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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

Compound:	REGN4461
Clinical Phase:	2
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interests and/or its trade secrets including the opportunity to object to such disclosure and/or provide redaction proposals.

AMENDMENT HISTORY

Overall Rationale for Amendment 1

The main purpose of this amendment is to change the SC weekly maintenance dose of REGN4461 from [redacted] mg QW to [redacted] mg QW.

Description of Change	Brief Rationale	Section # and Name
The maintenance dose of REGN4461 has changed from [redacted] mg QW to [redacted] mg QW.	New data from the ongoing REGN4461-GLD-1875 study in patients with generalized lipodystrophy (GLD) have emerged since this protocol was finalized. Lower observed drug concentrations in these patients suggest that GLD patients (who have very low leptin levels) have faster REGN4461 clearance than expected based on the FIH study (REGN4461-HV-1794) that was used as the basis for the PK model in both the familial partial lipodystrophy (FPLD) and GLD studies. Given the uncertainty surrounding PK in patients with FPLD (that share a characteristic with GLD patients of having low leptin levels), and the desire to ensure drug concentrations are in the fully therapeutic range, the dose is being increased to ensure study patients achieve a C_{trough} that saturates target-mediated clearance at approximately the same serum concentrations as targeted with the original dose of [redacted] mg QW. This dose was determined using an updated PK model based on all available data. While excess weight loss is unlikely in FPLD, a dose modification rule was added for the dose to be reduced from [redacted] mg to [redacted] mg during Treatment Period 2 (weeks 13-24) in case of excessive weight loss.	Clinical Study Protocol Synopsis – Treatment Section 1 Introduction Section 3.2.2 Rationale for Dose Selection Section 6.1 Study Description and Duration Figure 2 Study Flow Diagram Section 8.1 Investigational and Reference Treatments Section 8.4.1 Dose Modification

Description of Change	Brief Rationale	Section # and Name
Patients screened under the original protocol may re-screen for HbA1c and triglycerides (the only parameters required to be repeated) before entering the run-in period to reconfirm eligibility if the screening window (up to 10 weeks) has been exceeded.	In the GLD study there were large changes observed in TGs and HbA1c during the screening period. If the screening period is extended, we need to ensure patients still meet the eligibility criteria for the study.	Section 6.1 Study Description and Duration Section 9.1.1 Footnotes for the Schedule of Events Table 1: Screening and Placebo Run-in, Footnote 1 Appendix 1 Hemoglobin A1C, Triglyceride and Leptin Measurements
Removed the sentence that imaging data will be destroyed after 15 years.	Destruction of material after 15 years only applies to biological samples.	Section 9.2.2.11 Assessment of Hepatic Fat Content and Liver Size
The definition of baseline has been added to the Statistical Methods.	The definition was missing in the prior version of the protocol.	Section 11.4 Statistical Methods

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition/Term
ADA	Anti-drug antibody
ADIPO-IR	Adipose Insulin Resistance
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like protein 3
APLD	Acquired partial lipodystrophy
ApoC3	Apolipoprotein C3
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BPI-SF	Brief Pain Inventory – Short Form
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum observed concentration
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
C_{trough}	Trough concentrations
DNA	Deoxyribonucleic acid
DXA	Dual-energy X-ray absorptiometry
EC	Ethics Committee
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcomes Assessment
EDC	Electronic data capture
ELISA	Enzyme Linked Immunosorbent Assay
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FFA	Free fatty acids
FIH	First-in-human
FPLD	Familial partial lipodystrophy
GCP	Good Clinical Practice
GLD	Generalized lipodystrophy

GPS	Global Patient Safety
HADS	Hospital anxiety and depression scale
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LEPR	Leptin receptor
LIPO-IR	Lipoprotein Insulin Resistance Index
LLN	Lower limit of normal
MD	Multiple doses
MMTT	Mixed meal tolerance test
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-derived proton density fat fraction
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NODM	New onset of diabetes mellitus
PBO	Placebo run-in period
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PGIS	Patient Global Impression of Severity
PHQ-8	8-item patient health questionnaire depression scale
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PLD	Partial lipodystrophy
PRO	Patient reported outcome
QoL	Quality of life

QW	Weekly
RBC	Red blood cell
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
rhLeptin	Recombinant human leptin
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short form 36
sLEPR	soluble form of the leptin receptor
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TF	Trunk fat %/leg fat %
TG	Triglyceride
TLR	Trunk to leg fat ratio
TP1	Treatment Period 1
TP2	Treatment Period 2
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized Double-Blind Placebo-Controlled Study of the LEPR Agonist Antibody REGN4461 for the Treatment of Metabolic Abnormalities in Patients with Familial Partial Lipodystrophy
Site Locations	This is a multicenter study that will take place globally.
Principal Investigator	[redacted]
Objectives	Primary Objectives *The primary objectives will be evaluated for patients in cohort A (leptin <8.0 ng/ml) only*: • To evaluate the effect of REGN4461 on fasting triglycerides (TG) in patients with baseline leptin <8.0 ng/mL with elevated baseline fasting TG (>200 mg/dL) • To evaluate the effect of REGN4461 on hyperglycemia in patients with baseline leptin <8.0 ng/mL with elevated baseline hemoglobin A1c (HbA1c; >7.0%) Secondary Objectives *The following secondary objectives of the study will be evaluated for cohort B and for the combined set of cohorts A plus B:* • To evaluate the effect of REGN4461 on fasting TG levels in patients with hypertriglyceridemia (fasting TG >200 mg/dL). • To evaluate the effect of REGN4461 on glycemic control in patients with hyperglycemia (HbA1c >7.0%) *The following secondary objectives of the study will be evaluated for cohorts A and B separately, and for the combined set of cohorts A plus B:* • To evaluate the effect of REGN4461 on liver fat in patients with hepatic steatosis (baseline Hepatic Fat Fraction [Magnetic resonance imaging-derived proton density fat fraction, MRI-PDFF] ≥8.5%) • To evaluate the effect of REGN4461 on hunger • To evaluate safety and tolerability of REGN4461 • To characterize the concentration profile of REGN4461 over time • To assess immunogenicity to REGN4461

Study Design	This is a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of REGN4461 in patients with familial partial lipodystrophy (FPLD) and metabolic abnormalities (elevated fasting TG with or without elevated HbA1c) who are not receiving recombinant human leptin (rhLeptin) therapy. Patients 18 years of age or older with a clinical diagnosis of FPLD will undergo screening, including measurement of HbA1c, fasting TG, and leptin levels. A diagnosis of FPLD requires either a documented ClinVar pathogenic or likely pathogenic variant in a known FPLD gene or pathognomonic regional lipoatrophy by dual-energy X-ray absorptiometry (DXA). In addition, patients must have metabolic abnormalities (hypertriglyceridemia with or without hyperglycemia) and serum leptin level ≤20.0 ng/mL to be included. The study comprises a screening period lasting up to 10 weeks, a 4-week single-blind placebo run-in period (PBO), a 12-week double-blind placebo-controlled treatment period (TP1), a 12-week single-blind treatment period (TP2) during which all patients receive REGN4461, and a 16-week off-drug safety follow-up period. Patients will first be assigned to 1 of 2 cohorts based on baseline leptin levels at screening (cohort A: leptin <8.0 ng/mL; cohort B: leptin 8.0 to ≤20.0 ng/mL). These cohorts will then be randomized 1:1 into the following study arms: • Study arm 1: patients randomized to receive placebo for 12 weeks (TP1) followed by crossover to REGN4461 treatment for 12 weeks (TP2). • Study arm 2: patients randomized to receive REGN4461 treatment for 24 weeks (TP1 and TP2). Randomization will be stratified according to HbA1c at screening (HbA1c ≤7.0% or HbA1c >7.0%) within each cohort.
Study Duration	Study duration is up to 54 weeks.
End of Study Definition	The end of study is defined as the date the last patient either completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size:	Up to 40 patients will be enrolled.
Target Population:	Adult patients with a clinical diagnosis of FPLD, leptin ≤20.0 ng/mL and metabolic abnormalities who are not currently treated with rhLeptin.

Treatment

Study Drug	REGN4461
Dose/Route:	[redacted] mg/kg intravenously (IV) loading dose followed by weekly (QW) doses of [redacted] mg subcutaneously (SC).
Reference Drug **Dose/Route:**	Placebo matching REGN4461 is prepared in the same formulation without the addition of REGN4461.
Schedule:	Single-blind run-in period: All patients will receive an IV placebo infusion, followed by placebo SC QW injections administered subsequently for 3 weeks. Treatment period 1 (TP1): • Study arm 1: IV placebo infusion on day 1 followed by SC QW injections of placebo for 11 weeks starting on day 8 • Study arm 2: IV REGN4461 ([redacted] mg/kg) infusion on day 1 followed by SC injections of REGN4461 ([redacted] mg QW) for 11 weeks starting on day 8 Treatment Period 2 (TP2): • Study arm 1: IV REGN4461 ([redacted] mg/kg) infusion and SC placebo on day 85, followed by SC injections of REGN4461 ([redacted] mg QW) for 11 weeks starting on day 92 • Study arm 2: IV placebo and SC injection of REGN4461 ([redacted] mg) on day 85, followed by SC injections of REGN4461 ([redacted] mg QW) for 11 weeks starting on day 92

Endpoints

Co-Primary:	• Percent change in fasting serum TG from baseline to week 12 in patients with elevated baseline fasting TG (>200 mg/dL) and with baseline leptin <8.0 ng/mL (cohort A) • Absolute change in HbA1c from baseline to week 12 in patients with elevated baseline HbA1c (>7.0%) and with baseline leptin <8.0 ng/mL (cohort A)
Secondary:	*Note: Patients in study arm 1 must meet stability criteria during TP1 (a change in HbA1c ≤0.5 percentage points and a change in TG ≤25%) to be included for specific endpoints as indicated below.* *The following secondary endpoints will be analyzed for cohort B and for the combined set of cohorts A plus B:*

- Percent change in fasting serum TG from baseline to week 12 in patients with elevated baseline fasting TG (>200 mg/dL)
- Absolute change in HbA1c from baseline to week 12 in patients with elevated baseline HbA1c (>7.0%)

The following secondary endpoints will be analyzed for cohorts A and B separately, and for the combined set of cohorts A plus B:

- Percent change in fasting serum TG from baseline to week 12 compared to the percent change between week 12 and week 24 (study arm 1)
- Percent change in fasting serum TG from baseline to week 24 (study arm 2)
- Percent change in fasting serum TG after the first 12 weeks of exposure to REGN4461— from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1; patients must meet stability criteria)
- Change in HbA1c from baseline to week 12 compared to the change between week 12 and week 24 (study arm 1)
- Change in fasting glucose from baseline to week 12 compared to the change between week 12 and week 24 (study arm 1)
- Change in HbA1c from baseline to week 24 (study arm 2)
- Change in fasting glucose from baseline to week 24 (study arm 2)
- Change in HbA1c from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1; patients must meet stability criteria)
- Change in fasting glucose from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1)
- Percent change in liver fat (MRI-PDFF) from baseline to week 12, REGN4461 versus placebo in patients with baseline liver fat (MRI-PDFF) ≥8.5%.
- Percent change in liver fat (MRI-PDFF) from baseline to week 12 compared to the percent change between week 12 and week 24 (study arm 1) in patients with baseline liver fat (MRI-PDFF) ≥8.5%.
- Percent change in liver fat (MRI-PDFF) from baseline to week 24 (study arm 2) in patients with baseline liver fat (MRI-PDFF) ≥8.5%.

	• Percent change in liver fat (MRI-PDFF) from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1) in patients with baseline liver fat (MRI-PDFF) ≥8.5%. • Change on the daily lipodystrophy hunger questionnaire from baseline to week 12 and week 24 • The incidence and severity of treatment-emergent adverse events (TEAEs) • Concentrations of REGN4461 in serum over time • Immunogenicity of REGN4461 as determined by the incidence, titer and clinical impact of treatment-emergent anti-drug antibodies (ADAs) to REGN4461, over time compared to placebo
Procedures and Assessments	The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline characteristics of the study population: medical history, demographics, human immunodeficiency virus (HIV) serology, and hepatitis testing (hepatitis B surface antigen [HBsAg] and hepatitis C virus [HCV]), menstrual history, and pregnancy status. Efficacy procedures include: fasting TG assessment, fasting glucose assessment, HbA1c, fructosamine, insulin, lipid panel, urine creatinine and albumin, insulin sensitivity measurement, lipoprotein analysis by NMR, whole body composition by DXA, bioimpedance, liver volume and fat content by MRI, and patient-reported outcomes. Safety procedures include: body weight, height, vital signs, physical examination, menstrual history/pregnancy status reporting/ confirmation of contraception, and electrocardiogram (ECG). Laboratory procedures include: blood chemistry, hematology, lipid panel, urinalysis, pregnancy testing, and other laboratory testing.
Statistical Plan	No formal statistical hypothesis testing will be performed for this study. The size of the study is determined by feasibility assessments. Due to the limited number of identified PLD patients with low leptin and moderate metabolic abnormalities, up to 40 patients will be enrolled. With a total of 40 patients (20 per cohort, randomized in the ratio of 1:1 into REGN4461 arm and placebo arm), the primary analysis will be carried out on the 20 patients in lower leptin cohort A in TP1. Not all patients will necessarily have HbA1c >7.0%, ie, not all of the patients will be assessed for the HbA1c endpoint. From the feasibility work, it is estimated that 78% of the patients will have elevated baseline HbA1c. With 20 patients in cohort A (10 patients per study arm), the half-width of the 90% confidence

	interval in change from baseline to week 12 between the REGN4461 arm and the placebo arm for HbA1c is 1.4 percentage points, assuming the standard deviation (SD) of 1.81 %. For the TG, the half-width of the 90% confidence interval in logarithm transformed geometric mean ratio (GMR) (REGN4461 week12/baseline divided by placebo week12/baseline) is 0.67, assuming the SD for logarithm transformed fasting TG is 0.87. The SD is estimated from the subset samples of the extracted National Institutes of Health (NIH) study data.

