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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

Compound:	REGN4461
Clinical Phase:	2
Protocol Number:	R4461-GLD-1875
Protocol Version:	R4461-GLD-1875 Amendment 4
Amendment 4 Date of Issue:	*See appended electronic signature page*
Amendment 3 Admin Date of Issue:	08 Dec 2022
Amendment 3 Date of Issue:	12 Jul 2022
Amendment 2 Date of Issue:	25 Jun 2021
Amendment 1 Date of Issue:	24 May 2019
Original Date of Issue:	30 Jan 2019
Medical/Study Director:	[redacted]

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AMENDMENT HISTORY

Amendment 4

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	Clinical Protocol Synopsis: Study Design Section 3.1.2 Rationale for Study Design Section 6.1Study Description and Design Table 7 Open-Label Treatment Period 5 (OLTP 5) Section 9.1.5 Footnotes for the Schedule of Events Table 7: Open-Label Treatment Period 5, footnote 13 Section 9.1.6 Early Termination Visit

Amendment 3 Admin

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	Table 7 Open-Label Treatment Period 5 (OLTP 5)
		Section 3.1.2 Rationale for Study Design

Amendment 3

The original protocol along with Amendment 1 and Amendment 2 were designed to test 2 weight-based dosing regimens. The low dose ([redacted] subcutaneously [SC] once a week [QW] for patients [redacted] and [redacted] SC QW for patients [redacted]) was designed to achieve REGN4461 trough concentrations of [redacted], whereas the higher dose ([redacted] SC QW for patients [redacted] and [redacted] SC QW for patients [redacted]) was designed to achieve REGN4461 trough concentrations of [redacted]. Pre-specified interim analysis, conducted after the last patients reached the 8-week primary endpoint, [redacted]

[redacted] Simulations, updated using the higher clearance rates observed in this population, indicate that [redacted] SC QW for both weight tiers are more likely to achieve the target REGN4461 trough concentration of [redacted] and optimal pharmacodynamic effects. A 12-month treatment extension is being implemented to evaluate safety, pharmacodynamic effects and exposure for this higher dose.

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	Clinical Study Protocol Synopsis: Objectives, Study Design, Treatments, Study Duration Section 2.2 Secondary Objectives Section 3.1.2 Rationale for Study Design Section 3.1.3 Rationale for Dose Selection Section 3.1.4 Rationale for Endpoints Section 3.3.1 Risk-Benefit for REGN4461 Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 8.1 Investigational and reference Treatments Table 2 [redacted] Section 8.3.1 Dose Modification Section 8.7.1 Permitted Medications Section 9 Schedule of Events Table 6 Open-Label Treatment Period 4 (OLTP 4) Table 7 Open-Label Treatment Period 5 (OLTP 5) Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Treatment Period 4, footnote 18 (deleted)

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	Section 9.1.5 Footnotes for the Schedule of Events Table 7: Open-Label Treatment Period 5 Section 9.2.2.1 Vital Signs Section 9.2.2.2 Physical Examination, Body Weight, Height, and Tanner Stages Section 9.2.2.4 Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception Section 9.2.3 Laboratory Testing Section 9.2.4.1 Fasting Triglycerides Section 9.2.4.2 Fasting Glucose Section 9.2.4.3 Hemoglobin A1C Section 9.2.4.6 Lipid Panel Section 9.2.4.7 Urine Protein, Creatinine, and Albumin Section 9.2.4.11 Assessment of Body Composition Section 9.2.4.12 Assessment of Hepatic Fat Content and Liver Size** Section 9.2.4.13 Assessment of Liver Stiffness by Vibration-Controlled Transient Elastography (VCTE) Section 9.2.6.1 REGN4461 Concentration Measurements Section 9.2.6.2 Soluble LEPR (sLEPR) Section 9.2.6.3 Circulating Biomarkers

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	for Pharmacodynamic Assessments Section 9.2.6.4 Immunogenicity Measurements and Samples Section 11 Statistical Plan Section 11.4.1 Patient Disposition Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4.1 Adverse Events
		Section 3.1.2 Rationale for Study Design Section 3.1.3 Rationale for Dose Selection
		Section 3.1.2 Rationale for Study Design Section 6.1 Study Description and Duration Section 8.3.2.1 Reasons for Permanent Discontinuation of Study Drug Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Treatment Period 4, footnote #1

