fixed categorical effects of treatment sequence group (group A versus group B), time point

[redacted], treatment-by-time point interaction, baseline value, and baseline by visit interaction. Contrast and estimate statements will be used to assess the treatment effects (LS means with confidence intervals) and R4461 mean difference from placebo with nominal p-value. An unstructured covariance structure will be used (if that does not converge, then structured covariance structures such as autoregressive heterogeneous [ARH] will be assessed). Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

To support interpretation of the fasting glucose and HbA1C results at week 8, descriptive summaries will be provided at each visit in the DBTP1(collected up to the day of the last study treatment administration + 14 days). Mean changes (±SE) will be plotted over time by the treatment sequence group. A spaghetti plot will be provided for individual patient data over time by the treatment sequence group.

5.7.1.2. Analysis of the Primary Endpoint: Change in WMG from Baseline

For the DBTP1 primary comparison of the R4461 group to the placebo group, the change from baseline in WMG at week 8 will be analyzed in the FAS population for the subgroup of patients with baseline HbA1C≥7%. The analysis method is an analysis of covariance (ANCOVA) to compare study treatment group differences (R4461 versus Placebo). This model will include the fixed categorical effects of study treatment sequence (treatment sequence A versus treatment sequence B), and continuous fixed covariate baseline value. Missing data will be imputed using multiple imputation based on other observed measurements, assuming Missing At Random. Missing WMG values will be imputed 100 times to generate 100 complete data sets. The results from the 100 analyses using ANCOVA model will be combined using Rubin's formulae. Summary statistics including LS means change from baseline, standard error (SE), and corresponding 95% confidence interval will be provided for each treatment group. Mean difference between treatments with associated 95% CI and nominal p-value will also be provided.

To support interpretation of the WMG modelled results at week 8, a descriptive summary of raw data will be provided at week 8 (collected up to the day of the last study treatment administration + 14 days).

5.7.1.3. Analysis of the Primary Endpoint: Percent Change in TG from Baseline

For the DBTP1 primary comparison of the R4461 group to the placebo group, the percent change from baseline in fasting TG at week 8 will be analyzed in the FAS population for the subgroup of patients with baseline TG ≥250 mg/dL (Triglyceride Analysis Set). The analysis method is a robust regression model (Mehrotra 2012) to compare study treatment group differences (R4461 versus Placebo), with the endpoint as the response variable using M-estimation (using SAS ROBUSTREG procedure). A natural log transformation will be applied to the TG value prior to analysis, aiming to provide a relatively normal data distribution. This model will include the fixed categorical effects of study treatment sequence (treatment sequence A versus treatment sequence B), and continuous fixed covariate of log transformed baseline value. Missing data will be imputed using multiple imputation based on other observed measurements, assuming Missing At Random. Data will be log-transformed before imputation process and then back transformed

to create the imputed data sets using the TRANSFORM statement of SAS MI procedure. Missing triglyceride values will be imputed 100 times to generate 100 complete data sets. The results from the 100 analyses using ROBUSTREG model will be combined using Rubin's formulae. Summary statistics including LS means percent change from baseline, standard error (SE), corresponding 95% confidence interval will be provided for each treatment group. Mean difference between treatment groups with associated 95% CI and nominal p-value will also be provided.

To support interpretation of the fasting TG results at week 8, descriptive summaries will be provided at each visit in the DBTP1(collected up to the day of the last study treatment administration + 14 days). Median changes (Q1, Q3) will be plotted over time by the treatment sequence group. A spaghetti plot will be provided for individual patient data over time by the treatment sequence group.

5.7.1.4. Analysis of Primary Efficacy Endpoints: Subgroup Analyses

The following subgroup of interest will be evaluated. Given the small number of patients in at least one subgroup level, an interaction term of treatment by subgroup in period 1 will not be used. The patient subgroup of interest will be analyzed as described above for each primary efficacy endpoint.

- Objective evidence of low total body fat mass (TOT_PFAT) as demonstrated by DXA, or of low leptin levels as defined below, assessed during the baseline assessment:

  Less than 20% total body fat by DXA (females), or less than 14% total body fat. (males)
  OR
  Leptin levels ≤8.0 ng/ml.

5.7.1.5. Supplemental Analyses of Primary Efficacy Endpoints

Change from week 8 to week 16 for patients in Treatment Arm A will be provided to estimate the treatment effect of the low dose. If the patients do not have a significant reduction in HbA1c or TG from baseline to week 8, defined as change in HbA1c (absolute value change is less than -0.4%, change in TG [percent change] is less than -20%), then their data from week 8 to week 16, after they have switched to the low dose of REGN4461, will be pooled with data from baseline to week 8 for patients in Treatment Arm B, to evaluate the treatment effect of low dose on the primary efficacy endpoints. Similarly, if there is not a significant reduction from baseline to week 8 for patients in Treatment Arm A, data from patients in Treatment Arm A (change from week 16 to week 24) will be pooled together with data from patients in Treatment Arm B (change from week 8 to week 16) to estimate the treatment effect of increasing the dose from a low-dose regime to a high-dose regime. These supplemental efficacy endpoints will be analyzed as described above for each of the primary efficacy measures (with the single exception, nominal p-values will not be provided).

5.7.2. Analysis of Secondary Efficacy Variables

The seven secondary efficacy endpoints will be descriptively summarized at baseline and each post baseline visit (collected up to the day of the last study treatment administration + 14 days). Efficacy endpoint data will be summarized by at least patient number, mean, median, 95% CI, SD, min and max. These tables will be provided twice, once for patients in the FAS population and again for the subgroup of patients as follows:

- Patient subgroup HbA1c ≥ 7%: HbA1C (Periods 2 and 3 only), WMG (Periods 2 and 3 only), fasting glucose (Periods 2 and 3 only), glucose infusion rate (insulin sensitivity-clamp), glucose clearance rate (K_{ITT} from insulin sensitivity-ITT, glucose AUC0-4 during MMTT
- Patient subgroup TG ≥ 250mg/dL: fasting TG (Periods 2 and 3 only)

Analysis of Primary Efficacy Measures at Week 16 and Week 24

For the primary efficacy measures (HbA1C, fasting glucose, WMG, fasting TG) at week 16 and 24, these secondary efficacy endpoints will be analyzed for within–patient changes to baseline. The method of analysis is as described above in section 5.7.1 (with the single exception, nominal p-values will not be provided).

Supplemental Analysis of MMTT

The secondary efficacy measure MMTT will also be analyzed as described above in SAP Section 5.7.1.5 for the HbA1C measure.

Efficacy Composite Endpoint HbA1C and TG

For this composite endpoint, the method of analyses is a mixed-effect model with repeated measures (MMRM) approach at week 8 in the FAS population. The analyses details will include the fixed categorical effects of treatment sequence group (group A versus group B), time point (week 8), treatment-by-time point interaction. Contrast and estimate statements will be used to assess the treatment effects (LS means with 95% confidence intervals) and R4461 mean difference from placebo, with 95% CI.

5.8. Analysis of Safety Data

Safety results will be summarized four times, specifically by study treatment sequence within each cumulative period (specifically, period 1, period 1+2, and period 1 + 2 + 3) in the DBTP, by study treatment dose groups and combined doses (regardless of study treatment sequence) in the DBTP, and in the OLTP 4 by double-blind treatment sequence and all patients receiving open-label study treatment, and in OLTP 5 for all patients, unless otherwise noted. Double-blind treatment period safety summaries will be presented containing all patients in the double-blind safety analysis set, open-label treatment period safety summaries will be presented with patients from respective open-label safety analysis set. No formal inferential testing will be performed for the DBTP or OLTP. Summaries will be descriptive in nature.

Note: Caution should be used when interpreting the results of the summary by study treatment dose groups and combined doses (regardless of study treatment sequence) in the DBTP. In this

analysis the carry over effect from period to period is ignored since a washout period was not designed into this study between active study treatment periods.

Definitions

For the analysis of safety data, the following definitions will be used to summarize data:

- Study treatment sequence A: Defined as patients receiving placebo followed by low-dose, followed by high-dose (Periods 1, 2 and 3 respectively)
- Study treatment sequence B: Defined as patients receiving low-dose, followed by high-dose followed by high-dose (Periods 1, 2 and 3 respectively)
- Study treatment dose groups: Defined as patients receiving placebo, low-dose, high-dose (all high dose periods, including study treatment sequence B Period 3), regardless of study treatment sequence.

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 (i.e., exposed but not randomized) will be listed separately.
- PCSV values 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 periods, 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 periods.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to Global Analysis Windows defined in Appendix 10.2 in order 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 periods (i.e. blinded treatment period 1, blinded treatment period 1 + 2, blinded treatment period 1 +2 + 3) by DBTP study treatment sequence, by study treatment dose groups and combined doses (regardless of study treatment sequence) in the DBTP, in OLTP 4 by double-blind treatment sequence and all patients, and in OLTP 5 by all patients, and OLTP combined (OLTP 4 + OLTP 5) for all patients, unless otherwise noted. 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, HLGT, HLT, and PT will be provided for all TEAEs, serious TEAEs, and TEAE leading to permanent treatment discontinuation. Multiple occurrences of the same event in the same patient will be counted only once in a table. 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.