1. INTRODUCTION

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

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

Few therapeutic options are available to patients with metabolic complications caused by PLD and no available treatment targets the underlying lipoatrophy. Treatments for diabetes, hypertriglyceridemia, and fatty liver disease are the same as in patients without lipodystrophy, consisting of lifestyle modifications, anti-diabetic agents (including insulin), and lipid-lowering therapies (eg, statins and fibrates). However, PLD patients with severe metabolic sequelae are often resistant to standard of care treatments. Recombinant methionyl human leptin (metreleptin, Myalept®) is approved in Europe and Japan for the complications of leptin deficiency in patients with PLD, but not in the United States. Early clinical experience demonstrated that a mixed population of lipodystrophy patients (80% PLD) with low leptin (<4 ng/ml) might be more likely to respond to metreleptin therapy (Diker-Cohen, 2015), whereas later studies indicated that PLD patients with higher leptin levels are also likely to respond (Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document METRELEPTIN (BLA STN125390), 2013). Daily dosing of metreleptin is required and adverse effects include risk of immunogenicity with ~85% of patients developing binding antibodies to metreleptin. In clinical trials, ~6% of patients with generalized lipodystrophy developed neutralizing antibodies associated with adverse events (AEs) consistent with loss of endogenous leptin activity (MYALEPT [Package Insert], 2014). Thus, there is an unmet need for effective therapies in PLD that are safer than metreleptin, administered less frequently, and can treat patients who have developed neutralizing antibodies to the only approved therapy, metreleptin.

REGN4461 (IgG4 isotype) is a fully human antibody that binds and activates the leptin receptor (LEPR). REGN4461 is not related to endogenous leptin, and therefore should not have elevated risks of anti-drug antibodies (ADAs) cross-reacting with endogenous leptin.

A 2-part first-in-human (FIH) study of REGN4461 has been completed (R4461-HV-1794, Parts A and B). In Part A, [redacted] were studied.

REGN4461 was generally well-tolerated. In Part B, the effects of REGN4461 on food intake, appetite, body composition, and body weight in overweight or obese subjects with low baseline leptin levels were assessed. In FIH Part B, 12-weeks of REGN4461 treatment was associated with ~2.2% weight loss in cohorts with low baseline leptin levels (<8.0 ng/mL) while patients who received placebo had weight gain of 0.6%. These findings are consistent with prior observations with metreleptin, and with the mechanism of action of REGN4461 as a LEPR agonist.

A phase 2 randomized, double-blind, placebo-controlled study of efficacy and safety of REGN4461 in patients with generalized lipodystrophy (GLD) who are not receiving recombinant methionyl human leptin (rhLeptin, metreleptin) therapy (Study R4461-GLD-1875) is ongoing. In this GLD study, the blinded treatment period consisted of 24 weeks and included three 8-week periods, with each period assigned for patients to receive placebo, low dose or high dose REGN4461. Patients were randomized to 1 of 2 treatment arms. One treatment arm received placebo, low dose and high dose REGN4461 in that sequence. The other arm correspondingly received low dose, high dose and high dose REGN4461. All patients received a single IV loading dose of [redacted] at the beginning of the first treatment period in which they received REGN4461, followed by [redacted]) SC injections that were based on baseline weight. For patients with baseline weight [redacted], the low dose was [redacted]. For patients with weight [redacted], the low dose was [redacted]. The safety and PK data in patients with GLD helped to inform the dose selected for this study, R4461-PLD-20100, in patients with PLD.

Additional clinical experience with REGN4461 comes from the 18-month long treatment of a now 20-year-old female with acquired partial lipodystrophy (APLD) and neutralizing antibodies to metreleptin who is being treated under an individual patient expanded access protocol. The patient had a marked reduction in serum triglycerides (TG), hemoglobin A1c (HbA1c) and hepatic fat following administration of REGN4461 out to 52 weeks of treatment. Specifically her baseline TG were 1288 mg/dL and had been consistently averaging less than 500 mg/dL while her drug concentrations were at levels predicted to be effective. Similarly, her baseline HbA1c was 9.5% and was reduced to 8.0%. Finally, her hepatic fat was 29.9% at baseline and was reduced to 8.0% during treatment with REGN4461.

Based on preclinical and clinical studies performed to-date, it is hypothesized that low-leptin PLD patients will benefit from the LEPR agonist antibody, REGN4461, and therefore PLD patients with a range of lower leptin levels will be enrolled in order to explore the relationship between leptin levels and response to REGN4461 in this study. The primary analysis of this study includes PLD patients with leptin levels <8.0 ng/mL (cohort A). A second cohort of PLD patients with leptin levels 8.0 ng/mL to ≤20.0 ng/mL (cohort B) will also be assessed (separately) given analyses of individualized patient data from the National Institutes of Health (NIH) which indicated patients with leptin level ≤20.0 ng/mL had a better response to metreleptin than did those with leptin level >20.0 ng/mL. A combined analysis of the 2 cohorts will also be performed in order to determine the effect of REGN4461 on endpoints in patients with leptin levels within a broader range (≤20.0 ng/ml). An Investigational Use Only (IUO) assay is being developed for stratification and patient selection purposes; study eligibility and cohort allocation will be determined using the leptin Enzyme Linked Immunosorbent Assay (ELISA) developed and validated under Clinical Laboratory Improvement Amendments (CLIA) guidelines.

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

2. STUDY OBJECTIVES

2.1. Primary Objectives

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

- To evaluate the effect of REGN4461 on fasting TG in patients with baseline leptin <8.0 ng/mL with elevated baseline fasting TG (>200 mg/dL)
- To evaluate the effect of REGN4461 on hyperglycemia in patients with baseline leptin <8.0 ng/mL with elevated baseline HbA1c (>7.0%)

2.2. Secondary Objectives

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

- To evaluate the effect of REGN4461 on fasting TG levels in patients with hypertriglyceridemia (fasting TG >200 mg/dL)
- To evaluate the effect of REGN4461 on glycemic control in patients with hyperglycemia (HbA1c >7.0%)

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

- To evaluate the effect of REGN4461 on liver fat in patients with hepatic steatosis (baseline Hepatic Fat Fraction [Magnetic resonance imaging-derived proton density fat fraction, MRI-PDFF] ≥8.5%)
- To evaluate the effect of REGN4461 on hunger
- To evaluate safety and tolerability of REGN4461
- To characterize the concentration profile of REGN4461 over time
- To assess immunogenicity to REGN4461

2.3. Exploratory Objectives

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

- To evaluate the effect of REGN4461 on insulin sensitivity
- To evaluate the effect of REGN4461 on pain
- To evaluate the effect of REGN4461 on depression
- To evaluate the effect of REGN4461 on anxiety
- To evaluate the effect of REGN4461 on body weight
- To evaluate the effect of REGN4461 on regional body composition
- To evaluate the effect of REGN4461 on Quality of Life (QoL)

- [redacted]
- To determine if bioimpedance measurements can be used as adequate surrogates for dual-energy X-ray absorptiometry (DXA) to measure regional body composition in patients with FPLD

3. HYPOTHESIS AND RATIONALE

3.1. Clinical Hypothesis

There is no statistical hypothesis. The clinical hypothesis is that REGN4461 treatment will be associated with numeric improvements in metabolic abnormalities in FPLD patients with baseline serum leptin levels <8.0 ng/mL.

3.2. Rationale

3.2.1. Rationale for Study Design

Rationale for Selection of Study Population:

This is a randomized, double-blind, placebo-controlled, study of the efficacy and safety of REGN4461 in patients with FPLD and metabolic abnormalities (elevated fasting TG with or without elevated HbA1c) who are not receiving recombinant human leptin (rhLeptin) therapy. The central hypothesis is that LEPR agonism will be effective in treating metabolic complications of leptin deficiency in PLD patients with low baseline leptin levels. This relationship between baseline leptin levels and REGN4461 response was borne out in the FIH R4461-HV-1794 Part B, where patients with leptin levels <5 ng/mL had the most robust response (weight loss), patients with leptin levels 5 ng/mL to 8 ng/mL had an intermediate response, and patients with leptin >8 ng/mL had no response.

The primary analyses of this study, therefore, include PLD patients with leptin levels <8.0 ng/mL (cohort A). A second cohort of PLD patients with leptin levels 8.0 ng/mL to ≤20.0 ng/mL (cohort B) will also be assessed (separately) given analyses of individualized patient data from the NIH which indicated patients with leptin level ≤20.0 ng/mL had a better response to metreleptin than did those with leptin level >20.0 ng/mL. Study eligibility and cohort allocation will be determined using an IUO leptin ELISA.

Partial lipodystrophy includes FPLD and APLD. The majority of patients that were studied in PLD metreleptin trials had FPLD. Acquired PLD patients comprise ~15% of PLD patients. Acquired PLD is thought to be caused by immune destruction of adipocytes. These patients can have one or more autoimmune diseases, eg, Type 1 diabetes, that might confound responses to leptin agonist therapy. For this reason, APLD patients are excluded from enrollment in this study.

Consensus diagnostic criteria for FPLD has been elusive (Brown, 2016). The phenotype of FPLD is similar to “metabolic syndrome” that affects 30% of individuals in the United States (US) (Moore, 2017). The main clinical distinction between common metabolic syndrome and FPLD is the selective loss of adipose tissue in FPLD patients, which can be a subtle and often overlooked physical exam finding. For this reason, regional lipoatrophy and metabolic complications, while not sufficient, are required inclusion criteria in this study.

A documented pathogenic gene variant in an FPLD-associated gene adds additional confidence to the diagnosis of FPLD. Currently Online Mendelian Inheritance in Man has categorized FPLD1-7 of which FPLD2-7 are monogenic and caused by mutations in *LMNA, PPARG, PLIN1, CIDEC, LIPE,* and *CAV1* respectively. Mutations in additional genes such as *PIK3R1, ADRA2A PCYT1A*, *AKT2, ZMPSTE24, PSMB8, WRN, POLD1* and *BLM* have also been associated with FPLD. Of

note, the genetic architecture of FPLD is such that there are a multitude of variants within each gene, each impacting a small number of affected individuals. For the purpose of this protocol a pathogenic variant is defined as a variant that has been rated as pathogenic or likely pathogenic by ClinVar for familial partial lipodystrophy. ClinVar in turn assesses genetic variants using guidelines set forward by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards, 2015). The pathogenicity of genetic variants has been validated by ClinVar for only a small fraction of the genetic variants that have been associated with FPLD in the literature. For this reason, additional objective criteria was introduced based on the defining attributes of PLD: selective loss and altered distribution of body fat. These criteria are based on DXA scans and were formulated using published data for PLD patients (Meral, 2018) alongside large databases of control subjects such as the National Health and Nutrition Examination Survey (NHANES). The DXA-based inclusion criteria quantify the increased ratio of trunk adipose to limb adipose tissue in FPLD subjects. DXA criteria that can discriminate between control and FPLD subjects were established based on the United Kingdom (UK) Biobank dataset and published data (Meral, 2018). The algorithm was tested with the NHANES database and demonstrated a specificity of >99% in females. Next the DXA algorithm was tested on an unpublished dataset from the NIH demonstrating a sensitivity of 95% to 97% in females. A similar approach was used to develop DXA criteria for FPLD in males resulting in similar sensitivity and specificity.

Patients with either moderate abnormalities of both HbA1c (>7.0%) and TG (>200 mg/dL), or a more severe abnormality of TG (>450 mg/dL), with normal or mildly abnormal HbA1c (up to 7.0%) are included. These inclusion criteria are met by the majority of FPLD patients and allow for separate analysis of REGN4461 treatment effects on each metabolic parameter.

The study includes adult patients only. Familial PLD is generally a progressive disease with pubertal onset of fat loss and a long delay between signs/symptoms and diagnosis. As such there is not a large population of pediatric patients with high unmet medical need.

Rationale for Study Endpoints:

The co-primary endpoints are the change in TG from baseline to week 12, and the change in HbA1c from baseline to week 12 in patients in cohort A. These co-primary endpoints were specifically selected because improvements in either or both parameters would help address the highest unmet medical need for PLD patients.

Significant heterogeneity in the response of fasting TG and HbA1c was observed in the metreleptin clinical trials. Given the uncertainty in treatment effect in FPLD patients and the limited number of FPLD patients, secondary endpoints include within-group analyses of all patients receiving their first 12 weeks of REGN4461. This includes individuals in study arm 1 (TP2) and study arm 2 (TP1). In addition, for Study Arm 1, the within group change for TP1 (placebo treatment) will be compared to TP2 (REGN4461 treatment).

The secondary endpoints also include analyses of fasting TG and HbA1c in the higher leptin cohort B. While data from Part B of REGN4461-HV-1794 suggest that a leptin level <8.0 ng/mL might identify individuals most likely to respond, some data suggest response to LEPR agonism in individuals with higher serum leptin, up to 20.0 ng/mL. Analyses of responses in cohort B will therefore allow for more accurate determination of a REGN4461-responsive patient population.