Description of Change	Brief Rationale	Section # and Name
[redacted]		
[redacted]		Clinical Study Protocol Synopsis: Treatments Section 6.1 Study Description and Duration Section 8.1 Investigational and Reference Treatments Table 6 Open Label Treatment Period 4 (OLTP 4) Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open Label Treatment Period 4
[redacted]		Section 9.2.4.12 Assessment of Hepatic Fat Content and Liver Size**
[redacted]		Title Page
[redacted]		Clinical Study Protocol Synopsis: Treatments Section 3.3.1 Risk-Benefit for REGN4461 Table 3 Screening and Placebo Run-In Section 9.1.1 Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In, footnote #7 Table 4 Double-Blind Treatment Period 1 Section 9.1.2 Footnotes for the Schedule of Events Table 4: Double Blind Treatment Period 1, footnote #7 Table 5 Double-Blind Treatment Periods 2 and

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	3 Section 9.1.3 Footnote for the Schedule of Events Table 5: Double Blind Treatment Periods 2 and 3, footnote #6 and #21(deleted) Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open Label Extension Open Label Treatment Period 4, footnotes #7, and #9 Section 11.4.6 Analysis of Anti-Drug Antibody Data

Amendment 2

The main purpose of this amendment is to modify the inclusion criteria for study eligibility to select a patient population that is most likely to have generalized lipodystrophy and therefore would be most likely to respond to REGN4461 treatment.

Language was also added to remind investigators to discontinue REGN4461 treatment starting at week 52 in patients who, in their opinion, do not demonstrate clinical benefit to REGN4461, and to continue REGN4461 treatment at and beyond week 52 (until a common treatment end date) only in patients who demonstrate a clinical benefit in response to REGN4461.

Adjustments to study assessments were made to improve the timing and quality of the data obtained and to decrease patient burden. Other more minor changes were made to align with the sponsor's latest protocol template, to acknowledge impact of the COVID-19 pandemic on the study, and to increase clarity. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Brief Rationale	Sections Changed
[redacted]	[redacted]	Section 7.2.1 Inclusion Criteria, criterion #2

Description of Change	Brief Rationale	Sections Changed
[redacted]		
[redacted]	[redacted]	Clinical Study Protocol Synopsis: Study Design Section 3.1.2 Rationale for Study Design Section 6.1 Study Description and Duration Section 8.3.2.1 Reasons for Permanent Discontinuation of Study Drug Table 6: Open-Label Extension Section 9.1.4Footnotes for the Schedule of Events Table 6: Open-Label Extension, footnote s #1c and #1d (added)
[redacted]	[redacted]	Section 7.2.1 Inclusion Criteria, criterion #6

Description of Change	Brief Rationale	Sections Changed
[redacted]		
		Section 7.2.2 Exclusion Criteria, criterion #4 (added)
		Section 7.2.2 Exclusion Criteria, criterion #7
		Section 7.2.2 Exclusion Criteria, criterion #12 (added)
		Section 7.2.2 Exclusion Criteria, criterion #11 (removed) Section 7.2.2 Exclusion Criteria, criterion #13
		Section 7.2.2 Exclusion Criteria, criterion #14

Description of Change	Brief Rationale	Sections Changed
[redacted]	[redacted]	
[redacted]	[redacted]	Section 7.2.2 Exclusion Criteria, criterion #16
[redacted]	[redacted]	Clinical Study Protocol Synopsis: Dose/Route/Schedule Section 3.1.3 Rationale for Dose Selection Figure 1: Study Flow Diagram Section 8.3.1 Dose Modification
[redacted]	[redacted]	Height measurement: Table 3: Screening and Placebo Run-In

Description of Change	Brief Rationale	Sections Changed
[redacted]	[redacted]	Physical examination: Table 6: Open-Label Extension Lipid panel and free fatty acids: Section 9.1.2 Footnotes for the Schedule of Events Table 4: Double Blind Treatment Period 1, footnote #15 Section 9.1.3 Footnotes for the Schedule of Events Table 5: Double Blind Treatment Periods 2 and 3, footnote #13 Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open Label Extension, footnote #13 Section 9.2.4.9 Mixed Meal Tolerance Test Hematology and blood chemistry: Table 3: Screening and Placebo Run-In Section 9.1.1 Footnote for the Schedule of Events Table 3: Screening and Placebo Run-In, footnote #12 (added) ADA sample collection removed from [redacted] Table 6: Open-Label Extension [redacted] Section 6.1 Study Description and Duration Table 6: Open-Label Extension Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Extension, footnote #1 Removal of all whole blood RNA sample collections: Section 5.6 Pharmacodynamic, Other Biomarker, and Research Variables Section 9.2.7 Pharmacodynamic and Exploratory Biomarker Procedures