AE incidence tables will present data by SOC sorted alphabetically and PT sorted by decreasing frequency 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;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT
- 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 relationship (related/not related) to REGN4461
- All TEAEs by maximum severity (i.e., mild, moderate, or severe)

Analysis of all treatment emergent serious adverse event(s)

- All Serious TEAEs by primary SOC, HLGT, HLT, and PT
- All Serious TEAEs by primary SOC and PT

- All Serious TEAEs relationship (related/not related) to REGN4461

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

- All TEAEs leading to permanent treatment discontinuation, by primary SOC, HLGT, HLT, and PT
- 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 post-treatment) 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 infusion reactions and injection site reactions will be summarized by patient frequency (%) as defined in section 4.8.1.3. TEAE's will be presented by SOC and PT.

The following summaries will also be presented for infusion reactions TEAEs:

- Intensity of the event (mild, moderate, or severe)
- Number of infusion reactions in the DBTP per patient

The following summaries will also be presented for injection site reactions TEAEs

- Intensity of the event (mild, moderate, or severe)
- Summary by preferred ISR term

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 periods. 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 periods 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.

Drug-induced liver injury

For respective treatment period, an evaluation of drug-induced serious hepatotoxicity (eDISH) with the graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented using post-baseline values during respective TEAE periods. Note that the ALT and total bilirubin values are presented on a logarithmic scale.

Patient listing of possible Hy's law cases identified (i.e., patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with ALT, AST, ALP, total bilirubin, and if available direct and indirect bilirubin will be provided.

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 to the day of 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 periods 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 periods 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. Tanner Stages

Tanner stages (outcome categories of 1, 2, 3, 4, 5) will be summarized for adolescent patients (<18 years of age), by patient frequency and percentage at baseline and each post-baseline visit (collected up the day of the last dose of study treatment + 14 days). Post baseline Tanner stage categories will also be assessed by the patient's Tanner stage at baseline.

5.8.8. Physical Exams

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

5.9. Analysis of Other Variables

All measurements, scheduled or unscheduled, will be assigned to Global 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 (treatment arm A, treatment arm B) at weeks 8, 24 and 52 for patient in the MRI analysis set. Mean difference between treatments with associated 95% CI will also be provided at week 8.

[redacted]

Change from baseline in liver stiffness as assessed by VCTE at week 52 will be descriptively summarized by treatment group (treatment arm A, treatment arm B) in patients in FAS and have the week 52 assessment.

Change from baseline in body composition (including lean mass and fat mass) using DXA at weeks 8, 24, and 52 will be descriptively summarized by treatment group (treatment arm A, treatment arm B) in patients in FAS and have at least one post-baseline assessment.

Change from baseline in total sLEPR at [redacted], will be descriptively summarized by treatment group (treatment arm A, treatment arm B) in patients in FAS and have at least one post-baseline assessment.

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 (e.g. HbA1c, glucose, WMG, and TG) may be evaluated descriptively.

5.11. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 4.11 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category and maximum titer observed in patients in the ADA analysis set.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:

Treatment-emergent is further sub-categorized as:

  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - 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 REGN4461 will be explored by treatment groups. Plots of individual REGN4461 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])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., 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 Quality of Life Variables

The summary of results for quality-of-life variables will be presented by treatment groups (treatment arm A, treatment arm B) containing patients from the full analysis set, unless otherwise specified.

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

For the SF-36 and PedsQL, 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 and PedsQL analysis set respectively.

5.13. Analysis of Clinical Outcome Assessment

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

For each item in the Hunger and Eating Behaviors questionnaire, the variables representing the number of days in a week that a patient reports a response in each category and the variable for the number of days in a week with missing data will be treated as continuous and summarized using descriptive statistics (mean, median, SD, min, max, Q1, Q3) for each week. Similarly, for each item, the percentage of days in a week out of the number of non-missing days that a patient reports the pre-specified categories (Section 4.13) will be treated as continuous and summarized using descriptive statistics (mean, median, SD, min, max, Q1, Q3) for each week. Additionally, the weekly average value and change from baseline will be summarized using mean, median, SD, min, max, Q1, Q3 for each post baseline visit.

For categorical variables from the Sensation of Body Temperature PRO and the PGI-S Hunger, the frequency and percentage in each category will be displayed at baseline and weeks 8, 16 and 24. Shift tables from baseline will be conducted among those with a baseline value at weeks 8, 16 and 24. For the PGI-C Hunger, the frequency and percentage in each category will be displayed at weeks 8, 16 and 24.

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 date 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 5.7.1 and Section 5.7.2.

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; e.g., 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 or taken into account 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 (i.e. efficacy analysis windows for Part B efficacy and global analysis windows for others). 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: PK and Safety Analysis for Part A

An interim analysis will be performed after at least 4 patients complete [redacted] as of the cut-off date of Dec 1, 2021. The goal of the interim analysis is to assess whether the doses selected achieved the expected drug concentrations and PK profiles, and effects on glycemic and lipid parameters.

7.2. Timing of Planned Analyses

The first-step analysis will be conducted as soon as all patients have been randomized and all data through week 36 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, as well as the open-label week 36 visit in Period 4.

The second-step analysis will be conducted as soon as all patients have been randomized and all data through week 56 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 pharmacokinetic and safety measures.

The third-step analysis will be conducted as soon as all patients have been randomized and all data through week 64 has been entered, cleaned and locked. The third-step analysis will be conducted on all randomized patients who receive study treatment. These statistical analyses will include efficacy, pharmacokinetic and safety measures.

The fourth-step analysis will be conducted as soon as all patients have been randomized and all data through week 76 has been entered, cleaned and locked. The fourth-step analysis will be conducted on all randomized patients who receive study treatment. These statistical analyses will include efficacy, pharmacokinetic and safety measures.

7.3. Fifth Step and Final Analysis

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

7.4. 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 analyses performed at first through fourth step analyses:

- Any lipid assessments within efficacy analysis windows up to the OLTP 5 week 52 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

1. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. WHO Multicenter Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization; 2006.
3. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct 4;367(14):1355-60. doi: 10.1056/NEJMsr1203730.
4. FDA. Briefing Document: BLA 125390, Myalept (metreleptin for injection). 2013; Research CfDEa, editorFDA Maryland.
5. Myalepta. Myalepta [product label on the internet]. Windsor (UK): Aegerion Pharmaceuticals Ltd., 2018. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004218/WC500253136.pdf 2018.
6. Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics. 2012 Dec;68(4):1250-9. doi: 10.1111/j.1541-0420.2012.01780.x.

10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
In patients with elevated baseline HBA1c (HbA1c ≥7%), absolute change from baseline to the end of the DBTP 1 in: – HbA1c (week 8) – Fasting glucose (week 8) – WMG (week 8) In patients with elevated baseline fasting TG (fasting TG ≥250 mg/dL), percent change from baseline to the end of the DBTP 1 in fasting TGs	Glycemic Analysis Set Triglyceride Analysis Set	MMRM		No	