The percent change in hepatic fat (assessed by magnetic resonance imaging-derived proton density fat fraction [MRI-PDFF]) is a key secondary endpoint and the analysis is structured to understand whether there are different responses by cohort. There is 1 published study of the effects of metreleptin on hepatic steatosis in FPLD patients (Simha, 2012). It reported a baseline mean liver hepatic fat of 13.8% with a standard deviation (SD) of 6.1% in 24 patients with FPLD. In this open-label observational study, a 43% reduction in percent hepatic fat (SD of 27%, coefficient of variation of 63%) was reported after 3 months of metreleptin treatment. It is anticipated that REGN4461 will improve hepatic steatosis, similar to what has been observed with metreleptin therapy (Javor, 2005) (Oral, 2002) (Petersen, 2002) (Brown, 2018a) (Brown, 2018b).

While HbA1c provides an excellent estimate of average glucose levels, it does not provide information on insulin sensitivity. Non-invasive measurements of insulin sensitivity will be used including the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which incorporates measures of fasting insulin and glucose. Also 2 additional surrogate measurements of insulin sensitivity will be analyzed. First is the Lipoprotein Insulin Resistance Index (LIPO-IR) which incorporates the amount and size distribution of lipoproteins to estimate insulin sensitivity given the known changes in lipoprotein profiles that occur across a wide range of insulin sensitivity (Shalaurova, 2014). The final surrogate of insulin sensitivity is the Adipose Insulin Resistance (ADIPO-IR), which incorporates fasting serum insulin and free fatty acid (FFA) levels.

FPLD patients are known to suffer from severe hunger, thought to be mediated by leptin deficiency, and this might be improved with REGN4461 treatment. This will be measured using the lipodystrophy hunger questionnaire. In addition to hunger, a number of mental health issues, particularly depression and anxiety have been observed at high rates in lipodystrophy patients (Calabrò, 2020). Regeneron Pharmaceuticals, Inc. (Regeneron) hosted a lipodystrophy patient panel in 2018, consisting mostly of PLD patients, which also identified pain as an important concept to patients. A subsequent interview study with 18 PLD patients also confirmed this feedback. Therefore, to assess whether REGN4461 could impact these patient-centric issues, a number of clinical outcomes assessments (COAs) will be used in this study to assess hunger, pain, QoL, depression and anxiety.

[redacted] It will be important to determine whether this potential weight loss is due to loss of adipose tissue, hepatic fat, or muscle mass. For this reason, body composition (whole-body DXA) will be determined at baseline, at the end of TP1 and TP2. The whole-body DXA provides measures of fat mass, lean mass, and bone mass in different regions of interest including arm, legs and trunk. Arm and leg lean mass is predominantly made up of skeletal muscle and is a good proxy for appendicular muscle mass (Kim, 2002) while a large component of trunk lean mass is organs other than skeletal muscle. In addition, patients will have bioimpedance measurements to assess regional fat and lean mass. The purpose of this is to see if bioimpedance may be used as a surrogate for the "gold standard" DXA body composition inclusion criteria in subjects with PLD in future studies.

Rationale for Selected Elements of Study Design

Screening period (up to 10 weeks duration): There is significant heterogeneity in metabolic abnormalities among PLD patients. One study reported a mean fasting TG in FPLD patients of 1058 mg/dL with a SD of 1745 mg/dL (Ajluni, 2017). Fasting TG are also variable from day to

day within individual patients (Bookstein, 1990). Therefore, the protocol allows for multiple visits within the screening period for measurement of fasting TG and the averaging of multiple fasting TG observations will improve the accuracy of the fasting TG estimate in the baseline period. Leptin levels are also known to be variable and will therefore be measured at least twice during the screening period.

Placebo run-in period: Enrollment in a clinical trial can significantly affect a patient's diet and adherence to standard-of-care diabetes and hyperlipidemia medications, and thus impact study endpoints. In the initial study of metreleptin, as an example, the effect of study enrollment in improvement of TG was nearly as large as the effect of 1-month of metreleptin therapy (Oral, 2002). For this reason, a 4-week placebo run-in will be used so that any enrollment effect on baseline parameters occurs prior to randomization.

Stratification: A randomized and placebo-controlled study design is chosen to test the efficacy of REGN4461 and control for placebo and study effects on diet. Randomization will be stratified by HbA1c (≤7.0% or >7.0%) within each cohort to ensure that baseline HbA1c is similar between study arms, as not all FPLD patients have high HbA1c.

Treatment Periods: Two treatment periods are included to increase the number of patients who receive active study drug while blinded to treatment allocation, and to increase the power to detect within-group treatment effects and evaluate safety/tolerability. An analysis of REGN4461 treatment effects in patients in study arm 1 (placebo during TP1 and REGN4461 during TP2) is therefore included in secondary endpoints. Note that for endpoints evaluated in this manner, the values at the end of TP1 will serve as the beginning measurement for TP2.

The duration of the treatment periods (12 weeks per treatment period) was chosen to provide enough time for the primary metabolic parameters to improve. In one reported study composed of generalized lipodystrophy (GLD) and PLD (36% PLD), initiation of metreleptin improved, and in some patients normalized, fasting glucose and fasting TG within days (Brown, 2018b). In another report of GLD and PLD (70% PLD), the nadir in fasting TG was observed in the first month of metreleptin initiation (Vatier, 2016). Small reductions in HbA1c have been demonstrated within 2-weeks of starting metreleptin treatment (n=15) (Brown, 2018b). Furthermore, in another study 85% of the 12-month effect of metreleptin in HbA1c was observed by 4 months (1.1% reduction at 4 months and 1.4% reduction at 12 months) (Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document METRELEPTIN (BLA STN125390), 2013). A 3-month treatment period is also long enough to see improvements in hepatic steatosis in PLD patients (Simha, 2012) which have been reported to improve within 2-weeks of metreleptin initiation (Brown, 2018b).

Safety follow-up: A 16-week off-drug follow-up period will follow TP2. The length of this period is determined based on clinical and preclinical data suggesting that pharmacodynamic (PD) effects of REGN4461 should persist less than 16-weeks following the final dose. In Part B of REGN4461-HV-1794, subjects who lost weight during 12-weeks of REGN4461 treatment began to regain weight shortly after drug cessation and had returned to their approximate pre-treatment weights by the end of 16 weeks. The maximum observed concentration (C_{max}) of REGN4461 for all subjects 99 days (about 14 weeks) following the final dose was 0.336 mg/L. This concentration is less than the C_{max} of the lowest REGN4461 dose tested in a preclinical murine model of lipodystrophy (0.48 mg/L), which was associated with no significant PD effects (eg, change in

body weight or blood glucose levels). In summary, little to no pharmacological effects are anticipated at the end of the proposed 16-week follow-up.

3.2.2. Rationale for Dose Selection

The REGN4461 dose regimen for this study is a [redacted] mg/kg IV loading dose followed by QW maintenance doses of [redacted] mg SC.

REGN4461 dose levels and dosing frequency have been selected based on PK/ PD analyses of body-weight effect data in healthy cynomolgus monkeys; tolerability, PK, and efficacy data from the FIH study in healthy volunteers (R4461-HV-1794); and preliminary PK and safety data in the phase 2 study in patients with GLD (R4461-GLD-1875).

REGN4461 was well-tolerated in adult volunteers in R4461-HV-1794, with an acceptable safety profile. In this FIH trial, safety, tolerability, and PK were assessed in an initial single ascending dose portion of the trial with doses up to [redacted] In a second portion of this trial (Part B), an exploratory assessment of efficacy was evaluated in otherwise healthy subjects with high body mass index (BMI) and either low (<5.0 ng/mL) or higher (>8.0 ng/mL) leptin levels at baseline under a single regimen of a [redacted] IV maintenance doses administered every 3 weeks for a total of 12 weeks. The results of this study provided evidence of weight loss at trough concentrations (C_{trough}) of REGN4461 (at the end of the dosing interval), ranging between approximately [redacted] mg/L. Additionally, a favorable safety profile was observed across this study. In comparing the concentration-time profiles between subjects with low and high leptin levels at baseline, subjects with low leptin levels tended to have lower systemic REGN4461 concentrations, indicative of faster drug clearance. Based on the totality of these data, the goal of the current dose selection is to achieve and maintain trough concentrations of REGN4461 sufficient to provide efficacy with an appropriate risk/benefit profile. As such, a dosing paradigm targeting a C_{trough} at steady-state ($C_{trough,ss}$) was selected that maximizes target engagement, as determined by predominantly linear elimination and saturation of target-mediated clearance.

In the ongoing study in GLD patients (R4461-GLD-1875), 16 patients have enrolled and have received study drug during the double-blind treatment period at doses up to [redacted] mg SC QW of REGN4461. Of the 16 patients, 8 patients were randomized to receive 8 weeks of placebo followed by 16 weeks of REGN4461, and 8 patients were randomized to receive REGN4461 for the first 24 weeks. As of 28 Mar 2022, total exposure to either REGN4461 or placebo during the double-blind treatment period is approximately 317 patient-weeks. Fifteen patients (93.4%) have entered the open label treatment period and received study drug at doses of either [redacted] mg SC QW (for patients [redacted]) or [redacted] mg SC QW (for patients [redacted]). Total exposure to REGN4461 during the open label treatment period is approximately 249 patient-weeks.

Unblinded data is presented below using a data cutoff of 01 Dec 2021 (n=15).

Two patients (13.3%) experienced a combined total of 4 serious adverse events (SAEs) during periods of exposure to REGN4461, all of which were considered not related to study drug by the Investigator and Sponsor. All SAEs have etiologies that can be attributed to pre-existing conditions.

- Three SAEs (Anastomotic ulcer, Stoma site infection, Acute kidney injury) occurred in a patient with an acquired form of lipodystrophy (which are associated with high rates of autoimmune disease) and pre-existing inflammatory bowel disease complicated by large intestine perforation and ileostomy. The patient developed a stoma ulcer and underwent elective surgery for resection/revision. The stoma site became infected and the patient underwent an elective laparotomy with stoma repositioning. Two weeks later, the patient developed acute kidney failure which was attributed to the laparotomy procedure by the Investigator.
- One SAE (Abdominal pain upper) occurred in a patient with a history of colon perforation requiring colostomy. This patient has congenital GLD type 4 (CGL4), which is characterized by abnormal colonic motility. The patient was admitted to the hospital for IV antibiotics and received an enema for constipation.
- One SAE occurred in a patient with a history of leiomyomas and recurrent uterine polyps who was admitted to the hospital for elective surgery to remove an endometrial polyp.

One patient (6.7%) experienced 3 non-serious TEAEs of severe intensity during periods of exposure to REGN4461, all of which were considered not related to study drug by the Investigator.

- Three severe TEAEs (Electrolyte imbalance, Hypocalcaemia, Acute kidney injury) occurred in a patient who underwent an elective laparotomy for corrective treatment of a stoma infection, described in further detail above, which is considered contributory to these events.

One patient (6.7%) experienced 1 SAE of severe intensity while receiving placebo. This SAE was considered not related to study drug by the Investigator and Sponsor.

- One SAE (Pancreatitis necrotising) occurred in a patient with underlying hypertriglyceridemia. Administration of a mixed meal tolerance test (MMTT) the day prior to event occurrence was considered a potentially contributory factor by the Investigator.

The most commonly reported TEAEs (occurring in ≥2 patients and in no patients while receiving placebo), in patients during periods of exposure to REGN4461 in the double-blind treatment period include Hypoglycaemia (4 patients; 26.7%), Abdominal pain (2 patients; 13.3%), Diarrhoea (2 patients; 13.3%), Fatigue (2 patients; 13.3%), Nasopharyngitis (2 patients; 13.3%), and Thrombocytopenia (2 patients; 13.3%). The most commonly reported TEAEs (occurring in ≥2 patients), in patients in the open-label treatment period is Vomiting (2 patients; 50.0%).

Of the 2 patients who experienced TEAEs of Thrombocytopenia during periods of exposure to REGN4461, a single value (nadir of $158x10^9$/L) below the lower limit of normal (LLN) ($163x10^9$/L) was reported in 1 patient (baseline count of $208x10^9$/L at screening) and persistent values (nadir of $134x10^9$/L) below the LLN were reported in 1 patient (baseline count of $188x10^9$/L at screening). Neither of these patients had decreases in platelet values that would be indicative of a risk of spontaneous bleeding, and neither reported concurrent events of any-cause bleeding.

Hypoglycaemia was monitored as an adverse of event of special interest (AESI) in this patient population, all of whom had pre-existing diabetes requiring insulin therapy. The majority of

hypoglycaemia events reported were of mild intensity and did not meet protocol-specified criteria (<54 mg/dL) to qualify as an AESI. Two patients (13.3%) experienced 3 TEAEs of Hypoglycaemia that met the criteria to qualify as an AESI, none of which were considered related to study drug. Both of these patients experienced hypoglycaemia only during scheduled insulin sensitivity assessments (hyperinsulinemic euglycemic clamp or insulin tolerance test) involving high dose infusion of insulin. Hypoglycaemia events not meeting AESI criteria occurred in 3 patients (20.0%), all of which were symptomatic and corresponded with blood glucose readings between 54-70 mg/dL, and none of which required medical intervention. No patients experienced a TEAE of Hypoglycaemia while receiving placebo.

To date, no safety signals or concerns have been identified from the ongoing review of safety data from R4461-GLD-1875.