Description of Change	Brief Rationale	Sections Changed
[redacted]	[redacted]	Section 9.2.9.1 Whole Blood RNA Samples (Optional) Section 9.2.9 Future Biomedical Research (Optional) Section 9.2.9.1 Pharmacogenomic Analysis (Optional) Table 3: Screening and Placebo Run-In Table 4: Double-Blind Treatment Period 1 Table 5 : Double-Blind Treatment Periods 2 and 3 Table 6: Open-Label Extension
		Table 6: Open-Label Extension
		Table 5: Double Blind Treatment Periods 2 and 3 Section 9.2.5.6 Patient Global Impression of Change
		Section 8.1 Investigational and Reference Treatments
		Clinical Study Protocol Synopsis: Procedures and Assessments Table 3: Screening and Placebo Run-In (assessment added) Section 9.1.1 Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In, footnote #7 Section 9.1.2 Footnotes for the Schedule of Events Table 4: Double Blind Treatment Period 1, footnote #7 Section 9.1.3 Footnotes for the Schedule of Events Table 5: Double Blind Treatment Periods 2 and 3, footnote #6 Section 9.1.4 Footnotes for the Schedule of Events Table 6:

Description of Change	Brief Rationale	Sections Changed
[redacted]		Open-Label Extension, footnote #7 Section 9.2.2.2 Physical Examination, Body Weight, Height, and Tanner Stages
[redacted]		Section 3.1.4 Rationale for Endpoints Table 5: Double-Blind Treatment Periods 2 and 3 (assessment added) Section 9.1.3 Footnotes for the Schedule of Events Table 5: Double Blind Treatment Periods 2 and 3, footnote #17 (added) Table 6: Open-Label Extension (assessment added) Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Extension, #20 (footnote added) Section 9.2.5.7 Exit Interview in Relation to Hunger and Eating Behavior PROs
[redacted]		Section 9.1.1 Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In, Footnote #8 Section 9.1.2 Footnotes for the Schedule of Events Table 4: Double-Blind Treatment Period 1, Footnote #22 Section 9.1.3 Footnotes for the Schedule of Events Table 5: Double-Blind Treatment Periods 2 and 3, Footnote #21 Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Extension, Footnote #18 Section 9.2.2.2 Physical Examination, Body Weight, Height, and Tanner Stages
[redacted]		Section 9.1.1 Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In, footnote #13 Section 9.1.2 Footnotes for the Schedule of Events Table 4:

Description of Change	Brief Rationale	Sections Changed
[redacted]		Double Blind Treatment Period 1, footnote #17 Section 9.1.3 Footnotes for the Schedule of Events Table 5: Double Blind Treatment Periods 2 and 3, footnote #15 Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Extension, footnote #15
		Section 3.1.4 Rationale for Endpoints Section 6.1 Study Description and Duration Section 9.2.8 [redacted]
		Section 8.7.2 Permitted Medications
		Section 5 Study Variables Section 9.1.1 Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In, footnote #4
		Section 3.1.2 Rationale for Study Design
		Section 8.3.2 Study Drug Discontinuation Section 9.1.6 Early Termination Visit
		Section 8.5.1 Blinding

Description of Change	Brief Rationale	Sections Changed
[redacted]	[redacted]	
[redacted]	[redacted]	Table 3: Screening and Placebo Run-In Section 9.1.1 Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In, footnote #2 Table 4: Double-Blind Treatment Period 1 Table 5: Double-Blind Treatment Periods 2 and 3 Table 6: Open-Label Extension Section 9.2.4.5 Insulin/C-peptide
[redacted]	[redacted]	Section 9.1.2 Footnotes for the Schedule of Events Table 4: Double-Blind Treatment Period 1, footnote #13 Section 9.1.3 Footnotes for the Schedule of Events Table 5: Double-Blind Treatment Periods 2 and 3, footnote #11 Section 9.1.4 Footnotes for the Schedule of Events Table 6: Open-Label Extension, footnote #11 Section 9.2.4.8 Insulin Sensitivity Measurement
[redacted]	[redacted]	Section 9.2.3 Laboratory Testing
[redacted]	[redacted]	Section 9.2 Study Procedures

Description of Change	Brief Rationale	Sections Changed
[redacted]		Section 8.7 Concomitant Medications and Procedures
		Section 9.2.3 Laboratory Testing
		Section 3.1.2 Rationale for Study Design
		Section 6.1 Study Description and Duration
		Section 11.4.3 Efficacy Analyses Section 11.4.3.2 Secondary Efficacy Analysis Clinical Study Protocol Synopsis: Statistical Plan Section 11.2 Justification of Sample Size
		Section 4.3 Exploratory Endpoints Section 5.6 Pharmacodynamic, Other Biomarker, and Research Variables
		Section 1 Introduction Section 3.1.1 Rationale for Study Population
		Title page