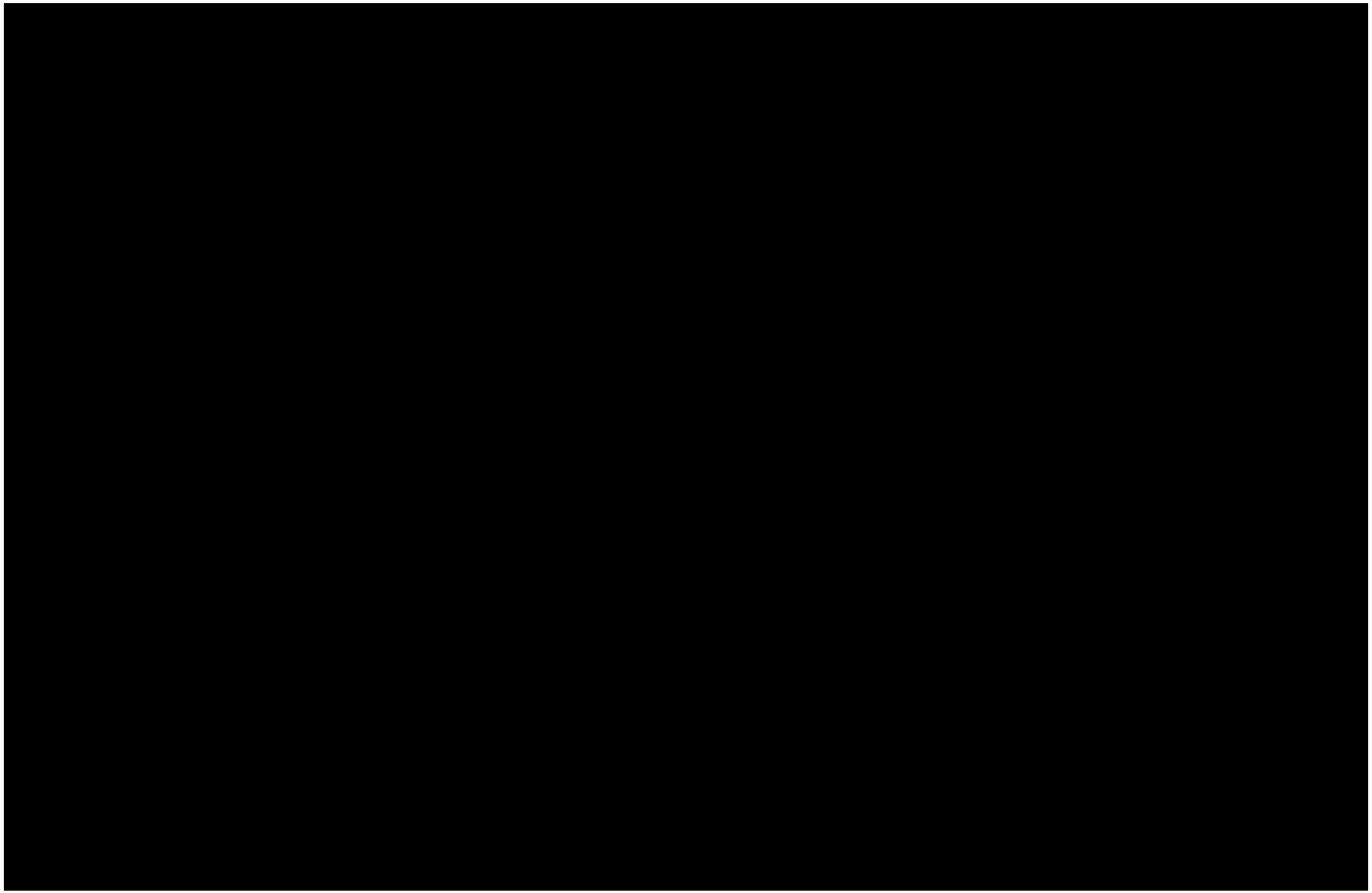
10.2. Windows for Analysis Time Points

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 Study Day 1.
2. Open-label study day is defined as the number of days since the first open-label study treatment administration+1
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 1: General Global Analysis Windows



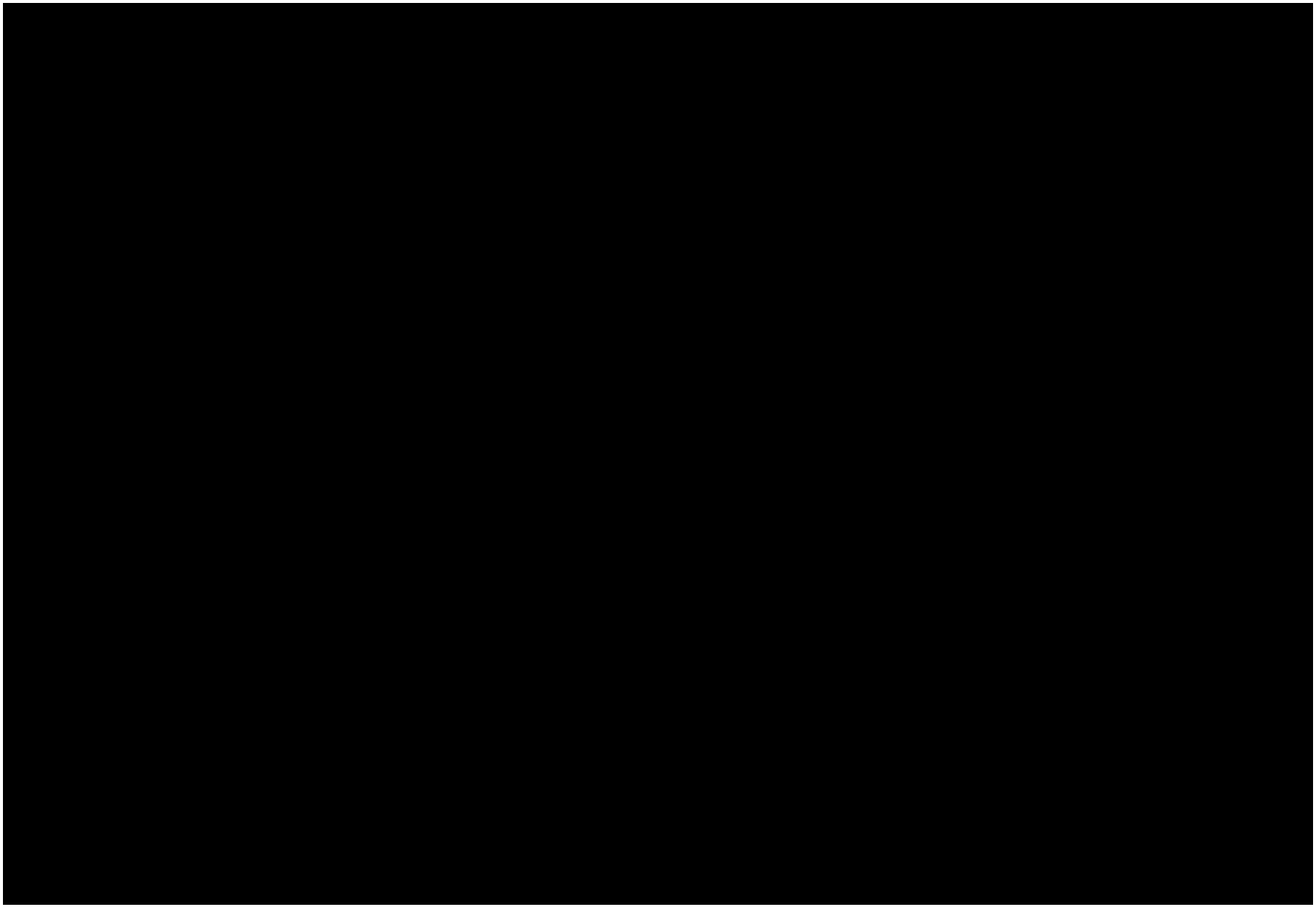


Table 2: Efficacy Analysis Windows

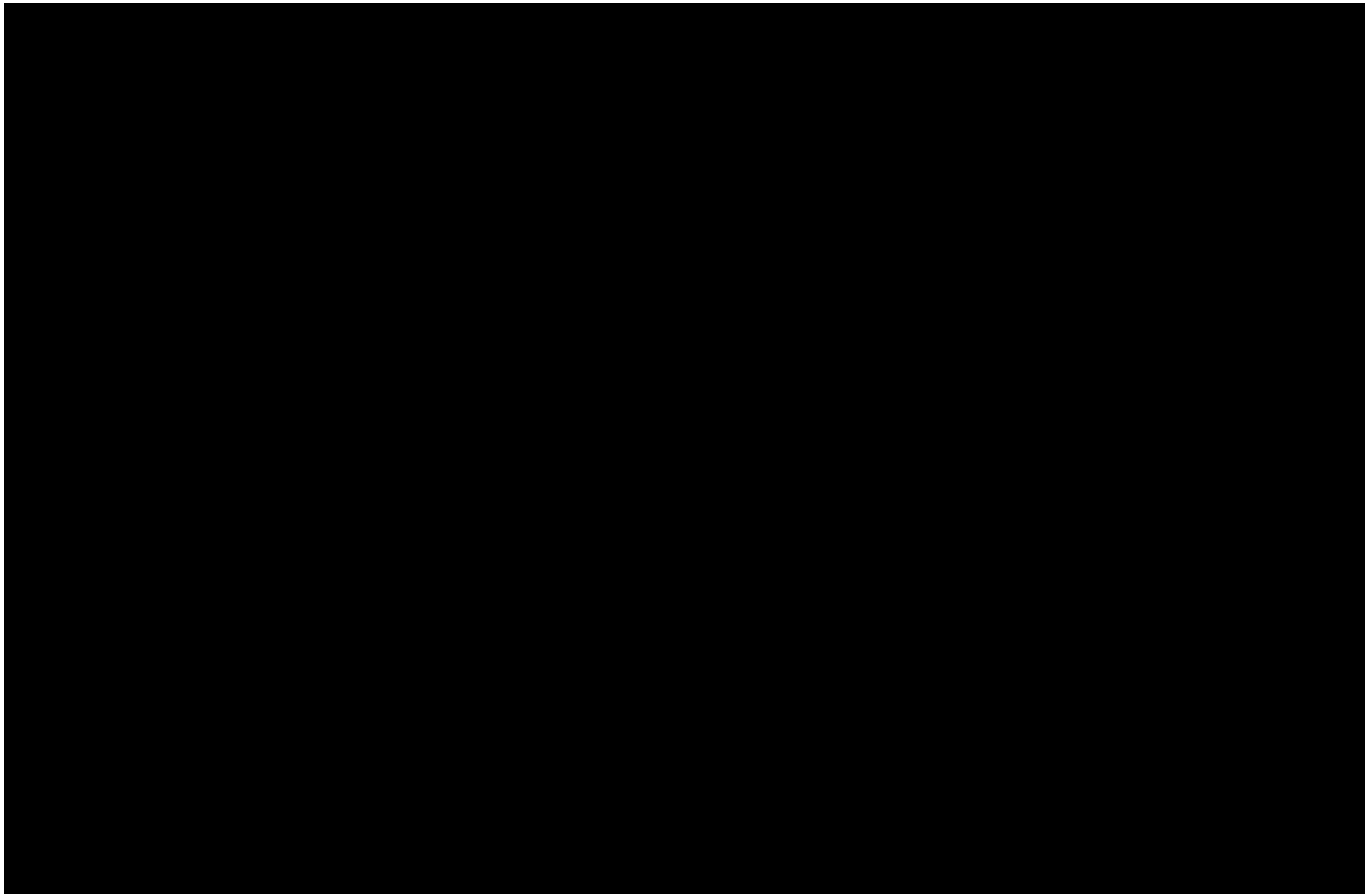


Table 3: Double-blind treatment period – Period Windows

For those measurements that are collected cumulatively over time (example AE's), analyses performed within the 8-week period windows will use the following definitions to bin observations. Observations will be binned based on the start date of the measurement.