To aid in the transition from an all IV dosing paradigm used in the FIH study (Part B) to SC dosing for maintenance following the initial IV loading dose, a Population PK model utilizing all existing REGN4461 concentration data was employed. Using this model, a [redacted] mg/kg IV loading dose was chosen to rapidly achieve target steady-state trough concentrations that should maximize target engagement, estimated as approximately [redacted] mg/L.

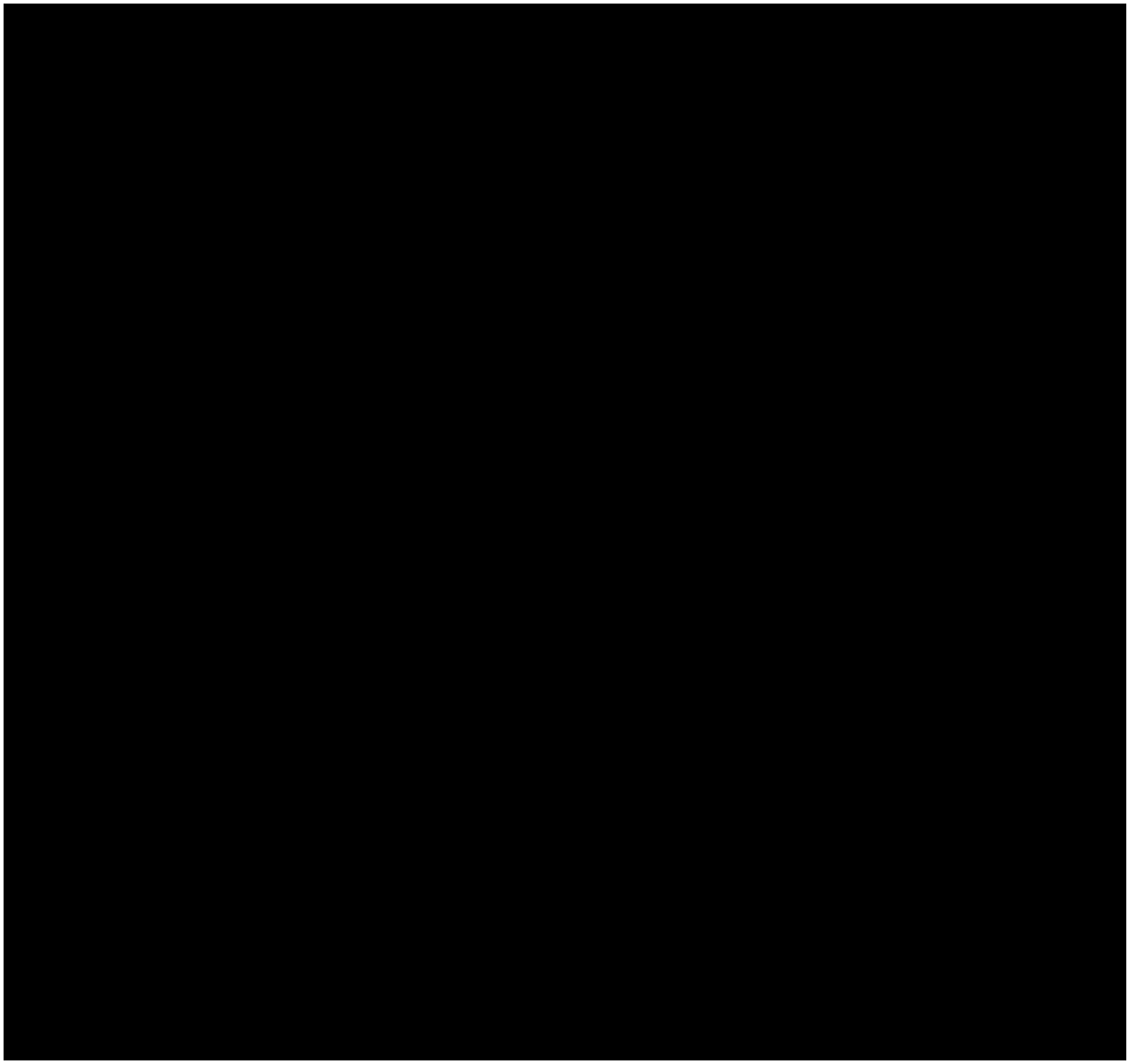
Emerging PK data from the ongoing GLD study (R4461-GLD-1875; data cut-off date of 01 Dec 2021) were assessed. The low dose (ie, [redacted] mg or [redacted] mg SC QW for body weights of [redacted] and [redacted], respectively) was predicted to achieve C_{trough} of approximately [redacted] mg/L while the high dose (ie, [redacted] mg or [redacted] mg SC QW for body weights of [redacted] and [redacted], respectively) was predicted to achieve C_{trough} of approximately 100 mg/L. However, the observed C_{trough} concentrations from this GLD study demonstrated lower than predicted values (Figure 1). The Population PK model was refined to include these emerging PK data. The refined model demonstrated faster clearance in GLD, suggesting that the REGN4461 target-mediated clearance is faster in GLD patients than previously estimated for low leptin overweight/obese healthy subjects (Study R4461-HV-1794) presumably due to higher expression of LEPR. Therefore, the dose regimen for this PLD study was revised to [redacted] mg SC QW based on the refined Population PK assuming clearance values similar to those observed for GLD to achieve the C_{trough} of [redacted] mg/L as originally intended for this protocol. To guard against the theoretical concern of excess weight loss with a LEPR agonist, a dose modification rule has been incorporated to allow a reduction of dose in individual patients that experience excess weight loss during the second treatment period. Recognizing that PLD patients may have heterogenous LEPR expression, unlike the GLD patients, the dose modification to [redacted] mg SC QW will allow for mitigation of excess weight loss if experienced by PLD patients. The [redacted] mg SC weekly dose of REGN4461 is being administered to a compassionate use patient with PLD, resulting in steady state trough concentrations of REGN4461 of approximately [redacted] mg/L.

Predicted area under the curve ($AUC_{cumulative}$) over the entire 24-week on-treatment period for patients receiving active treatment throughout (study arm 2) [redacted] of the $AUC_{cumulative}$ at the no observed adverse effect level (NOAEL) estimated from a PK model derived from 3 preclinical toxicology studies in cynomolgus monkeys. In the FIH study (Study R4461-HV-1794), single doses of up to [redacted] IV every 3 weeks for 3 doses following a [redacted] were administered to healthy subjects and overweight/obese subjects, respectively. The mean C_{max} values following the [redacted] were >7-fold and >2-fold

higher, respectively, than predicted mean C_{max} for the [redacted] mg SC QW dose regimen proposed for this study. The mean C_{trough} concentrations following the [redacted] mg/kg IV MD ranged from 60.7 mg/L to 160 mg/L across cohorts, and, therefore, were approximately 0.6-fold to 1.6-fold the predicted mean C_{trough} for the [redacted] mg SC QW dose regimen proposed for this study. REGN4461 was well tolerated in Study R4461-HV-1794 at these exposures.

Given the existing clinical and non-clinical safety data, the risk/benefit, and the observed trend of lower systemic concentrations in subjects with low leptin levels, a dosing regimen predicted to achieve exposures within the range associated with efficacy is supported.

Figure 1: Preliminary Mean (±SD) Concentrations of Total REGN4461 in Serum by Nominal Time and Treatment Arm in Patients with Generalized Lipodystrophy (Study R4461-GLD-1875; PKAS)



[redacted]

3.2.3. Rationale for Analysis

The primary analyses are between-group comparisons (change in REGN4461 arm between baseline and week 12 versus change in placebo arm between baseline and week 12). The HbA1c and TG endpoints will be analyzed only in those individuals with corresponding pre-specified elevated baseline values. This will maximize our ability to determine treatment effects in a small study with heterogeneous baseline characteristics and inclusion criteria (Section 7.2.1).

3.3. Risk-Benefit

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

3.3.1. Risk-Benefit of REGN4461

As part of its therapeutic benefits, REGN4461 is expected to increase insulin sensitivity in patients with FPLD. If FPLD patients are taking medications with the potential to cause hypoglycemia (insulins or sulfonylureas), a rapid improvement in insulin sensitivity could result in hypoglycemia if the doses of insulin and sulfonylurea are not adjusted properly during the study. With any study involving diabetics there is a chance of hyperglycemia as well. For this reason, adverse events of special interest (AESIs) related to hypoglycemia, new onset of diabetes mellitus (NODM), and the development of new or worsening autoimmune disease have been defined for this study and require expedited reporting to the Sponsor (see Section 10.1.3 for a detailed description).

However, the potential benefits of REGN4461 to improve metabolic abnormalities in patients with FPLD outweighs these potential risks. A risk-benefit statement with respect to the overall development program is provided in the latest version of the Investigator's Brochure.

4. ENDPOINTS

4.1. Primary Endpoints

The co-primary endpoints are:

- Percent change in fasting serum TG from baseline to week 12 in patients with elevated baseline fasting TG (>200 mg/dL) and with baseline leptin <8.0 ng/mL (cohort A)
- Absolute change in HbA1c from baseline to week 12 in patients with elevated baseline HbA1c (>7.0%) and with baseline leptin <8.0 ng/mL (cohort A)

4.2. Secondary Endpoints

Note: Patients in study arm 1 must meet stability criteria during TP1 (a change in HbA1c ≤0.5 percentage points and a change in TG≤25%) to be included for specific endpoints as indicated below.

The following secondary endpoints will be analyzed for cohort B and for the combined set of cohorts A plus B:

- Percent change in fasting serum TG from baseline to week 12 in patients with elevated baseline fasting TG (>200 mg/dL)
- Absolute change in HbA1c from baseline to week 12 in patients with elevated baseline HbA1c (>7.0%)

The following secondary endpoints will be analyzed for cohorts A and B separately, and for the combined set of cohorts A plus B:

- Percent change in fasting serum TG from baseline to week 12 compared to the percent change between week 12 and week 24 (study arm 1)
- Percent change in fasting serum TG from baseline to week 24 (study arm 2)
- Percent change in fasting serum TG after the first 12 weeks of exposure to REGN4461— from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1; patients must meet stability criteria)
- Change in HbA1c from baseline to week 12 compared to the change between week 12 and week 24 (study arm 1)
- Change in fasting glucose from baseline to week 12 compared to the change between week 12 and week 24 (study arm 1)
- Change in HbA1c from baseline to week 24 (study arm 2)
- Change in fasting glucose from baseline to week 24 (study arm 2)
- Change in HbA1c from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1; patients must meet stability criteria)
- Change in fasting glucose from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1)

- Percent change in liver fat (MRI-PDFF) from baseline to week 12, REGN4461 versus placebo in patients with baseline liver fat (MRI-PDFF) ≥8.5%.
- Percent change in liver fat (MRI-PDFF) from baseline to week 12 compared to the percent change between week 12 and week 24 (study arm 1) in patients with baseline liver fat (MRI-PDFF) ≥8.5%.
- Percent change in liver fat (MRI-PDFF) from baseline to week 24 (study arm 2) in patients with baseline liver fat (MRI-PDFF) ≥8.5%.
- Percent change in liver fat (MRI-PDFF) from baseline to week 12 (study arm 2) and from week 12 to week 24 (study arm 1) in patients with baseline liver fat (MRI-PDFF) ≥8.5%.
- Change on the daily lipodystrophy hunger questionnaire from baseline to week 12 and week 24
- The incidence and severity of treatment-emergent adverse events (TEAEs)
- Concentrations of REGN4461 in serum over time
- Immunogenicity of REGN4461 as determined by the incidence, titer and clinical impact of treatment-emergent ADAs to REGN4461, over time compared to placebo

4.3. Exploratory Endpoints

Note: All exploratory endpoints will be analyzed for cohorts A and B separately as well as the combined set of cohorts A plus B.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demographics (eg, age, race, weight, height, etc), disease characteristics (including fasting glucose, HbA1c, fasting insulin, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], fasting TG, total cholesterol, leptin levels, BMI, percentages of body fat and liver fat, trunk/leg fat ratio derived from DXA [TLR; trunk fat %/leg fat %], FPLD type [or gene/variant], HOMA-IR, FFA, and ADIPO-IR), medical history (eg, diabetes, hypertriglyceridemia, nonalcoholic fatty liver disease [NAFLD]), and medication history (including lipid modifying therapies and control of diabetes) for each patient.

5.2. Efficacy Variables

Efficacy variables include TG, HbA1c, fasting glucose, fasting TG, liver fat content (MRI-PDFF), and lipodystrophy hunger questionnaire outcomes.

5.3. Safety Variables

Safety variables include AEs, body weight, vital signs, 12-lead electrocardiogram (ECG), physical examination, and laboratory safety tests.

5.4. Pharmacokinetic Variables

The PK variable is the concentration of total REGN4461 at each time point. Samples in this study will be collected using a sparse sampling schedule, eg, only 1 blood sample for drug concentration measurement is collected at any single clinic visit, except on day 1 and day 85, corresponding to study drug infusions where multiple samples will be taken on the same day.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples in this study will be collected at the clinic visits.

5.6. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and biomarker variables include markers of insulin sensitivity, perception of pain, symptoms of depression and anxiety, body weight, regional body composition, perception of quality of life, potential biomarkers of safety and efficacy of REGN4461 administration (ie, markers of insulin resistance, hepatic steatosis, and hypertriglyceridemia including ANGPTL3 and ApoC3), and fat measures and fat ratios as measured by bioimpedance and DXA.

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of REGN4461 in patients with FPLD and metabolic abnormalities (elevated fasting TG with or without elevated HbA1c) who are not receiving rhLeptin therapy.