Description of Change	Brief Rationale	Sections Changed
[redacted]		Clinical Study Protocol Synopsis: End of Study Definition Section 3.3 Benefit-Risk Section 6.1.2 End of Study Definition Section 8.4.2.1 Systemic Injection Reactions Section 9.1 Schedule of Events Section 9.2.9 Future Biomedical Research (Optional) Section 9.2.9.1 Pharmacogenomic Analysis (Optional) Section 10.3.2 Serious Adverse Event Section 10.6 Safety Monitoring Section 13.1 Monitoring of Study Sites
[redacted]		Throughout the protocol. Section 3.1.2 Rationale for Study Design (removed redundant text not relevant to this section)

Amendment 1

The following table outlines the changes made to the protocol and the affected sections.

Change and Rationale for Change	Section Changed
[redacted]	Section 7.2.1 Inclusion Criteria #2, #4, #5 Section 7.2.2 Exclusion Criteria #10, #12, Clinical Study Protocol Synopsis: Secondary Objectives, Procedures and Assessments Section 1 Introduction Section 10.4.3. Other Events that Require Accelerated Reporting to Sponsor Section 10.3.3 Adverse Events of Special Interest Section 8.4.1.2 Termination of the Intravenous Infusion Section 8.7.2 Permitted Medications Section 9.2.2.2 Physical Examination, Body Weight, Height and Tanner Stages Table 6 Open-Label Extension Section 6.1.1 Sub-Study Section 23 References

Change and Rationale for Change	Section Changed
[redacted]	
[redacted]	Section 3.1.2 Rationale for Study Design Section 6.1 Study Description and Duration Study Flow Diagram Figure 1 Section 8.4.1.2 Termination of Intravenous Infusion Section 9.2.2 Study Procedures Section 9.2.2.5 Hypoglycemia monitoring (Section added) Section 9.2.3 Laboratory Testing Section 9.2.4.8 Insulin Sensitivity Measurement Section 9.2.4.11 Assessment of Body Composition Section 9.2.4.12 Assessment of Fat Content and Liver Size Section 9.2.4.13 Assessment of Liver Stiffness by vibration-controlled transient elastography Section 9.2.10 Future Biomedical Research (Optional)
[redacted]	Synopsis: Objectives and Secondary Endpoints Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 3.1.4 Rationale for Endpoints Section 4.2 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 5.2 Efficacy Variable Section 5.4 Pharmacokinetic Variables

Change and Rationale for Change	Section Changed
[redacted]	Section 5.6 Pharmacodynamic and Other Biomarker Variables Table 3 Footnote #4, #7, #11, #13, and #17 Table 4 Footnote #7, #12, #13, #14, #15, #18 and #19 Table 5 Footnote #6, #10, #11, #12, #13, #15, and #17 Table 6 Footnotes #7, #10, #11, #12, #13, #15, #16 and #17 Section 9.1.6 Unscheduled Visits Section 11 Statistical Plan
	Section 7.2.2 Exclusion Criterion #15
	Section 5.2 Efficacy Variable Section 5.4 Pharmacokinetic Variables Section 5.6 Pharmacodynamic and other Biomarker Variables Section 8.1 Investigational and Reference Treatments Section 9.1.1 Table 3 Footnote #2, #3, #5, #12 Section 9.1.2 Table 4 Footnote #2, #4, Section 9.1.3 Table 5 Footnote #3, #19 Section 9.1.4 Table 6 Footnote #1, #5, #9 #14 #19 Section 9.2.2.1 Vital Signs Section 9.2.4.9 Mixed Mean Tolerance Test Section 9.2.5.1 Daily Appetite and Eating Behavior PRO Section 9.2.6 Pharmacokinetic, Drug Concentration, Immunogenicity Samples Section 9.2.6.3 Circulating Biomarker for Pharmacodynamic Assessment Section 9.2.10 Future Biomedical Research (Optional)

Change and Rationale for Change	Section Changed
[redacted]	Section 11.3.7 MRI Analysis Set Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.5.1 Analysis of Drug Concentration Data
	Section 9.1 Schedule of Events: Table 4 Double-Blind Treatment Period 1 and Table 5 visit numbers Throughout the protocol