- The blinded treatment Period 1 is defined as the day from first dose of study drug to the day before study drug administered at the week 8 visit.
- The blinded treatment Period 2 is defined as the time from the study drug administered at the week 8 visit to the day before study drug administered at the week 16 visit.
- The blinded treatment Period 3 is defined as the time from the study drug administered at the week 16 visit to the week 24 visit for those patients not proceeding into the OLTP. For those patients proceeding into the OLTP, Period 3 ends the day before first study drug administered in OLTP.

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

Table 4 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	N/A
Development of new or worsening of autoimmune disease	Yes	N/A
Hypersensitivity reactions	Yes	• CMQ 'Hypersensitivity, which is defined as Hypersensitivity SMQ (narrow) excluding the following PTs: o Injection site dermatitis,

		○ Injection site eczema, ○ Injection site hypersensitivity, ○ Injections site rash, ○ injection site reaction, ○ Injection site recall reaction, ○ Injection site urticaria, ○ Injection site vasculitis

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

10.4. 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	

Parameter	PCSV	Comments
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN and baseline ALT≤3 ULN or Total bilirubin ≤ 2 ULN	
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.

Parameter	PCSV	Comments
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.
HbA1c	HbA1c ≥10.5% AND increase in HbA1c of ≥1.5% from baseline value	
Albumin	≤25 g/L	

Parameter	PCSV	Comments
Hematology		
WBC	<4.5 GIGA/L or 4,500 /mm3 (12 to 17 yrs) >13.5 GIGA/L or 13,500 /mm3 (12 to 17 yrs) < 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	<1.2 GIGA/L or 1,200 /mm3 (2 to 17 yrs) > 1 ULN (2 to 17 yrs) < 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	< 1.55 mmol/L or10.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL (2 to 17 yrs) ≤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	

Parameter	PCSV	Comments
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 (12 to 17 yrs) ≥130 mmHg and increase from baseline ≥20 mmHg (12 to 17 yrs) ≤ 90 mmHg and decrease from baseline ≥ 20 mmHg (18 yrs +) ≥ 160 mmHg and increase from baseline ≥ 20 mmHg (18 yrs +)	
DBP	≤54 mmHg and decrease from baseline ≥10 mmHg (12 to 17 yrs) ≥78 mmHg and increase from baseline ≥10 mmHg (12 to 17 yrs) ≤ 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 (12 to 17) ≥120 bpm and increase from baseline ≥20 bpm (12 to 17) ≤45 bpm and decrease from baseline ≥20 bpm (18 yrs +) ≥120 bpm and increase from baseline≥20 bpm (18 yrs +)	
PR	≥ 180 ms (12 to 17 yrs) >220 ms and increase from baseline ≥20 ms (18 yrs +)	

Parameter	PCSV	Comments
QRS	≥ 110 ms (12 to 17 yrs) >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 (Boys, Male) 451-470 ms (Girls, Female) Prolonged*: >450 ms (Boys, Male) > 470 ms (Girls, Female) QTc ≥500 ms Increase versus baseline (Males and Females) Borderline 30-60 ms Prolonged*: >60 ms	To be applied to QTcF correction formulas

10.5. NMR Lipoprotein analysis

The following data fields are reported in the Lipoprotien NMR. The data are analyzed by two separate algorithms (denoted 3 and 4 respectively). Therefore, names have a 3 or 4 at the end of the data field label. For example, VLDLCP3 is the VLDL & chylomicron particles (total) using algorithm 3 and VLDLCP4 is the VLDL & chylomicron particles (total) using algorithm 4. Some of the variables are measured identically regardless of which algorithm is used, for example ELP_TC which is the total cholesterol.

VLDL & Chylomicron Particles (total)	**nmol/L**	**VLDLCP3**
Large VLDL & Chylomicron Particles	**nmol/L**	**VLCP3**
Medium VLDL Particles	**nmol/L**	**VMP3**
Small VLDL Particles	**nmol/L**	**VSP3**
LDL Particles (total)	**nmol/L**	**LDLP3**
IDL Particles	**nmol/L**	**IDLP3**
Large LDL Particles	**nmol/L**	**LLP3**

Small LDL Particles (total)	**nmol/L**	**LSP3**
HDL Particles (total)	**µmol/L**	**HDLP3**
Large HDL Particles	**µmol/L**	**HLP3**
Medium HDL Particles	**µmol/L**	**HMP3**
Small HDL Particles	**µmol/L**	**HSP3**
VLDL Size	**nm**	**VZ3**
LDL Size	**nm**	**LZ3**
HDL Size	**nm**	**HZ3**
Non-gender specific		**LPIR**
Total Cholesterol	**mg/dL**	**ELP_TC**
HDL Cholesterol	**mg/dL**	**ELP_HDLC**
Triglycerides	**mg/dL**	**ELP_TG**
ApoB	**mg/dL**	**ELP_APOB**

LDL Cholesterol	**mg/dL**	**ELP_LDLC**
VLDL Cholesterol	**mg/dL**	**ELP_VLDLC**
Non HDL Cholesterol	**mg/dL**	**ELP_NONHDLC**

AND

VLDL & Chylomicron Particles (total)	**nmol/L**	**VLDLCP4**
Large VLDL & Chylomicron Particles	**nmol/L**	**VLCP4**
Medium VLDL Particles	**nmol/L**	**VMP4**
Small VLDL Particles	**nmol/L**	**VSP4**
LDL Particles (total)	**nmol/L**	**LDLP4**
IDL Particles	**nmol/L**	**IDLP4**
Large LDL Particles	**nmol/L**	**LLP4**
Small LDL Particles (total)	**nmol/L**	**LSP4**

HDL Particles (total)	**µmol/L**	**HDLP4**
Large HDL Particles	**µmol/L**	**HLP4**
Medium HDL Particles	**µmol/L**	**HMP4**
Small HDL Particles	**µmol/L**	**HSP4**
VLDL Size	**nm**	**VZ4**
LDL Size	**nm**	**LZ4**
HDL Size	**nm**	**HZ4**
Non-gender specific		**LPIR**
Total Cholesterol	**mg/dL**	**ELP_TC**
HDL Cholesterol	**mg/dL**	**ELP_HDLC**
Triglycerides	**mg/dL**	**ELP_TG**
ApoB	**mg/dL**	**ELP_APOB**
LDL Cholesterol	**mg/dL**	**ELP_LDLC**

VLDL Cholesterol	**mg/dL**	**ELP_VLDLC**
Non HDL Cholesterol	**mg/dL**	**ELP_NONHDLC**

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. Calculation for Efficacy Variables

Weighted Mean Glucose (WMG) (mg/dL)	$\frac{\frac{(X_{t-15}+X_{t0})*(t_0-t_{-15})}{2}+\frac{(X_{t0}+X_{t1})*(t_1-t_0)}{2}+\ldots\frac{(X_{t10}+X_{t11})*(t_{11}-t_{10})}{2}}{t_{11}-t_{-15}}$ Note: X_{ti} is the value of glucose at time t_i (actual time) t_{-15}= -15 minutes (pre-meal) (MMTT CRF) t_0= 0 minutes (pre-meal) (MMTT CRF) t_1= 30 minutes (MMTT CRF) t_2= 60 minutes (MMTT CRF) t_3= 90 minutes (MMTT CRF) t_4= 120 minutes (MMTT CRF) t_5= 180 minutes (MMTT CRF) t_6= <30 mins prior to lunch (WMG CRF) t_7= 120 mins after lunch (WMG CRF) t_8= <30 mins prior to dinner (WMG CRF) t_9= 120 mins after dinner (WMG CRF) t_{10}= 10 PM or Bedtime (WMG CRF) t_{11} = next morning fasting glucose measurement
Glucose AUC_{0-4} during an MMTT (mg/dL*minutes)	$\frac{(X_{t1}+X_{t0})*(t_1-t_0)}{2}+\frac{(X_{t1}+X_{t2})*(t_2-t_1)}{2}+\ldots.\frac{(X_{tn}+X_{t(n-1)})*(t_n-t_{(n-1)})}{2}$ Note: X_{ti} is the value of glucose at time t_i t_0= 0 minutes t_1= 30 minutes t_2= 60 minutes t_3= 90 minutes t_4= 120 minutes t_5= 180 minutes
Glucose infusion rate per kg body mass during hyperinsulinemia-euglycemic clamp (mg/Kg/min)	The following time points have been defined: t_1= 'Beginning of steady state sampling – Time 0' t_2 = 'Steady state – 5 mins' t_3 = 'Steady state – 10 mins'