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

The study comprises a screening period lasting up to 10 weeks, a 4-week single-blind placebo run-in period (PBO), a 12-week double-blind placebo-controlled treatment period (TP1), a 12-week single-blind treatment period (TP2) during which all patients receive REGN4461, and a 16-week off-drug safety follow-up period (Figure 2). All study drug will be given by study staff and not administered by the patient.

Screening period (up to 10 weeks duration); day -98 up to day -29

Patients will undergo screening assessments as per the Schedule of Events (Table 1) to determine their eligibility. These include, but are not limited to a whole-body DXA scan, HbA1c, fasting TG and leptin levels. Patients will have repeated assessments of fasting TG and leptin given their biological variability as detailed in Appendix 1 and summarized below:

- Initially, 2 measurements of fasting TG levels will be performed. If the 2 measurements are concordant (fall into the same TG range: (i) less than or equal to 200 (ii) greater than 200 and less than or equal to 450 (iii) greater than 450 mg/dL) the measures will be sufficient to determine eligibility; if they are discordant, a third measure will be obtained and the geometric average of the 3 measures will determine patient eligibility.
- Initially, 2 measurements of leptin levels will be performed. If the 2 measurements are concordant (fall into the same leptin range: (i) less than 8.0 (ii) greater than or equal to 8.0 and less than or equal to 20.0 (iii) greater than 20.0 ng/mL) the measures will be sufficient to determine patient disposition; if they are discordant, a third measure will be obtained and the arithmetic average of the 3 measures will determine patient disposition. Patients will be assigned to a cohort based on the mean baseline leptin levels (<8.0 ng/mL [cohort A] or 8.0 to 20.0 ng/mL [cohort B]; Section 6.1.1).
- For those patients screened and found eligible under the original protocol, HbA1c and triglycerides assessments will be repeated to reconfirm eligibility of the patient if the screening window of 10 weeks has been exceeded by the time the relevant approvals for Protocol Amendment 1 are in place. Patients screened under the original protocol who do not enter the placebo run-in period within the prescribed visit window will not be considered screen failures, nor will they be considered a deviation provided repeat HbA1c and triglycerides are obtained prior to initiating the placebo run-in as part of Amendment 1. Note: patients who enter screening under the amendment will be

required to adhere to the 10-week screening schedule or it will be considered a deviation.

4-week single blind placebo run-in period (PBO); day -28 to day -1

All patients who meet eligibility criteria will receive placebo by IV infusion on day -28, followed by SC QW injections of placebo starting at day -21. Patients will be observed at least 4 hours after IV infusion to maintain study blinding. Fasting lipid and glucose levels will be collected weekly. Patients will receive training on electronic COA (eCOA) using a device to record COA measures such as hunger, pain, QoL, depression, and anxiety disorders. Patients will undergo baseline body composition by DXA and bioimpedance. Additionally, 2 baseline assessments of liver volume (MRI) and liver fat content (MRI-PDFF) will be performed; the first and second MRI must be performed on separate days.

12-week double-blind placebo-controlled treatment period (TP1); Day 1 until week 12

Baseline testing occurs in the screening period and the placebo run-in period (see Table 1). After baseline testing, patients in each cohort will be randomized 1:1 to study arm 1 (placebo in TP1 and REGN4461 in TP2) or study arm 2 (REGN4461 in TP1 and TP2), and stratified based on screening HbA1c (HbA1c ≤7.0% or HbA1c >7.0%) within each cohort.

On day 1, the first dose will be administered IV ([redacted] mg/kg REGN4461 or placebo) and patients will be observed for at least 4 hours. Starting on day 8, patients will receive matched volumes of SC administered REGN4461 ([redacted] mg QW) or placebo, respectively, once weekly for a total of 11 SC doses. Fasting blood draws will be taken every 2 weeks according to Table 2.

During the final 2 weeks of TP1, fasting blood draws will be performed weekly (weeks 10, 11, 12). The mean (geometric for TG and arithmetic for all other measures) of these 3 measurements will be taken as the end measure of TP1 and beginning measurement for TP2. Bioimpedance will be assessed during a mandatory in-clinic study visit (week 12). At the end of TP1, patients will undergo liver MRI and whole-body DXA.

12-week single-blind treatment period (TP2); Day 85 until week 24

On day 85 (week 12), patients will receive double-blind dosing in order to maintain blinding to study arm assignment and will then be observed for at least 4 hours:

- Study arm 1: IV loading dose of REGN4461 ([redacted] mg/kg) followed by SC placebo;
- Study arm 2: placebo IV infusion followed by SC REGN4461 ([redacted] mg).

Starting at week 13, REGN4461 ([redacted] mg SC QW) will be administered in a single-blind manner to patients in both study arms (patient remains blinded to treatment allocation). Fasting TG and glucose measurements will occur every 2 weeks through week 20 (Table 2). During the final 2 weeks of TP2, fasting blood draws will be performed weekly (weeks 22, 23, 24). The mean (geometric for TG and arithmetic for all other measures) of these 3 measurements will be taken as the end measure of TP2. Bioimpedance will be assessed during the mandatory in-clinic visit (week 24). At week 24, patients will undergo liver MRI and whole-body DXA.

16-week off-drug safety follow-up period; Day 169 until week 40

This period will be used to monitor efficacy (glycemic, lipid parameters, daily lipodystrophy hunger patient reported outcome [PRO]), safety (hematology, chemistry, urinalysis, vital signs and AEs), PK and PD assessments as REGN4461serum concentrations decline.

All non-mandatory in-clinic outpatient visits are eligible for home nursing visits if the service is supported in the relevant country/location of the site and will be referred to as 'remote visits'; the patient can use this service for all or some of the eligible visits.

Figure 2: Study Flow Diagram

6.1.1. Description of Study Cohorts

The study will enroll 2 cohorts:

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

Cohort assignment is based on at least 2 and at maximum 3 leptin measurements obtained during the screening period.

Patients in each cohort will be randomized 1:1 to a study arm and stratified based on screening HbA1c (HbA1c ≤7.0% or HbA1c >7.0%).

- Study arm 1: patients randomized to placebo for 12 weeks who will crossover to REGN4461 for 12 weeks
- Study arm 2: patients randomized to receive REGN4461 for 24 weeks

The total planned enrollment is 40 patients: 20 patients in each cohort (A and B); and 10 patients within each study arm (1 and 2) per cohort.

6.1.2. End of Study Definition

The end of study is defined as the date the last patient either completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

No formal interim analysis will be performed in the study. Periodic data reviews may be performed by selected unblinded Sponsor physicians and a statistician with no direct involvement in the study. A first-step analysis will occur after the last patient completes week 12.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

A total of 40 patients are planned, with 20 patients per cohort (A and B). Each cohort will be randomized 1:1 into study arm 1 or study arm 2.

7.2. Study Population

Adult patients with a clinical diagnosis of FPLD, leptin ≤20.0 ng/mL and metabolic abnormalities who are not currently treated with rhLeptin.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female, ≥18 years of age at the screening visit.
2. Clinical diagnosis of familial partial lipodystrophy:
   a) Altered body fat distribution including lipoatrophy at one or more sites, as determined by physical examination

   AND

   b) Metabolic sequelae of partial lipodystrophy, as evidenced by a medical history of at least 1 of the following:
      i) Fasting hypertriglyceridemia as evidence by multiple readings >150 mg/dL
      ii) Diabetes as evidenced by American Diabetes Association criteria
      iii) Hepatic steatosis as evidenced by liver ultrasound (Grade II-III) or MRI-PDFF (>5.6%)

   AND EITHER (c) or (d)

   c) History of known pathogenic mutation in an FPLD-related gene (Section 3.2.1)
   OR
   d) [redacted]
3. Fasting leptin level ≤20.0 ng/mL

Note: Refer to Appendix 1 for actions based on leptin results.

4. Presence of significant metabolic abnormalities satisfying 1 of the following:
   a) HbA1c >7.0% AND fasting TG >200 mg/dL

   OR

   b) Fasting TG >450 mg/dL

5. Stable body weight within the 3 months prior to screening (no gain or loss of >5% current weight)
6. Stable diet during the past 3 months defined as no major change in macronutrient composition (eg, starting or stopping diets such as Adkins, Paleo, Vegetarianism, Veganism).
7. No clinically meaningful change in diabetes medication regimen in the 3 months prior to screening (addition, subtraction, or change in dosing). Changes in insulin dosing within 3 months are allowed if the change is <30% of the total daily dose.
8. No clinically meaningful change (addition, subtraction, or dose change) in medications for hyperlipidemia taken by prescription or over the counter (including fish oil or niacin) for the past 3 months prior to screening.
9. Willing and able to comply with clinic visits and study-related procedures.

   Note: patients incapable of completing COA assessments or unable to undergo MRI will not be excluded.
10. Provide informed consent signed by study patient or legally acceptable representative.

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Treatment with metreleptin within 3 months of the screening visit
2. Patients with a diagnosis of generalized lipodystrophy
3. Patients with a diagnosis of acquired lipodystrophy
4. Patients with a medical history of bone marrow transplant, use of an immune check-point inhibitor, or central nervous system tumor involving the hypothalamus.
5. Patients with clinically significant hematologic abnormalities such as neutropenia, lymphopenia, or lymphadenopathy at screening
6. Treatment with over-the-counter or prescription medications for weight loss begun within 3 months prior to the screening visit
7. Treatment with oral glucocorticoids >7.5 mg prednisone equivalents per day or plans to begin treatment with oral glucocorticoids >7.5 mg prednisone equivalents per day during the study period
8. Treatment with oral estrogens begun within 6 months prior to the screening visit
9. Any malignancy, eg, lymphoma, within the past 1 year, prior to screening visit except for fully treated basal cell or squamous epithelial cell carcinomas of the skin or carcinoma in situ of the cervix or anus
10. Estimated glomerular filtration rate (GFR) of <30 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation at screening
11. History of heart failure hospitalization, myocardial infarction, stroke, clinically-significant arrhythmia (eg, ventricular tachycardia, or any arrhythmia requiring medication adjustment

to control), transient ischemic attack, unstable angina, percutaneous or surgical revascularization procedure (coronary, carotid, or peripheral vascular), or intracardiac device placement (eg, pacemaker) within 3 months before the screening visit

12. Advanced heart failure (New York Heart Association Class 3 to 4) or severe and uncontrolled hypertension at screening
13. Current diagnosis of Type 1 diabetes mellitus
14. History of human immunodeficiency virus (HIV) or HIV seropositivity at screening visit
15. Uncontrolled infection with hepatitis B or hepatitis C infection or known active tuberculosis at screening.

    Patients will be tested for hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening. Patients with hepatitis B (HBV sAg+) who have controlled infection (serum HBV DNA polymerase chain reaction (PCR) that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA per local standards. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug. Patients who are hepatitis C virus antibody-positive (HCVAb+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.
16. A patient who has a documented, positive reverse-transcriptase polymerase chain reaction (RT-PCR) or serology test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be enrolled provided the patient has: (A) Recovered from COVID-19 (all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient should be resolved), and (B) Had 2 negative results from a health authority-authorized nucleic acid amplification (PCR) test for SARS-CoV-2 taken at least 48 hours apart, or (C) Documented vaccination.
17. Participation in any clinical research study evaluating an investigational product (IP) or therapy within 3 months and less than 5 half-lives of IP prior to the screening visit. Participation in clinical research studies that only involve procedures (eg, muscle biopsies, glycemic clamps) or testing (eg, MRI) that will not interfere with the current study is permitted.
18. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study
19. Alcohol consumption >21 drinks per week for males or >14 drinks per week for females
20. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor.
21. Pregnant or breastfeeding women.
22. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the beginning of the placebo run-in period, during the

study, and for at least 16 weeks after the last dose. Highly effective contraceptive measures include:

a. Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable), associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening

   Note: If patients are using oral estrogen hormonal contraception, they must have initiated it at least 6 months prior to the screening visit.

b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
c. bilateral tubal ligation;
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
e. sexual abstinence†, ‡.

*WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as age >50 years old and with no periods for 12 months.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

23. Sexually active adult men who are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period and for 16 weeks after the last dose of study drug: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for 16 weeks after the last dose of study drug.

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination (ET) visit, and associated end of treatment (EOT) assessments, as described in Section 9.1.3.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.4.2.

7.4. Replacement of Patients

Patients prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable patients. The Medical/Study Director, in cooperation with the Study Biostatistician, will decide whether to replace a withdrawn patient.

Patients enrolled and withdrawn from the study any time prior to randomization will not be considered evaluable for assessment and will be replaced with another patient. All patients who have received a dose of study drug will be included in an as treated analysis.

If a patient is replaced after randomization, the replacement patient will receive the randomization assignment of the patient s/he is replacing.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The REGN4461 dose regimen for this study is [redacted] mg/kg IV followed by doses of [redacted] mg SC QW. Placebo product to match to REGN4461 is prepared in the same formulation without the addition of REGN4461. All administration of REGN4461 or placebo is to be performed by study staff and no self-administration of REGN4461 or placebo will occur.

Dosing Schedule:

- **Single-blind run in:** all patients will receive an IV placebo infusion on day -28, followed by placebo SC QW injections administered subsequently for 3 weeks starting on day -21.
- **Treatment period 1**:
  - Study arm 1: IV placebo infusion on day 1 followed by SC QW injections of placebo for 11 weeks starting on day 8
  - Study arm 2: IV REGN4461 ([redacted] mg/kg) infusion on day 1 followed by SC injections of REGN4461 ([redacted] mg QW) for 11 weeks starting on day 8
- **Treatment Period 2:**
  - Study arm 1: IV REGN4461 ([redacted] mg/kg) infusion followed by SC placebo on day 85, followed by SC injections of REGN4461 ([redacted] mg QW) for 11 weeks starting on day 92
  - Study arm 2: IV placebo followed by SC injection of REGN4461 ([redacted] mg) on day 85, followed by SC injections of REGN4461 ([redacted] mg QW) for 11 weeks starting on day 92

Investigational drug formulation and instructions on dose preparation are provided in the pharmacy manual for in-clinic visits and in the nursing manual for remote visits.

8.2. Run-in Treatment

There will be a 4-week single-blind placebo run-in period (day -28 to day -1). At the beginning of the placebo run-in period, patients will receive an IV placebo infusion, followed 1 week later by SC QW injections of placebo, administered for 3 weeks.

8.3. Background Treatment

Standard of care for metabolic abnormalities including stable (ie, no changes within the past 3 months of the screening visit) medications for diabetes and hyperlipidemia.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

After treatment period 1, REGN4461 dose level may be decreased from [redacted] mg to [redacted] mg if the following criteria are met:

1. for patients with baseline BMI >20: either BMI<20 kg/m^2 OR weight loss >10%
2. for patients with baseline BMI ≤20: in the opinion of the study investigator the weight loss is adverse

For patients with BMI >20 kg/m^2, any decision to decrease the dose level will be made by the Sponsor, in discussion with the investigator.

If a patient's dose is reduced from [redacted] mg to [redacted] mg, their dose cannot be increased during TP2.

8.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug before entering TP1 (day 1) will be contacted to assess any adverse events (AEs) but will not be asked to return for the remaining study visits.

Patients who permanently discontinue from study drug after entering TP1 should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.3.

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Confirmation of pregnancy as evidenced by a positive serum pregnancy test
- Serious or severe allergic reactions considered related to study drug
- Severe liver injury or dysfunction for which no other reason can be found to explain, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. Liver injury is defined as follows:
- For individuals with normal baseline transaminase and liver enzyme levels:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN) or
  - ALT or AST >5X ULN on consecutive visits at least 2 weeks apart or
  - ALT or AST >3X ULN and total bilirubin >2X ULN (or international normalized ratio [INR] >1.5)
- For individuals with abnormal baseline transaminase and liver enzyme levels:
  - ALT or AST >3X over baseline and total bilirubin >2X over baseline (or INR >1.5)

- Patient withdraws consent
- Investigator's clinical judgment that it is in the best interest of the patient

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action in the patient's best interest and as clinically indicated. However, the Regeneron medical monitor should be contacted as soon as possible. Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical monitor.

A special case for temporary discontinuation of study drug relates to a positive urine pregnancy test If there is a positive urine pregnancy test, a confirmatory serum pregnancy test will be performed. Study treatment will not be administered until a negative serum pregnancy test is obtained. If the serum pregnancy test is negative the patient can continue in the study. A positive serum pregnancy test will result in permanent discontinuation of study drug administration.

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.5. Management of Acute Reactions

8.5.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.2.4) and graded using the grading scales as instructed in Section 10.3.1.

8.5.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.5.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.5.2. Acute Injection Reactions

8.5.2.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.3.1.

Acute systemic reactions following injection of study drug by SC administration should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.5.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.3.1.

8.6. Method of Treatment Assignment

All patients will enter a 10-week screening period during which screening assessments will be performed, including fasting TG and leptin levels, to determine eligibility. All eligible patients will enter the 4-week single-blind placebo run-in period. Upon completion of the 4-week run-in period, up to 40 patients will be randomized in a 1:1 ratio to study arm 1 (placebo in TP1 and REGN4461 in TP2) or study arm 2 (REGN4461 in TP1 and TP2) according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to HbA1c levels (HbA1c ≤7.0% or HbA1c >7.0% at the screening visit) within each cohort.

8.7. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Investigators and the sponsor will be blinded to specific endpoints, including, but not limited to HbA1c, fasting glucose, fasting TG and other lipids, and MRI imaging, for the entire length of the treatment period (up to week 24).

Selected individuals not involved in the conduct of the study may have access to unblinded data, as needed, for safety review or other data review.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.4.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IVRS/IWRS, which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment

assignment. In the event there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed/returned to the sponsor or designee.

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.10. Concomitant Medications and Procedures

Any treatment administered and/or procedures (eg, vaccination, apheresis) performed from the time of informed consent to the end of the follow-up period will be considered concomitant medication and/or procedures, respectively. This includes medications and/or procedures that were started before the study and are ongoing during the study.

Every attempt should be made to keep concomitant medications, including over-the-counter medications and dietary supplements, stable throughout the entire duration of the study, unless in

the judgement of the treating physician a safety concern warrants medication addition, discontinuation, or a dose modification.

Documentation of concomitant medications and/or procedures, including medication dosing, will occur at the time points specified in Table 1 and Table 2. Changes in concomitant medication and procedures that occur during the course of the study must be recorded.

8.10.1. Prohibited Medications

Prohibited medications are:

- Recombinant human leptin (metreleptin, Myalept®), starting 3 months prior to study start and throughout the duration of the study
- Treatment with over-the-counter or prescription medications for weight loss begun within 3 months prior to the screening visit

8.10.2. Permitted Medications

All medications except those listed in Section 8.10.1 are permitted.

Diabetes medications: If a patient is taking diabetes medications at the beginning of the study, study drug will be added to existing therapy. Insulin and insulin secretagogues (eg, sulfonylureas) may be decreased in dose or discontinued in response to low blood glucose levels (fasting glucose <90 mg/dL), a large and clinically-significant decrease in fasting blood sugar (eg, 50% decrease in fasting glucose from prior values) signs/symptoms consistent with hypoglycemia, or if a safety concern arises. Otherwise, all attempts should be made to continue the patient's current diabetes medication regimen. New hyperglycemia requiring medical treatment (rescue therapy) should be managed with insulin and reported as an AESI according to Section 10.2.3.

New hyperglycemia requiring treatment is defined as follows:

Fasting glucose ≥250 mg/dL on 2 occasions including symptoms consistent with hyperglycemia AND increase in fasting glucose >50 mg/dL above baseline

The insulin dose used will be determined by the treating physician after careful review of the patient's diabetes history and prior diabetes treatment history, and all treatment decisions will be recorded.

Lipid-lowering medications: If a patient is taking lipid-lowering medications at the beginning of the study, study drug will be added to existing therapy. No changes (addition, discontinuation, or dose adjustments) to lipid lowering medications (prescription or over the counter and including fish-oil and niacin) should be made during the course of the study, unless needed for safety.

Glucocorticoids are permitted so long as the patient has been on a low dose (ie, ≤7.5 mg prednisone equivalents daily) which has been stable for 6 months prior to screening, with no plans for increasing the dose during the study.

Oral estrogens are permitted as long as they have been initiated at least 6 months prior to the screening visit. Estrogens are permitted for routes other than oral.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

Study assessments and procedures are presented by study period and visit in Table 1 and Table 2.

Table 1: Schedule of Events: Screening and Placebo Run-In

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

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

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

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

9.1.1. Footnotes for the Schedule of Events Table 1: Screening and Placebo Run-in

1. Patients may be re-screened if they fail the screening for reasons related to incidental or transitory conditions (eg, medication use, concomitant illness, medical condition). If patients are re-screened within the original 10-week screening period, only screening test(s) (eg, an out-of-range lab value) that resulted in initial screen failure should be repeated. All patients will be monitored for 4 hours following IV placebo infusion to maintain study blinding. For those patients screened and found eligible under the original protocol, HbA1c and triglycerides assessments will be repeated to reconfirm eligibility of the patient if the screening window of 10 weeks has been exceeded by the time the relevant approvals for Protocol Amendment 1 are in place.
2. Procedures may be conducted on different days during the screening period, if needed. Blood draws for laboratory testing at the screening visit will be collected in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
3. Procedures may be conducted by trained study staff at a remote location (ie, at home visits, work, and/or school).
4. Visit 2 has to occur at least 7 days after visit 1. Visit 3 is conditional upon the results of results from visit 1 and visit 2. Visit 3 may not be required in all patients depending on the results from visit 1 and visit 2.
5. Medical history should include detailed lipodystrophy history including prior medication/IPs, genetic diagnosis (if known), and results of any previous anti-metreleptin antibody testing (if applicable).
6. Monitoring by qualified study personnel may be performed as a telephone contact or an in-clinic or inpatient assessment. A telephone contact may be converted to an in-person site visit if in the opinion of qualified study personnel that a direct, in-person assessment would aid assessment of safety or clarify concomitant medication use and adjustment. For diabetic patients, all monitoring assessments will include asking about symptoms of hypoglycemia (per local standards), a review of the patient's home glucometer readings (if applicable), and patient education regarding the importance of blood glucose monitoring and how to recognize symptoms of hypoglycemia (per local standards). Diabetic patients should be reminded to call the site if any signs or symptoms of hypoglycemia occur.
7. All safety assessment should be performed before study drug administration.
8. Vital signs should be recorded prior to IV study drug infusion, and approximately 120 minutes post-IV infusion or prior to SC study drug injection.
9. Body weight should be measured with patient in a gown after voiding (empty bladder) using a calibrated scale. Patients should empty pockets and remove shoes, belts, outer-layer clothing, or any other heavy wearable prior to being weighed.
10. The ECG can be performed up to 24 hours prior to study drug administration.
11. Blood (for safety, efficacy and biomarkers) and urine samples are to be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately

before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure.

12. If there is a positive urine pregnancy test, a confirmatory serum pregnancy test will be performed. Study treatment will not be administered until a negative serum pregnancy test is obtained. If the serum pregnancy test is negative the patient can continue in the study. A positive serum pregnancy test will result in permanent stopping of study drug administration.
13. Please refer to Appendix 1 for actions based on Hb1Ac, TG, and leptin results.
14. Patients must be in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
15. Patients must receive eCOA training at the time they receive the eCOA device.
16. Two DXA scans will be performed as follows: Screening DXA will be performed at either visit 1 or visit 2. The second DXA will be performed during the run-in period and can be performed from day -28 to day 1 prior to dosing of study drug. Two baseline liver volume and liver fat content MRI-PDFF scans will be obtained from day -28 to day 1 prior to dosing. These 2 MRI-PDFF scans must be performed on separate days at least 24 hours apart and up to a maximum of 28 days apart. Patients may be required to fast at least 5 hours prior to the scans.
17. DNA should be collected at visit 1, but can be collected at any visit after obtaining consent.

Table 2: Schedule of Events: TP1, TP2 and Off-Drug Follow up

Study Period	Double Blind Treatment Period (TP1)												Single Blind Treatment Period (TP2)												EOT/ET[12]	Off-Drug Safety Follow up Period			EOS
	In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit	In-Clinic Outpatient visit or Remote visit											In-Clinic Outpatient visit				
Visit Number:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Day:	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	197	225	253	281
±visit window (d):		±3	±3	±3	±3	±3	±3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7	± 7
Week:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40
Patient Disposition																													
Randomization[1]	X																												
Treatment																													
Administer Study Drug (REGN4461/Placebo)[2] (IV)	X												X																
Administer Study Drug (REGN4461/Placebo)[2] (SC)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Concomitant Medications and Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

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

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

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

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

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

Abbreviations: ADA=antidrug antibodies; ANGPTL3=angiopoietin-like protein 3; BPI-SF=brief pain inventory – short form; DNA=deoxyribonucleic acid; DXA=dual-energy X-ray absorptiometry; EOS=end of study; EOT=end of treatment; ET=early termination; HADS=hospital anxiety and depression scale;

HbA1c=hemoglobin A1c; HDL-C=high density lipoprotein cholesterol; IV=intravenous; LDL-C=low density lipoprotein cholesterol; MRI=magnetic resonance imaging; NMR=nuclear magnetic resonance; PK=pharmacokinetic; SC=subcutaneous; sLEPR=soluble leptin receptor; WOCBP=women of childbearing potential

9.1.2. Footnotes for the Schedule of Events Table 2: TP1, TP2 and Off-Drug Follow-Up

1. Randomization can occur within 24 hours prior to day 1 study drug administration if necessary.
2. All patients will be monitored for 4 hours following infusion on day 1 and day 85. For patients undergoing apheresis, study drug will be administered after the apheresis procedure.
3. Monitoring by qualified study personnel may be performed as a telephone contact or an in-clinic or inpatient assessment. A telephone contact may be converted to an in-person site visit if in the opinion of qualified study personnel a direct, in-person assessment would aid assessment of safety or clarify concomitant medication use and adjustment. For diabetic patients, all monitoring assessments will include asking about symptoms of hypoglycemia (per local standards), a review of the patient's home glucometer readings (if applicable), and patient education regarding the importance of blood glucose monitoring and how to recognize symptoms of hypoglycemia (per local standards). Diabetic patients should be reminded to call the site if any signs or symptoms of hypoglycemia occur.
4. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
5. Vital signs should be recorded prior to IV study drug infusion, and approximately 120 minutes post-IV infusion (on day 1 and day 85) and prior to SC study drug injection (on day 85).
6. 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.
7. Study assessments, urine, and blood (safety, efficacy and biomarkers) samples will be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments, urine, and blood samples will be collected immediately before the lipid-apheresis procedure.
8. If there is a positive urine pregnancy test, a confirmatory serum pregnancy test will be performed. Study treatment will not be administered until a negative serum pregnancy test is obtained. If the serum pregnancy test is negative, the patient can continue in the study. A positive serum pregnancy test will result in permanent stopping of study drug administration.
9. 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.
10. Liver volume (MRI) and liver fat content (MRI-PDFF) and whole body DXA scans may be performed up to14 days prior to visits 20 and 32. Patients may be required to fast at least 5 hours prior to the scans.