	t_4 = 'Steady state – 15 mins' t_5 = 'Steady state – 20 mins' t_6 = 'Steady state – 25 mins' t_7= 'End of steady state – 30 mins' INSBEDS = Bedside whole blood Glucose (Mean) Sample collection time = INSTIM Time of change in D20 infusion: INSTM Body mass (DXA) = TOT_FAT + TOT_LEAN + TOT_BMC Fat free mass (FFM) = TOT_LEAN + TOT_BMC Step 1: Calculate the Mean rate of D20 infused steady state (M): $M = \frac{((INSTM_{t1} - INSTIM_{t1}) * D20MLHR_{t1}) + (INSTM_{t2} - INSTM_{t1}) * D20MLHR_{t2}) + (INSTM_{t3} - INSTM_{t2}) * D20MLHR_{t3}) + \ldots (INSTIM_{t7} - INSTM_{t6}) * D20MLHR_{t7}))}{INSTIM_{t7} - INSTIM_{t1}}$ Step 2: Calculate Total Glucose Infusion Rate (GIR_{total}) (mg/Kg/min) = (M * 20) / (body mass * 6) Step 3: Calculate Space correction (SC): $INSBEDS_{t7} - INSBEDS_{t1} * 1.9) / INSTIM_{t7} - INSTIM_{t1}$ Step 4: M_{TOTAL} (whole body glucose metabolism) = GIR_{total} – SC
Glucose infusion rate normalized for Fat free mass (mg/Kg/min)	$M_{FFM}=M_{TOTAL}$ * (Body mass/FFM)
Glucose clearance rate (k_{ITT}) during Insulin-tolerance Test (% mg/dL/min)	The following time points have been defined: t_2 = 'Post insulin administration – 5 mins' t_4 = 'Post insulin administration – 15 mins' K_{ITT} is the percent change in glucose over time. For K_{ITT} we are calculating the percent change in glucose from time t_2 to t_4. K_{ITT} = ((Bedside whole blood Glucose (Mean)$_{t2}$ - Bedside whole blood Glucose (Mean)$_{t4}$)/

	(Bedside whole blood Glucose (Mean)$_{t2}$))/(t_4-t_2) Calculate K_{ITT} for each visit to calculate change from BL.

10.8. Detailed Description of the Multiple Imputation Procedure

The following is a detailed description of the multiple imputation procedure which will be used for analysis of the secondary efficacy endpoints.

In general, the missing pattern is anticipated to be not monotone, a two-step approach will be used:

- Step 1: the MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern. Set the SEED=17100 option in SAS MI procedure
- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method. Set the SEED=34200 option in SAS MI procedure

The imputation model for step 1 will include the values of the analyzed parameter at baseline and planned time-points up to week 24.

The imputation model for step 2 will include the same variables as in step 1 with the following additional variables:

- age, BMI, and gender (age and BMI included as continuous variables).

Non-continuous variables included in the imputer's model (i.e., gender) are not expected to be missing.

In addition, for continuous efficacy variables anticipated to have a non-normal distribution (i.e. TG), data will be log-transformed before imputation process and then back-transformed to create the imputed data sets using the TRANSFORM statement of SAS MI procedure.

For variables other than those continuous efficacy variables anticipated to have a non-normal distribution (i.e. TG), for each simulation leading to negative imputed value, another value will be redrawn using MINIMUM option of SAS MI procedure.

The number of imputations (100) will be informally verified by replicating sets of 100 imputations and checking whether the combined results are stable. If not stable, the number of imputations will be increased and informally checked as above, and thus continued until stable estimates are obtained.

10.9. Schedule of Time and Events

Table 3: Screening and Placebo Run-In Schedule of Events

Study Period	Screening	Placebo Run-In			
	In-Clinic Outpatient Visit[1,2]	In-Clinic Outpatient Visit[2]	In-Clinic Outpatient Visit or Remote Visit[3]		
Visit Number:	[redacted]				
Day:					
±Visit Window (d):					
Week:					
Screening/Baseline					
Informed Consent	X				
Inclusion/Exclusion	X	X			
Medical History[4]	X				
Demographics	X				
HIV Serology and Hepatitis Testing (HBsAg, HCV)	X				
Treatment and Medications					
[redacted]					
Safety[6]					
Vital Signs	X	X	X	X	X
Height[7]	X				
Weight[7]	X	X			
Physical Examination[8]	X	X			
Tanner Staging	X				

Study Period	Screening	Placebo Run-In			
	In-Clinic Outpatient Visit[1,2]	In-Clinic Outpatient Visit[2]	In-Clinic Outpatient Visit or Remote Visit[3]		
Visit Number:					
Day:					
±Visit Window (d):					
Week:					
Electrocardiogram[9]	X				
Adverse Events	X	X	X	X	X
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[10]	X	X	X	X	X
Laboratory Testing[11]					
Hematology	X	X[12]			
Blood Chemistry	X	X[12]			
Pregnancy Test (WOCBP)[10]	Serum	Urine			
Urinalysis	X				
Leptin		X			
Efficacy[11]					
Fasting Triglycerides and Glucose[2]	X[2]	X[2]			X
HbA1c, Fructosamine	X	X			
Insulin/C-peptide[2]	X[2]	X[2]			
Urine Protein, Creatinine, Albumin		X			
COA Training[13]		X			
Daily Appetite Hunger and Eating Behavior PRO[13]		X ← →			X
Sensation of Body Temperature PRO		X			
SF-36 Questionnaire/PedsQL™ [14]		X			

Study Period	**Screening**	**Placebo Run-In**			
	In-Clinic Outpatient Visit[1,2]	**In-Clinic Outpatient Visit[2]**	**In-Clinic Outpatient Visit or Remote Visit[3]**		
Visit Number:	[redacted]				
Day:					
±Visit Window (d):					
Week:					
Patient Global Impression of Severity		X			
Liver MRI (volume/fat content)[15]		X			
VCTE[15]		X			
Whole body DXA[15]		X			
PK/Biomarkers Procedure/Samples[16]					
Endocrine Hormones[17]		X			X
ANGPTL3, PCSK9, sLEPR		X			X
[redacted]					

10.9.1. Footnotes for the Schedule of Events Table 3: 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 4-week screening period, only screening test(s) (eg, an out-of-range lab value) that resulted in initial screen failure should be repeated.
2. Procedures may be conducted on different days during the screening/baseline period, if needed. Blood draws for laboratory testing at the screening visit and visit 2 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 (ie, at home visits, work, and/or school).
4. Medical history should include detailed lipodystrophy history including prior medication/investigational products, genetic diagnosis (if known), imaging results, leptin levels (if known) and results of any previous anti-metreleptin antibody testing (if applicable).
5. [redacted]
6. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
7. 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. In individuals under 18 years of age, standing height should be recorded at least every 3 months using a stadiometer. Patients should be instructed to remove footwear and stand upright with their heels together. Tanner staging for pubertal development should be performed at least every 3 months until patient reaches Tanner stage 5.
8. Complete physical examination will be performed at screening (visit 1) and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.

9. The electrocardiogram (ECG) can be performed up to 24 hours prior to study drug administration.
10. Menstrual events and pregnancy status of WOCBP will be monitored throughout the study. A serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed locally (eg, point-of-care) at subsequent visits. A positive urine pregnancy test should be confirmed with a serum test.
11. Study assessments should be performed, and blood 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. Samples for hematology and blood chemistry analysis do not need to be collected at visit 2 if visits 1 and 2 occur within 48 hours of each other.
13. Patients must receive eCOA training at the time they receive the eCOA device. Additionally, patients must be trained on the Daily Appetite Hunger and Eating Behavior PRO prior to completion of PRO assessments. Patients will be instructed to fill out the Daily Appetite Hunger and Eating Behavior PRO on a daily basis. The site will check the patient's adherence to completion of all study questionnaires at each designated visit.
14. SF-36 is to be completed by patients 18 years or older, and PedsQL^{TM} is to be completed by patients 12 to 17 years of age. The PedsQL^{TM} will be a PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
15. Liver fat content and liver volume MRI scans, VCTE, and whole body DXA will be performed only at sites where these techniques are available. Liver MRI scans, VCTE, and whole body DXA can be performed from day -28 to day 1 prior to dosing of study drug.
16. Biomarker blood draw samples will be collected pre-dose.
17. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone (Protocol Section 9.2.7.1).
18. DNA can be collected at any visit after obtaining consent.

Table 4: Double-Blind Treatment Period 1 Schedule of Events

Study Period	**Baseline Assessment**		**Double-Blind Treatment Period 1**								
	In-Clinic Stay[1]				**In-Clinic Outpatient Visit or Remote Visit[2]**						
Visit Number:	[redacted]										
Day:											
±Visit Window (d):											
Week:											
Patient Disposition											
Clinic Admission	X										
Clinic Discharge				X							
Randomization			X[3]								
Treatment and medications											
[redacted]											
Safety[5]											
Vital Signs	X	X	X[6]	X	X	X	X	X	X	X	X
Height[7]			X								
Weight[7]			X[8]		X	X		X		X	
Tanner Staging[7]			X								
Physical Examination[22]			X								
Electrocardiogram[9]		X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Baseline Assessment**		**Double-Blind Treatment Period 1**								
	In-Clinic Stay[1]				**In-Clinic Outpatient Visit or Remote Visit[2]**						
Visit Number:											
Day:											
±Visit Window (d):											
Week:											
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[10]		X			X	X	X	X	X	X	X
Laboratory Testing[11]											
Hematology			X			X		X			X
Blood Chemistry			X			X		X			X
INR/PTT, Platelets (Local Lab)	X										
Pregnancy Test (WOCBP)[10]		X						X			
Urinalysis			X			X		X			X
Leptin[12]			X[12]								
Efficacy[11]											
Fasting Triglycerides and Glucose[12]			X[12]								X[12]
HbA1c			X					X			
Fructosamine			X					X			
Insulin/C-peptide[12]			X[12]								
Lipid Panel [12]			X[12]								
Urine Protein, Creatinine, Albumin			X								
Insulin Sensitivity Measurement [13, 14]			X								

Study Period	**Baseline Assessment**		**Double-Blind Treatment Period 1**								
	In-Clinic Stay[1]				**In-Clinic Outpatient Visit or Remote Visit[2]**						
Visit Number:											
Day:											
±Visit Window (d):											
Week:											
MMTT[15]		X									
Weighted Mean Glucose Assessment[16]		X									
COA Training[17]	X										
Daily Appetite Hunger and Eating Behavior PRO[17]	X ←										→ X
Sensation of Body Temperature PRO	X										
SF-36 Questionnaire/ PedsQL™ [18]	X										
Patient Global Impression of Severity	X										
PK/Biomarker/Drug Concentration and ADA Samples[19]											
REGN4461 Concentration Blood Sample			X		X	X					
ADA Sample			X								
Endocrine Hormones[20]			X					X			
ANGPTL3, PCSK9, sLEPR			X		X	X					
Immunophenotyping			X								

Study Period	Baseline Assessment	Double-Blind Treatment Period 1	
	In-Clinic Stay[1]	In-Clinic Outpatient Visit or Remote Visit[2]	
Visit Number:	[redacted]		
Day:			
±Visit Window (d):			
Week:			
[redacted]			

10.9.2. Footnotes for the Schedule of Events Table 4: Double-Blind Treatment Period 1

1. [redacted] All other patients may choose to be admitted on day -1. Patients will have the option to leave on the same day of study drug administration after being observed for at least 4 hours, provided all required assessments and procedures have been completed on that day.
2. Assessments/procedures other than those occurring during in-clinic stays may be conducted by trained study staff at a remote location (ie, at home visits, work, and/or school).
3. Randomization can occur within 24 hours prior to day 1 study drug administration if necessary.
4. [redacted]
5. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
6. Vital signs should be recorded [redacted]
7. In individuals under 18 years of age, standing height should be recorded at least every 3 months using a stadiometer. Patients should be instructed to remove footwear and stand upright with their heels together. Body weight must be measured after voiding (empty bladder) using a dedicated, calibrated scale. Patients should empty pockets and remove shoes, belts, outer-layer clothing, or any other heavy wearable prior to being weighed. Tanner staging for pubertal development should be performed at least every 3 months until patient reaches Tanner stage 5.
8. This body weight will be used for dose tier determination. Body weight may be measured up to 24 hours prior to day 1 study drug administration and must be measured prior to randomization.
9. The ECG can be performed up to 24 hours prior to study drug administration.
10. Menstrual events and pregnancy status of WOCBP will be monitored throughout the study. A urine pregnancy test will be performed locally (eg, point-of-care). A positive urine pregnancy test should be confirmed with a serum test.

11. Study assessments should be performed, and blood 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. 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.
13. Patients must be in a fasted state (after at least approximately a 12-hour fast) for insulin sensitivity assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Insulin sensitivity will be measured by clamp at sites where a qualified and experienced facility and staff are available. Blood samples for the clamp will be collected for the analysis of glucose, insulin, C-peptide at following times: 2 baseline samples within 30 minutes before starting insulin infusion and up to 4 samples during the 30 minutes steady state. Additional samples will be analyzed for point of care glucose measures during insulin infusion, as outlined in the study manual. [redacted]

    For sites that do not have the ability to perform a clamp study but do have a qualified and experienced ITT facility and staff, patients will undergo an ITT. Patients with a history of seizure disorder should not undergo ITT. Blood samples will be collected for the analysis of glucose, insulin, C-peptide timed as follows: 2 baseline samples before starting insulin administration and at 5, 10, 15, 20 and 30 minutes after starting the insulin administration. [redacted]
14. Patients presenting to sites without qualified and experienced facility and staff to perform a clamp or ITT will not undergo clamp or ITT evaluation. This procedure can be done within 3 days prior to day 1.
15. Patients must be in a fasted state (after at least approximately a 12-hour fast) prior to MMTT assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Blood samples will be collected on the days of the MMTT for the analysis of glucose, insulin, C-peptide, and TGs. Sampling times are as follows:

    - For glucose analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For insulin analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For C-peptide analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For TG analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes

    This procedure can be done within 3 days prior to day 1.

16. Additional blood samples will be collected on the days of WMG assessments, timed as follows: (1) less than 30 minutes prior to lunch, (2) 120±10 minutes after lunch, (3) less than 30 minutes prior to dinner, (4) 120±10 minutes after dinner, and (5) 10 PM or bedtime. This procedure must be done on the same day as MMTT. Blood samples will be analyzed for glucose, insulin and for C-peptide.
17. Patients must receive eCOA training at the time they receive the eCOA device. Additionally, patients must be trained on the Daily Appetite Hunger and Eating Behavior PRO prior to completion of PRO assessments. If the patient was previously trained on both the eCOA and the PRO assessments, no additional training is required at this time. Patients will be instructed to fill out the Daily Appetite Hunger and Eating Behavior PRO on a daily basis. The site will check the patient's adherence to completion of all study questionnaires at each designated visit.
18. SF-36 is to be completed by patients 18 years or older, and PedsQL™ is to be completed by patients 12 to 17 years of age. The PedsQL™ will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
19. Collection of blood samples for drug concentration on day 1 will be pre-infusion/injection and at the end of infusion ±15 mins. On other visits, drug concentration and biomarker samples will be collected pre-dose. Samples for sLEPR, ANGPTL3, and PCSK9 should be collected at the time points that drug concentration is measured. On all visits ADA and drug concentration samples should be collected prior to administration of drug.
20. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone.
21. [redacted]
22. Complete physical examination will be performed on day 1 (visit 8) and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.

Table 5: Double-Blind Treatment Periods 2 and 3 Schedule of Events

Study Period	Double-Blind Treatment Period 2										Double-Blind Treatment Period 3								
	In-Clinic Stay[1]			In-Clinic Outpatient Visit or Remote Visit [2]							In-Clinic Stay[1]		In-Clinic Outpatient Visit or Remote Visit[2]						
Visit Number:	[redacted]																		
Day:																			
±Visit Window (d):																			
Week:																			
Patient Disposition																			
Clinic Admission	X										X								
Clinic Discharge			X									X							
Treatment and Medications																			
[redacted]																			
Safety[4]																			
Vital Signs	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[6]		X										X							
Weight[6]		X		X	X		X		X			X	X	X		X		X	
Tanner Staging[6]		X										X							

Study Period	Double-Blind Treatment Period 2										Double-Blind Treatment Period 3								
	In-Clinic Stay[1]			In-Clinic Outpatient Visit or Remote Visit [2]							In-Clinic Stay[1]		In-Clinic Outpatient Visit or Remote Visit[2]						
Visit Number:																			
Day:																			
±Visit Window (d):																			
Week:																			
Physical Examination[21]		X										X							
Electrocardiogram[7]		X																	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[8]		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Laboratory Testing[9]																			
Hematology		X			X		X			X		X		X		X			X
Blood Chemistry		X			X		X			X		X		X		X			X
Pregnancy Test (WOCBP)[8]		X					X					X				X			
Urinalysis		X			X		X			X		X		X		X			X
Leptin[10]		X[10]																	
Efficacy[9]																			
Fasting Triglycerides and Glucose[10]		X[10]								X[10]		X[10]							X[10]
HbA1c		X					X					X				X			
Fructosamine		X					X					X				X			
Insulin/C-peptide[10]		X[10]										X[10]							