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

9.1.3. Early Termination Visit

Patients who withdraw from the study will be asked to return to the clinic for 2 visits: an EOT/ET visit and an end of study visit. The EOT/ET visit should take place within 5 days of treatment discontinuation, if possible. A final end of study visit should take place with assessments 16 weeks after the last dose of study drug as described in Table 2.

Patients who have discontinued study drug but who remain in the study will enter the off-drug follow-up period (Table 2) after completing the early termination visit. In the off-drug follow-up period, patients will continue with monthly visits until 16 weeks after last dose of study drug. Each of these monthly visits will consist of safety assessments, including laboratory tests.

Sexually active patients who discontinue the study prematurely should be reminded to maintain highly effective contraceptive measures for 16 weeks after the last dose of study drug.

9.1.4. Unscheduled Visits

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

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: medical history, demographics, HIV serology, and hepatitis testing (HBsAg, HCV).

9.2.2. Efficacy Procedures

9.2.2.1. Fasting Triglycerides

Samples should be collected after the patients have fasted for at least approximately 12 hours. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Sample times are provided in Table 1 and Table 2.

9.2.2.2. Fasting Glucose

Samples should be collected after the patients have fasted for at least approximately 12 hours. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Sample times are provided in Table 1 and Table 2.

9.2.2.3. Hemoglobin A1C

Hemoglobin A1C will be collected at visits according to Table 1 and Table 2.

9.2.2.4. Fructosamine

Samples for fructosamine will be collected at visits according to Table 1 and Table 2.

9.2.2.5. Insulin

Samples for insulin will be collected at visits according to Table 1 and Table 2.

9.2.2.6. Lipid Panel

Samples for lipid panel LDL-C, HDL-C, total cholesterol, and Apolipoprotein B will be collected at visits according to Table 1 and Table 2. For patients with TG >400 mg/dL, direct LDL-C measurement will be used. While the standard lipid panel measures the concentrations of these lipoproteins, lipoprotein size will be analyzed by NMR in a separate sample.

Samples should be collected after the patients have fasted for at least approximately 12 hours. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.

9.2.2.7. Urine Creatinine and Albumin

Samples for urine creatinine and albumin will be collected at visits according to Table 1 and Table 2.

9.2.2.8. Insulin Sensitivity Measurement

Insulin sensitivity will be assessed using non-invasive measurements of insulin sensitivity including the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) which incorporates measures of fasting insulin and glucose. [redacted] Samples for fasting glucose and insulin, and free fatty acids will be collected at visits according to Table 1 and Table 2.

9.2.2.9. Assessment of Body Composition

Whole body DXA imaging will be performed per the schedule outlined in Table 1 and Table 2. Patients may be required to fast at least 5 hours prior to the DXA scan. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. In addition to standard body composition parameters from DXA, a trunk/leg fat ratio (TLR) will be calculated as trunk fat%/leg fat%.

9.2.2.10. Bioimpedance

Bioimpedance will be assessed for all patients according to Table 1 and Table 2 .

9.2.2.11. Assessment of Hepatic Fat Content and Liver Size

Patients will undergo MRI scans to examine hepatic volume and fat content. Liver fat content analysis (MRI-PDFF) will be performed only at sites with advanced liver fat quantitation capability. Patients for whom MRI is contraindicated (eg, pacemaker) are still eligible to participate in the study but will not undergo MRI scans.

MRI will be performed per the schedule outlined in Table 1 and Table 2.

Patients may be required to fast at least 5 hours prior to an MRI scan. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Details of the MRI imaging protocol are included in the imaging manual.

Imaging data may be utilized for future biomedical research of REGN4461, GLD, and related diseases. The results of these future biomedical research analyses will not be presented in the clinical study report.

Note: The imaging scans in this study are performed for research purposes only. These research imaging scans are not intended to provide diagnosis of any disease. If any clinically significant findings are detected during the course of this study by the site's radiologist, the investigative site/investigator should comply with any country, local or institutional requirements and standard of care guidelines in communicating these findings to the study patient.

9.2.3. Safety Procedures

9.2.3.1. Body Weight and Height

Body weight will be assessed using calibrated scales according Table 1. Patients should void (empty bladder) prior to weight assessment. Patients should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

For measuring height, patients will be instructed to remove footwear and stand upright with their heels together. BMI will be calculated based on weight and height.

9.2.3.2. Vital Signs

Vital signs, including temperature, blood pressure, pulse and respiration will be collected after the patient has been sitting or in a supine position at time points according Table 1.

9.2.3.3. Physical Examination

A thorough and complete physical examination including waist and hip circumference will be performed at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.4. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 1 and Table 2. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT and QTcF intervals will be recorded. The ECG strips or reports will be retained with the source.

9.2.3.5. Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception

Assessment of menstrual cycle history for WOCBP will be conducted at baseline and at the visits specified in Table 1 and Table 2, to identify any changes in occurrence, frequency, or duration following study drug treatment.

9.2.3.6. Hypoglycemia Monitoring

It is recommended that all diabetic patients prescribed insulin or insulin secretagogues (eg, sulfonylureas or glinides) should be instructed to routinely monitor finger stick blood glucose using a glucometer.

Monitoring by qualified study personnel may be performed as a telephone contact or in-clinic assessment at the visits specified in Table 1 and Table 2. A telephone contact may be converted to an in-person site visit if in the opinion of qualified study personnel that a direct, in-person assessment would aid assessment of safety or clarify concomitant medication use and adjustment. For diabetic patients, all monitoring assessments will include asking about symptoms of hypoglycemia (per local standards), a review of the patient's home glucometer readings (if applicable), and patient education regarding the importance of blood glucose monitoring and how to recognize symptoms of hypoglycemia (per local standards). Diabetic patients should be reminded to call the site if any signs or symptoms of hypoglycemia occur.

9.2.4. Laboratory Testing

Detailed instructions for sample collection, along with the location for analysis, are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 1 and Table 2. On study visit days during which study drug will be administered, the laboratory samples are to be collected before the dose of study drug unless otherwise stated.

Fasting is only required for laboratory tests described as "fasting" (eg, fasting TG, fasting lipid panel, and fasting glucose).

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen (BUN)	Creatine phosphokinase (CPK)
Carbon dioxide	Aspartate aminotransferase (AST)	Gamma-glutamyl transferase (GGT)
Calcium	Alanine aminotransferase (ALT)	Gamma-glutamyl transferase (GGT)
Fasting Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes

White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose
Clarity	Blood
pH	Bilirubin
Specific gravity	Leukocyte esterase
Ketones	Nitrite
Protein	WBC

Fasting Lipid Panel

LDL-C	Apolipoprotein B
HDL-C	Triglycerides
Total Cholesterol	

Other Laboratory Tests

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

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.5. Clinical Outcomes Assessments

9.2.5.1. Lipodystrophy Hunger Questionnaire

The lipodystrophy hunger questionnaire was developed in order to assess hunger related behaviors among patients with lipodystrophy and was developed in accordance with the Food and Drug

Administration's (FDA's) guidance on PRO development. Patients will complete the PRO assessments daily. The Hunger questionnaire is self-administered and contains 4 items.

9.2.5.2. Brief Pain Inventory – Short Form Questionnaire

The BPI-SF measures pain and its interference with daily lives. It is a self-administered measure which consists of 15 items. There are 4 pain questions, measured on a 0 to 10 scale, where 0 is "no pain" and 10 is the "pain as bad as you can imagine." There are 7 interference questions, where 0 is "does not interfere" and 10 is "completely interferes." The remaining items are not numerically scored. There is no scoring algorithm, but "worst pain" or the arithmetic mean of the 4 severity items can be used as measures of pain severity; the arithmetic mean of the 7 interference items can be used as a measure of pain interference.

9.2.5.3. Short Form – 36

The Short Form – 36 Survey (SF-36) is a 36-item self-administered PRO measure assessing health-related quality of life (HRQoL) concepts relevant across age, disease, and treatment group. The SF-36 assesses physical functioning, limitations due to physical health bodily pain, general health, vitality, social functioning, limitations due to emotional problems, and mental health. Patients answer questions assessing these concepts over the previous week using 3-, 5-, or 6-point Likert scales; scores range from 0 to 100, with higher scores indicating better health.

9.2.5.4. Patient Health Questionnaire-8

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

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

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

9.2.5.5. Hospital Anxiety and Depression Scale Questionnaire

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

9.2.5.6. Patient Global Impression of Severity-Hunger

The Patient Global Impression of Severity (PGIS) – Hunger is a self-administered PRO assessing the patient's perception of their overall severity of hunger. The PGIS is not an efficacy measure; rather, it is an anchor-based assessment used to interpret meaningful change of the Hunger PRO.

9.2.5.7. Patient Global Impression of Severity- Pain

The PGIS – Pain is a self-administered PRO assessing the patient's perception of their overall severity of pain. The PGIS is not an efficacy measure; rather, it is an anchor-based assessment used to interpret meaningful change of the BPI-SF.

9.2.5.8. Patient Global Impression of Change- Hunger

The Patient Global Impression of Change (PGIC) – Hunger is a self-administered PRO assessing the patient's perception of their overall change in hunger since the beginning of the study. The PGIC is not an efficacy measure; rather, it is an anchor-based assessment used to interpret meaningful change of the Hunger PRO.

9.2.5.9. Patient Global Impression of Change- Pain

ThePGIC– Pain is a self-administered PRO assessing the patient's perception of their overall change in pain since the beginning of the study. The PGIC is not an efficacy measure; rather, it is an anchor-based assessment used to interpret meaningful change of the pain via the BPI-SF.

All COAs will be performed as outlined in Table 1 and Table 2.

9.2.6. Drug Concentration and Measurements

[redacted]

9.2.7. Immunogenicity Measurements and Samples

[redacted]

9.2.8. Pharmacodynamic and Exploratory Biomarker Procedures

[redacted]

9.2.8.1. Soluble LEPR (sLEPR)

Leptin circulates in the bloodstream both as a free entity and also can be bound to an sLEPR, which is generated via shedding of the LEPR ectodomain (Sinha, 1996) (Lammert, 2001). Soluble LEPR

is present in circulation of healthy subjects and patients with disease. It is a non-signaling form of the leptin receptor that is able to bind to leptin and may regulate its bioavailability (Lou, 2010). It is possible that REGN4461 bioavailability might be influenced by sLEPR levels. It is also possible that sLEPR levels might be influenced by REGN4461, either through increasing sLEPR stability or shedding from LEPR. Therefore, sLEPR will be assessed at time points noted in Table 1 and Table 2.

9.2.8.2. Angiopoietin-Like Protein 3 (ANGPTL3)

Angiopoietin-like protein 3 is an endogenous inhibitor of lipoprotein lipase, which regulates circulating levels of TG and LDL-C (Tikka, 2016). Levels of ANGPTL3 can be regulated by feeding, leptin, and/or insulin (Minicocci, 2012) (Nidhina Haridas, 2015). Levels of ANGPTL3 are elevated in patients with lipodystrophy and are reduced after treatment with metreleptin(Muniyappa, 2017). The reduction of ANGPTL3 following metreleptin treatment might affect lipase clearance of TG-rich lipoproteins. Therefore, ANGPTL3 might be a PD marker of REGN4461 activity, increasing leptin receptor signaling. ANGPTL3 will therefore be assessed at time points noted in Table 1 and Table 2. Modulation of ANGPTL3 is an exploratory measure.

9.2.8.3. Apolipoprotein C3 (APOC3)

Apolipoprotein C3 is an abundant lipoprotein in the blood and found on chylomicrons, VLDL, LDL and HDL particles. APOC3 is synthesized and secreted by hepatocytes in the liver, inhibits lipoprotein lipase and hepatic lipase, and modulates many known cardiovascular disease risk factors inclusive of atherosclerosis and coronary heart disease. APOC3 will be measured in blood from samples collected at timepoints indicated in Table 1 and Table 2. Modulation of APOC3 by REGN4461 activity is an exploratory measure.

9.2.8.4. Free Fatty Acids

Free Fatty Acids (FFA) represent metabolic byproducts of long-chain molecules from lipid-carboxylic acids in fat and other tissues. Free Fatty Acids will be measured in blood from samples collected at timepoints indicated in in Table 1 and Table 2. Modulation of FFA by REGN4461 is an exploratory measure.

9.2.9. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional samples will be collected for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.10. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction

should be collected on day 1/baseline (predose; Table 1), but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of PLD and related diseases. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses with which the sponsor is unable to comply, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN4461, other PLD clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of PLD as well as related lipodystrophic and metabolic diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or PLD and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all AEs occurring during the study data collection, from the time of signing the informed consent form (ICF) to the end of the study (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on serious adverse events (SAEs) (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All adverse events (serious and non-serious) must be reported to the sponsor with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event.

- **SAEs**.
- **Selected Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Hypoglycemia, defined as blood glucose <54 mg/dL, regardless of symptoms.
  - NODM

For patients with no diabetes at baseline:

a. Two values of fasting (≥8 hours) plasma glucose ≥126 mg/dL (7.0 mmol) during the treatment period

   OR

b. Two values of HbA1c ≥6.5% (48 mmol/mol) during the treatment period

   Patients who meet either of these criteria during the placebo run-in period will be considered to have diabetes at baseline.