Study Period	Double-Blind Treatment Period 2										Double-Blind Treatment Period 3								
	In-Clinic Stay[1]			In-Clinic Outpatient Visit or Remote Visit [2]							In-Clinic Stay[1]		In-Clinic Outpatient Visit or Remote Visit[2]						
Visit Number:																			
Day:																			
±Visit Window (d):																			
Week:																			
Lipid Panel[10]		X										X							
Urine Protein, Creatinine, Albumin		X										X							
Insulin Sensitivity Measurement[11,12]		X																	
MMTT[13]	X										X								
Weighted Mean Glucose Assessment[14]	X										X								
COA Training[15]	X																		
Daily Appetite Hunger and Eating Behavior PRO[15]	X ←																		→ X
Sensation of Body Temperature PRO	X										X								
SF-36 Questionnaire/ PedsQL™ [16]	X										X								
Patient Global Impression of Severity	X										X								
Patient Global Impression of Change	X										X								
Exit Interview	X[17]																		

Study Period	Double-Blind Treatment Period 2										Double-Blind Treatment Period 3								
	In-Clinic Stay[1]			In-Clinic Outpatient Visit or Remote Visit [2]							In-Clinic Stay[1]		In-Clinic Outpatient Visit or Remote Visit[2]						
Visit Number:	[redacted]																		
Day:																			
±Visit Window (d):																			
Week:																			
Liver MRI (volume/fat content) [18]	X																		
Whole body DXA[18]	X																		
PK/Biomarker/Drug Concentration and ADA Samples [19]																			
REGN4461 Concentration Blood Sample		X		X	X							X	X	X					X
ADA Sample		X																	
Immunophenotyping		X										X							
Endocrine Hormones[20]		X					X					X				X			
ANGPTL3, PCSK9, sLEPR		X		X	X							X	X	X					X
[redacted]																			

10.9.3. Footnotes for the Schedule of Events Table 5: Double-Blind Treatment Periods 2 and 3

1. In-clinic stay may begin within a ±2-day window. Patients will have the option to leave on the same day of study drug administration after being observed for at least 4 hours, provided all required assessments and procedures on that day have been completed.
2. Assessments/procedures other than those occurring during in-clinic stays may be conducted by trained study staff at a remote location (ie, at home visits, work, and/or school). However, during the [redacted]
3. [redacted]
4. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
5. Vital signs should be recorded prior to [redacted]
6. In individuals under 18 years of age, standing height should be recorded at least every 3 months using a stadiometer. Patients should be instructed to remove footwear and stand upright with their heels together. Body weight must be measured after voiding (empty bladder) using a dedicated, calibrated scale. Patients should empty pockets and remove shoes, belts, outer-layer clothing, or any other heavy wearable prior to being weighed. Tanner staging for pubertal development should be performed at least every 3 months until patient reaches Tanner stage 5.
7. The ECG can be performed up to 24 hours prior to study drug administration.
8. Menstrual events and pregnancy status of WOCBP will be monitored throughout the study. A serum pregnancy test will be performed at the screening and EOS visit and urine pregnancy test performed locally (eg, point-of-care) at subsequent visits. A positive urine pregnancy test should be confirmed with a serum test.
9. Study assessments should be performed, and blood 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.

10. 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.

11. Patients must be in a fasted state (after at least approximately a 12-hour fast) for insulin sensitivity assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Insulin sensitivity will be measured by clamp at sites where a qualified and experienced facility and staff are available. Blood samples for the clamp will be collected for the analysis of glucose, insulin, C-peptide at following times: 2 baseline samples within 30 minutes before starting insulin infusion and up to 4 samples during the 30 minutes long steady state. Additional samples will be analyzed for point of care glucose measures during insulin infusion, as outlined in the study manual. [redacted]

    Patients will undergo an ITT at sites where a qualified and experienced ITT facility and staff are available. Patients with a history of seizure disorder should not undergo ITT. Blood samples will be collected for the analysis of glucose, insulin and C-peptide timed as follows: two baseline samples before starting insulin administration and at 5, 10, 15, 20 and 30 minutes after starting the insulin administration. [redacted]

12. Patients presenting to sites without qualified and experienced facility and staff to perform a clamp or ITT will not undergo clamp or ITT evaluation. This procedure can be done within 3 days prior to day 57.

13. Patients must be in a fasted state (after at least approximately a 12-hour fast) prior to MMTT assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Blood samples will be collected on the days of the MMTT for the analysis of glucose, insulin, C-peptide, and TGs. Sampling times are as follows:

    - For glucose analysis, -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For insulin analysis, -15,0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For C-peptide analysis, -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For TG analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes

    This procedure can be done within 3 days prior to day 56 and 112.

14. Additional blood samples will be collected on the days of WMG assessments, timed as follows: (1) less than 30 minutes prior to lunch, (2) 120±10 minutes after lunch, (3) less than 30 minutes prior to dinner, (4) 120±10 minutes after dinner, and (5) 10 PM or bedtime. For patients who are discharged prior to completion of WMG blood draw assessments, the after-dinner and prior-to-bedtime assessments will not be required. This

procedure must be done on the same day as MMTT. Blood samples will be analyzed for glucose, insulin and for C-peptide.

15. Patients must receive eCOA training at the time they receive the eCOA device. Additionally, patients must be trained on the Daily Appetite Hunger and Eating Behavior PRO prior to completion of PRO assessments. If the patient was previously trained on both the eCOA and the PRO assessments, no additional training is required at this time. Patients will be instructed to fill out the Daily Appetite Hunger and Eating Behavior PRO daily through week 24. The site will check the patient's adherence to completion of all study questionnaires at each designated visit.
16. SF-36 is to be completed by patients 18 years or older and PedsQL™ is to be completed by patients 12 to 17 years of age. The PedsQL™ will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
17. Exit interviews will be conducted either during in-clinic stay for DBTP2 or between [redacted]
18. Liver volume and fat content MRI and whole body DXA scans may be performed up to 14 days prior to visit 17. These tests will only be performed at sites where these techniques are available. Patients may be required to fast at least 5 hours prior to an MRI scan.
19. Collection of blood samples for drug concentration on [redacted] will be pre-infusion and at the end of infusion ±15 mins. On other visits, drug concentration and biomarker samples will be collected pre-dose. Samples for sLEPR, ANGPTL3, and PCSK9 will be collected at the time points that drug concentration is measured. On all visits ADA and drug concentration samples should be collected prior to administration of drug.
20. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone.
21. Complete physical examination will be performed at the EOT and EOS visits and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.

Table 6: Open-Label Treatment Period 4 (OLTP 4) Schedule of Events

Study Period			**Treatment Period 4[1]**					
	In-Clinic[2]		**In-Clinic Outpatient Visit or Remote Visit**	**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:	[redacted]							
Day:								
±Visit Window (d):								
Week:								
Patient Disposition								
Clinic Admission	X							
Clinic Discharge		X						
Treatment and Medications								
[redacted]								
Safety[6]								
Vital Signs	X	X		X		X		X
Height[7]								
Weight		X		X		X		X
Tanner Staging[7]		X		X		X		X
Physical Examination		X		X		X		X
Adverse Events	X	X	X	X	X	X	X	X
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[8]		X	X	X	X	X	X	X

Study Period			Treatment Period 4[1]					
	In-Clinic[2]		In-Clinic Outpatient Visit or Remote Visit	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:								
Day:								
±Visit Window (d):								
Week:								
Laboratory Testing[9]								
Hematology		X		X		X		X
Blood Chemistry		X		X		X		X
INR/PTT, Platelets (Local Lab)								X
Pregnancy Test (WOCBP)[8]		X		X		X		X
Urinalysis		X		X		X		X
Efficacy[9]								
Fasting Triglycerides and Glucose[10]		X		X		X		X
HbA1c		X		X		X		X
Fructosamine		X		X		X		X
Insulin/C-peptide[10]		X		X		X		X
Lipid Panel[10]		X		X		X		X
Urine Protein, Creatinine, Albumin		X		X		X		X
Insulin Sensitivity Measurement [11,12]								X
MMTT[13]	X							
Weighted Mean Glucose Assessment[14]	X							
Daily Appetite Hunger and Eating Behavior PRO	X							
Sensation of Body Temperature PRO	X							
SF-36 Questionnaire/ PEDs QOL[15]	X							

Study Period			**Treatment Period 4[1]**					
	In-Clinic[2]		**In-Clinic Outpatient Visit or Remote Visit**	**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:								
Day:								
±Visit Window (d):								
Week:								
Patient Global Impression of Severity	X							
Patient Global Impression of Change	X							
Exit Interview								X[20]
Liver MRI (volume/fat content)[16]	X							X
Whole body DXA[16]	X							X
VCTE								X[16]
PK/Biomarker/Drug Concentration and ADA Samples[9]								
REGN4461 Concentration Blood Sample		X		X		X		X
ADA Sample		X		X				X
Endocrine Hormones[19]		X		X		X		X
ANGPTL3, PCSK9, sLEPR		X		X		X		X

10.9.4. Footnotes for the Schedule of Events Table 6: Open-Label Treatment Period 4

1. During the Open-Label Treatment Period, patients will be treated with study drug weekly. Study drug can be administered at the clinical site, by the site personnel or another healthcare professional at a remote location (eg, the patient's home, school, or place of work), or self-administered/administered by a designated person.
   a. If medication is administered by site personnel or another healthcare professional, study personnel will monitor AEs, concomitant medications, menstrual history/pregnancy status reporting/confirmation of contraception **weekly**. Diabetes and lipid medication adjustments must occur **at least once monthly** (see footnote 5).
   b. If patients are self-administering study drug or the study drug is being administered by a designated person, site personnel must assess the patient for AEs, concomitant medications, menstrual history/pregnancy status reporting/confirmation of contraception, and diabetes and lipid medications adjustments must occur **at least once monthly**. These assessments may occur via telephone contact or in-site assessments, at the discretion of the investigator.
2. In-clinic stay can begin within a ±2-day window. Patients will have the option to leave on the same day of study drug administration after being observed for at least 4 hours, provided no other procedures are required on that day.
3. Training for study drug administration must be performed and documented for all patients who choose to self-administer REGN4461 during OLTP 4. Training is not required for patients who choose to not self-administer study drug. Training may occur at any time during OLTP 4 prior to first self-administration. If an appropriate designee (eg, parent or caregiver) will administer study drug to the patient during OLTP 4, this individual will undergo training as above.
4. A medication administration diary will be provided to the patient/designee prior to initiation of self-administration or administration by a designated person such as a parent or caregiver. The diary must be completed upon each study drug administration. Training on the diary will be provided only to patients which will self-administer REGN4461.
5. [redacted]

6. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
7. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least approximately every 3 months until patient reaches Tanner stage 5.
8. Menstrual events and pregnancy status of WOCBP will be monitored through the EOS visit. A urine pregnancy test will be performed locally (eg, point-of-care). A positive urine pregnancy test should be confirmed with a serum test.
9. Study assessments should be performed, and blood 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. At all visits, PK, ADA, and ANGPTL3/PCSK9/sLEPR samples should be collected prior to the administration of drug.
10. 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.
11. Patients must be in a fasted state (after at least approximately a 12-hour fast) for insulin sensitivity assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
12. Insulin sensitivity will be measured by clamp at sites where a qualified and experienced facility and staff are available. Blood samples for the clamp will be collected for the analysis of glucose, insulin, C-peptide at following times: 2 baseline samples within 30 minutes before starting insulin infusion and up to 4 samples during the 30 minutes long steady state. Additional samples will be analyzed for point of care glucose measures during insulin infusion, as outlined in the study manual. [redacted]
13. Patients will undergo an ITT at sites where a qualified and experienced ITT facility and staff are available. Patients with a history of seizure disorder should not undergo ITT. Blood samples will be collected for the analysis of glucose, insulin and C-peptide timed as follows: two baseline samples before starting insulin administration and at 5, 10, 15, 20 and 30 minutes after starting the insulin administration. [redacted].
14. Patients presenting to sites without qualified and experienced facility and staff to perform a clamp or ITT will not undergo clamp or ITT evaluation. This procedure can be done within 3 days prior to day 365.
15. Patients must be in a fasted state (after at least approximately a 12-hour fast) prior to MMTT assessments. The duration of fasting may be shortened for patients with a

documented clinical contraindication to fasting. Blood samples will be collected on the days of the MMTT for the analysis of glucose, insulin, C-peptide, and TGs. Sampling times are as follows:

- For glucose analysis, -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
- For insulin analysis, -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
- For C-peptide analysis, -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
- For TG analysis, -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes

This procedure can be done within 3 days [redacted].

16. Additional blood samples will be collected on the days of WMG assessments, timed as follows: (1) less than 30 minutes prior to lunch, (2) 120±10 minutes after lunch, (3) less than 30 minutes prior to dinner, (4) 120±10 minutes after dinner, and (5) 10 PM or bedtime. For patients who are discharged prior to completion of WMG blood draw assessments, the after-dinner and prior-to-bedtime assessments will not be required. This procedure must be done on the same day as MMTT. Blood samples will be analyzed for glucose, insulin and for C-peptide.
17. SF-36 is to be completed by patients 18 years or older and PedsQL™ is to be completed by patients 12 to 17 years of age. The PedsQL™ will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
18. Liver volume and fat content MRI, whole body DXA may be performed up to 14 days prior to visit 37 and visit 65. VCTE may be performed up to 14 days prior to visit 65. These tests will only be performed at sites where these techniques are available. Patients may be required to fast at least 5 hours prior to an MRI scan.
19. [redacted]
20. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone (Protocol Section 9.2.7.1).
21. In the event that a patient has an early termination visit that occurs before week 8, the exit interview will be conducted during this visit.

Table 7: Open-Label Treatment Period 5 (OLTP 5) Schedule of Events

	Open-Label Period[1]											Off-Drug Follow-up Period			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:	[redacted]														
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Treatment and Medications															
[redacted]															

	Open-Label Period[1]											Off-Drug Follow-up Period			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:	[redacted]														
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Safety[5]															
Vital Signs[6]	X		X		X		X		X		X	X	X	X	X
Height[7]	X		X		X		X		X		X				X
Weight	X		X		X		X		X		X	X	X	X	X
Tanner Staging[7]	X		X		X		X		X		X		X		X
Physical Examination	X				X		X				X[12]				X[12]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Open-Label Period[1]											Off-Drug Follow-up Period			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:															
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[8]	X				X		X		X		X		X		X
Laboratory Testing[9]															
Hematology	X		X		X		X		X		X	X	X		X
Blood Chemistry	X		X		X		X		X		X	X	X		X
Pregnancy Test (WOCBP)[8]	X				X		X		X		X		X		Serum
Urinalysis	X				X		X		X		X				X

	Open-Label Period[1]											Off-Drug Follow-up Period			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:															
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Efficacy[9]															
Fasting Triglycerides and Glucose[10]	X		X		X		X		X		X	X	X		X
HbA1c	X				X		X		X		X		X		X
Lipid Panel[10]	X				X		X		X						X
Urine Protein, Creatinine, Albumin	X						X				X				X
Liver MRI (volume/fat content)[11]	X										X				
Whole body DXA[11]	X				X						X				
VCTE[11]	X										X				

	Open-Label Period[1]											Off-Drug Follow-up Period			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:															
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
PK/Biomarker/ Drug Concentration and ADA Samples[9]															
REGN4461 Concentration Blood Sample	X		X		X		X		X		X				X
ADA Sample	X						X				X				X
ANGPTL3, PCSK9, sLEPR	X		X		X		X				X				X

10.9.5. Footnotes for the Schedule of Events Table 7: Open-Label Treatment Period 5

1. During the open-label period, patients will be treated with study drug weekly. Study drug can be administered at the clinical site, by the site personnel or another healthcare professional at a remote location (eg, the patient's home, school, or place of work), or self-administered/administered by a designated person.
   a. If medication is administered by site personnel or another healthcare professional, study personnel will monitor AEs, concomitant medications, menstrual history/pregnancy status reporting/confirmation of contraception **weekly**. Diabetes and lipid medication adjustments must occur **at least once monthly** (see footnote 4).
   b. If patients are self-administering study drug or the study drug is being administered by a designated person, site personnel must assess the patient for AEs, concomitant medications, menstrual history/pregnancy status reporting/confirmation of contraception, and diabetes and lipid medications adjustments must occur **at least once monthly**. These assessments may occur via telephone contact or in-site assessments, at the discretion of the investigator.
2. Training for study drug administration must be performed and documented for all patients who choose to self-administer REGN4461 during OLTP 5. Training is not required for patients who choose to not self-administer study drug. Training may occur at any time during OLTP 5 prior to first self-administration. If an appropriate designee (eg, parent or caregiver) will administer study drug to the patient during OLTP 5, this individual will undergo training as above.
3. A medication administration diary will be provided to the patient/designee prior to initiation of self-administration or administration by a designated person such as a parent or caregiver. The diary must be completed upon each study drug administration. Training on the diary will be provided only to patients which will self-administer REGN4461.
4. [redacted]
5. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
6. Vital signs should be recorded [redacted]

7. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least every 3 months until patient reaches Tanner stage 5.
8. Menstrual events and pregnancy status of WOCBP will be monitored through the EOS visit. A serum pregnancy test will be performed at the EOS visit a urine pregnancy test will be performed locally (e.g, point-of-care). A positive urine pregnancy test should be confirmed with a serum test.
9. Study assessments should be performed, and blood 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.
10. 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.
11. Liver volume and fat content MRI and VCTE may be performed up to 14 days prior to [redacted]. Whole body DXA may be performed up to 14 days prior to [redacted]. If the patient had their [redacted] whole body DXA and/or liver MRI within 28 days prior to [redacted] the applicable procedure does not need to be repeated at [redacted] These tests will only be performed at sites where these techniques are available. Patients may be required to fast at least 5 hours prior to an MRI scan.
12. Complete physical examination will be performed at the EOT and EOS visits and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.

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Approval/eSignature	[redacted] 23-Aug-2022 20:34:35 GMT+0000

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