   - Hyperglycemia requiring treatment, defined as:

a. HbA1c ≥10.5% AND increase in HbA1c of ≥1.5% from baseline value

   OR

b. Fasting glucose ≥250 mg/dL on 2 occasions including symptoms consistent with hyperglycemia AND increase in fasting glucose >50 mg/dL above baseline

   - Development of new or worsening of autoimmune disease

- Moderate or severe hypersensitivity reactions
- Moderate or severe infusion reactions

Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 16 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.
- **Symptomatic Overdose**: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

For the AESIs based on a laboratory value, the AESI must be reported to Sponsor within 24 hours once the investigator confirms the abnormal laboratory value.

10.1.4. Other Adverse Events of Special Interest that Do Not Require Expedited Reporting to Sponsor

Although these AESIs do not require expedited reporting to the sponsor, the following events are of interest and will involve the collection of additional details in separate CRFs:

- Injection site reaction due to study treatment administration
- Mild infusion reactions due to study treatment administration
- Mild hypersensitivity reactions due to study treatment administration

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).

- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest for this study are detailed in Section 10.1.3.

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.3.1.

10.3. Evaluation of Severity and Causality

10.3.1. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

Mild: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

Severe: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

10.3.2. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical

judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

Include the following when applicable] For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.4. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety (GPS); Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.5. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN4461), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (REGN4461) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

No formal statistical hypothesis testing will be performed for this study. Based on the sample size, the analysis will be focused on estimation of the treatment effect.

11.2. Justification of Sample Size

The primary objective is to estimate the treatment effect of REGN4461 on glycemic and lipid parameters. The co-primary endpoints are the percent change in TG and change in HbA1c from baseline to week 12 between the placebo and REGN4461 arms in cohort A.

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

With a total of 40 patients (20 per cohort, randomized in the ratio of 1:1 into the REGN4461 arm and the placebo arm), the primary analysis will be carried out on the 20 patients in the lower leptin cohort A in TP1. The fact that it is unlikely that all of the patients will have HbA1c >7.0%, ie, not all of the patients will be assessed for the HbA1c endpoint, has also been accounted for. From the feasibility work, it is estimated that 78% of the patients will have elevated baseline HbA1c. With 20 patients in cohort A (10 patients per study arm; Table 3), the half-width of the 90% confidence interval in change from baseline to week 12 between the REGN4461 arm and the placebo arm for HbA1c is 1.4 percentage points, assuming the SD of 1.81%. For TG, the half-width of the 90% confidence interval in logarithm transformed geometric mean ratio (GMR) (REGN4461 week12/baseline divided by placebo week12/baseline) is 0.67, assuming the SD for logarithm transformed fasting TG is 0.87. The SD is estimated from the subset samples of the extracted NIH study data.

Table 3: Half-Width of the 90% Confidence Interval for Primary Endpoints

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

*Assuming 78% of the patients have elevated baseline HbA1c.

**The estimate of treatment effects for drug for HbA1c are -1.18%, and -52% for fasting TG. After adjusting for placebo effect, the between-group treatment effect estimate for HbA1c are -0.98%, and -47% for fasting TG. Assuming SD for HbA1c is 1.81%, and logarithm transformed fasting TG is 0.87 (SD of HbA1c and fasting TG is extracted from NIH study data).

†Assuming all patients have baseline HbA1c >7.0% and TG >200 mg/dL.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients who received any study drug and have at least 1 post-baseline assessment; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug.

11.3.4. Immunogenicity Analysis Set

The ADA analysis set includes all patients who received study drug and had at least 1 non-missing ADA result following the first dose of study drug.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, SD, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category. Unless otherwise specified, baseline is defined as the last available measurement obtained before the first dose of double-blind study drug.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who have signed the ICF
- The total number of randomized patients that received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The co-primary endpoints are the percent change in fasting serum TG from baseline to week 12 and the absolute change in HbA1c from baseline to week 12 between REGN4461 and the placebo arm in cohort A (leptin <8.0 ng/mL) patients. The glycemic endpoint will be evaluated in the subset of patients with baseline HbA1c > 7.0%. The fasting TG endpoint will be evaluated in the subset of patients with baseline TG >200 mg/dL. Logarithm transformation will be performed to normalize the fasting TG.

Summary statistics including the mean change (or percent change) from baseline, standard error (SE), corresponding 95% confidence interval, and nominal p-value will be provided by treatment group, using a mixed effect repeated measurement model (MMRM), which will account for the missing data. Nominal p-values will be provided as a measure of the strength of evidence. The model includes the factors (fixed effects) for treatment, week, randomization strata (screening HbA1c ≤7.0% or HbA1c >7.0%), strata-by-week interaction, and treatment-by-week interaction. Relevant baseline HbA1c, and/or TG will be included as a continuous covariate. Log-transformed TG will be transformed into percentage for presentation.

A non-parametric ranked analysis of covariance (ANCOVA) will be performed for the percent change in fasting serum TG from baseline to week 12 as a sensitivity analysis. The ranked ANCOVA model will be able to provide significance of the treatment effect as compared to placebo. Nominal p-values will be provided as a measure of the strength of evidence. Median treatment difference and 95% confidence interval can be derived from the Hodges-Lehmann estimation and Moses distribution free confidence interval respectively.

For the co-primary endpoints, mean changes (±SE) will be plotted over time by the treatment group. A spaghetti plot will be provided for co-primary endpoints by the treatment group. The intra-subject and inter-subject variability may be evaluated if data is appropriate.

11.4.3.2. Secondary Efficacy Analysis

For the secondary analysis, the change from baseline to week 12 will be compared to the change between week 12 and week 24 for study arm 1 to evaluate the treatment effect of REGN4461 on HbA1c and fasting TG.

For continuous secondary endpoints measured in the double-blind period, summary statistics, including the mean (or median) change from baseline, SE, 95% confidence interval, and nominal p-value when appropriate will be provided using the MMRM or ranked ANCOVA (fasting TG only). Descriptive statistics may be provided by subtype of PLD mutations.

For categorical secondary endpoints, appropriate tests, eg,: Fisher's exact test, will be used to evaluate the treatment effect.

In addition to the summary statistics described above, mean changes (±SE) will be plotted over time by the treatment group. A spaghetti plot will be provided for co-primary endpoints by the treatment group.

When combining patients from study arm 1 and study arm 2 for determining within-group effects after 12 weeks of REGN4461 treatment, patients in study arm 1 will only be included if they meet

stability criteria for TP1 (when they are receiving placebo). The stability criteria are a change in HbA1c ≤0.5 percentage points and a change in TG ≤25%.

11.4.4. Control of Multiplicity

Not applicable.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the last dose of study drug plus 7 days.
- The posttreatment period is defined as the end of the on-treatment period to the last study visit.

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

TEAEs will be summarized for each of the following periods: double-blind treatment period, single-blind treatment period, follow-up period, and combined across the treatment periods and follow-up period. Adverse events that occur prior to treatment period 1 (day 1) will be listed.

Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- Overview of TEAEs, ie, overall number (%) of patients with any TEAE, related TEAEs, serious TEAE, TEAEs leading to death, TEAEs leading to study discontinuation, or AESIs
- All TEAEs by primary SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.3.1), presented by SOC and PT
- TEAEs by causality relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs by primary SOC and PT
- Treatment-emergent AESIs
- Treatment-emergent AEs leading to discontinuation by primary SOC and PT
- Treatment-emergent SAEs leading to death, by primary SOC and PT

Deaths and other SAEs will be summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

11.4.5.3. Treatment Exposure

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

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

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

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

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

11.4.5.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

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

The treatment compliance will be presented by specific ranges for each treatment group and study period. The ranges of interest will be specified in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Descriptive statistics of concentrations of total REGN4461 in serum will be presented at each sampling time point. Plots of individual concentrations of total REGN4461 in serum will be presented by actual time point. Plots of summary statistics of individual concentrations of total REGN4461 in serum will be presented by nominal time point. No formal statistical analysis will be performed.

11.4.6.2. Analysis of Pharmacokinetic Parameters

Pharmacokinetic parameters may include, but are not limited to, the following:

- C_{max} – peak concentration
- C_{trough} – pre-dose concentrations both prior to and at steady-state

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses <9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
  - Persistent Response – Treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)

– High (titer >10,000)

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by patient, time point, and dose cohort/group will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Descriptive statistics of biomarkers by study visit and by treatment group will be generated. Summary statistics of biomarkers including mean and medians will be evaluated for change from baseline through the end of study.

11.5. Interim Analysis

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

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC), Medidata Rave.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- eCOA system – capture COA

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents,

that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each patient screened in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting

pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized Double-Blind Placebo-Controlled Study of the LEPR Agonist Antibody REGN4461 for the Treatment of Metabolic Abnormalities in Patients with Familial Partial Lipodystrophy and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. HEMOGLOBIN A1C, TRIGLYCERIDE AND LEPTIN MEASUREMENTS

HbA1c and TG

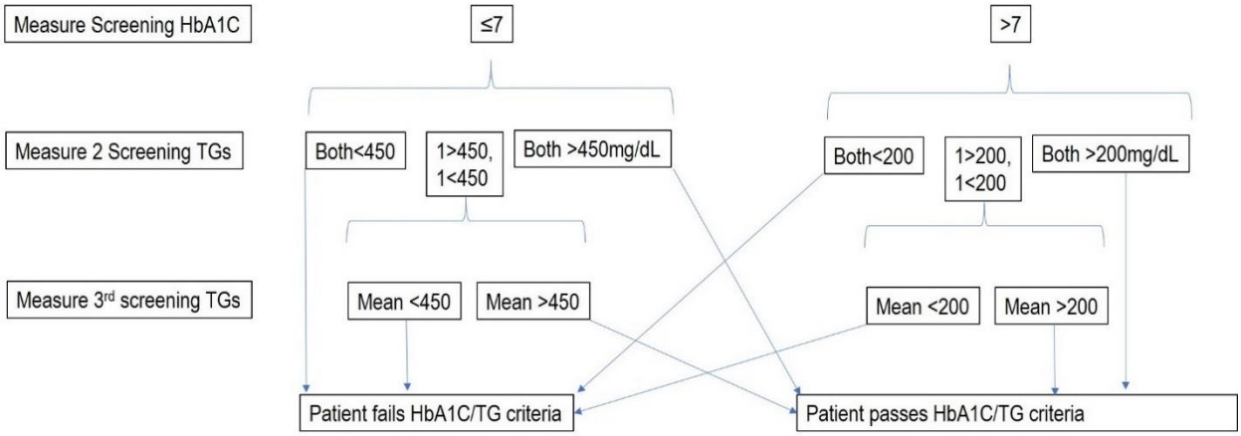
The actions taken based on triglycerides (TG) will depend on the screening hemoglobin A1C (HbA1c), as presented in Figure 3 and described below. Two fasting TG tests will be performed during the screening period.

If the HgbA1C is >7.0 and both screening TG>200 mg/dL, the patient will screen pass. If HbA1c is >7.0 and both screening TG<200 mg/dL, the patient will screen fail. If the HbA1c is >7.0 and 1 screening TG is >200 and the other is <200 mg/dL, a third screening TG will be obtained to determine the geometric mean of the three fasting triglyceride values. If the geometric mean TG is >200 mg/dL, the patient screen-passes and if the geometric mean TG is <200 mg/dL, the patient screen fails.

If HbA1c is <7.0% and both screening TG >450 mg/dL, the patient screen passes. If HbA1c <7.0% and both screening TG <450 mg/dL, patient screen fails. If HbA1c is <7.0% and 1 screening TG is >450 mg/dL and the other screening TG is <450 mg/dL, a third screening TG will be obtained, and the geometric mean of the 3 fasting TG values will be determined. If the geometric mean is >450 mg/dL, the patients screen passes and if the geometric mean <450 mg/dL, the patient screen fails.

For those patients screened and found eligible under the original protocol, screening triglycerides assessments will be repeated if the screening window of 10 weeks has been exceeded before the beginning of the placebo run-in period (visit 4). Visit 4 cannot occur until the relevant approvals for Protocol Amendment 1 are in place.

Figure 3: Screening Triglyceride and Hemoglobin A1c Measurements



Leptin

Two tests of leptin will be performed with an Investigational Use Only (IUO) Enzyme Linked Immunosorbent Assay (ELISA). If the 2 leptin levels are concordant for the 3 leptin ranges being considered (<8.0 ng/mL for cohort A, 8.0 to ≤20.0 ng/mL for cohort B, >20.0 ng/mL: not qualifying for study) the appropriate action will be taken based on that range (assigned to cohort A, B, or screen fail). If the 2 leptin values are discordant (fall in different ranges), a third leptin

level will be obtained, and the appropriate action will be taken on the arithmetic average of the 3 leptin levels.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Randomized Double-Blind Placebo-Controlled Study of the LEPR Agonist Antibody REGN4461 for the Treatment of Metabolic Abnormalities in Patients with Familial Partial Lipodystrophy

Protocol Number: R4461-PLD-20100

Protocol Version: R4461-PLD-20100 Amendment 1

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00140037 v2.0

Approval/eSignature	[redacted] 03-May-2022 15:37:44 GMT+0000
Approval/eSignature	[redacted] 03-May-2022 15:45:03 GMT+0000
Approval/eSignature	[redacted] 03-May-2022 19:21:18 GMT+0000
Approval/eSignature	[redacted] 04-May-2022 00:45:55 GMT+0000

Signature Page for VV-RIM-00140037 v2.0 Approved