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled Study of REGN4461, a Leptin Receptor Agonist Antibody, in Patients with Generalized Lipodystrophy
Site Location(s)	The study will be conducted globally at approximately 10 sites.
Principal Investigator	Rebecca Brown, MD; National Institutes of Health, United States
Objectives	The primary objectives of the study are to: • Estimate the effects of REGN4461 on glycemic parameters in the subset of patients with elevated baseline hemoglobin A1c levels (HbA1c ≥7%) • Estimate the effects of REGN4461 on fasting triglyceride levels in the subset of patients with elevated baseline fasting triglycerides (TG ≥250 mg/dL) The secondary objectives of the study are to: • Estimate the effects of REGN4461 on a composite endpoint of changes in either HbA1c or fasting TG for all patients • Estimate the effects of 3 dose levels of REGN4461 on glycemic parameters and fasting TG • Estimate the effects of REGN4461 on insulin sensitivity • Evaluate the safety and tolerability of REGN4461 • Evaluate the pharmacokinetics (PK) and immunogenicity of REGN4461
Study Design	This is a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of REGN4461 in patients with generalized lipodystrophy (GLD) who are not receiving recombinant methionyl human leptin (rhLeptin, metreleptin) therapy. The study comprises: • [redacted]

- [redacted]

  Note: Patients who complete the end of treatment (EOT) visit for Open Label Treatment Period 5 (OLTP 5) and have secured access to continued REGN4461 treatment through other means, (eg, another Regeneron-sponsored clinical trial, compassionate use, or an expanded access program), may forgo any or all of visits 119-121 and proceed to end of study (EOS) visit. These patients will be considered study completers.

- [redacted]

After the [redacted] single-blind placebo run-in period where baseline testing will be performed, patients will be randomized 1:1 to 1 of 2 [redacted] double-blind treatment arms, stratified based on screening HbA1c (HbA1c ≤8% or HbA1c >8%). The study design involves an intra-patient dose escalation to maximize information from each patient enrolled and to allow for intra-patient comparisons between dose levels. The 2 dose levels were selected to maximize the likelihood to observe efficacy and obtain exposure-response information to guide future clinical development.

Treatment Arm A: This arm consists of 3 sequential 8-week periods in which patients receive the following treatments:

- Placebo
- Low-dose REGN4461
- High-dose REGN4461

Treatment Arm B: This arm consists of 3 sequential 8-week periods in which patients receive the following treatments:

- Low-dose REGN4461
- High-dose REGN4461
- High-dose REGN4461

For DBTP 1-3 and OLTP 4, two dose levels ("high dose" and "low dose") of REGN4461 will be tested, and each dose level will be tiered [redacted].

Tier 1: patients [redacted]

- Low-dose REGN4461: [redacted] intravenous (IV) load [redacted] subcutaneous (SC) QW
- High-dose REGN4461: [redacted] SC QW

Tier 2: patients [redacted]

	• Low-dose REGN4461: [redacted] IV load [redacted] SC QW • High-dose REGN4461: [redacted] SC QW For OLTP 5, all eligible patients will receive a [redacted] IV loading dose [redacted] SC QW for [redacted]. Patients that experience excessive weight loss and/or clinically significant (in the opinion of the investigator) spontaneous hypoglycemia (<70 mg/dL), defined as hypoglycemia that occurs in the absence of exogenous insulin or insulin secretagogues, prior to OLTP 5 will be ineligible for the dose increase and will remain on their OLTP 4 dose. In addition, patients receiving [redacted] SC QW that experience excessive weight loss and or significant spontaneous hypoglycemia during OLTP 5 will decrease their weekly SC dose from [redacted] QW.
Study Duration	The study duration is expected to be at least 128 weeks, based on enrollment rate estimates.

End of Study Definition	The end of study is defined as the date that the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the patient can no longer be contacted by the investigator).
Population	
Sample Size:	Up to 26 patients will be enrolled
Target Population:	The target population is patients with a clinical diagnosis of GLD ≥12 years of age (or lower limit of age approved by Health Authority, Ethics Committee [EC], and Institutional Review Board [IRB]) who are not currently treated with metreleptin and have either HbA1c ≥7% or fasting TG ≥250 mg/dL.
Treatment(s)	
Study Drug:	REGN4461 Placebo matching REGN4461.
Dose/Route/Schedule:	In the initial 4-week single-blind run-in period, patients will receive IV placebo infusion, followed by placebo SC injections administered subsequently on a weekly basis for [redacted]. The dosing regimens of REGN4461 in the double-blind period will be tiered according to baseline body weight (Tier 1: [redacted], Tier 2: [redacted]), and are as follows: **Tier 1:** patients with baseline body weight [redacted]: • Low-dose REGN4461: [redacted] IV load [redacted] SC QW • High-dose REGN4461: [redacted] SC QW **Tier 2:** patients with baseline body weight [redacted]: • Low-dose REGN4461: [redacted] IV load [redacted] SC QW • High-dose REGN4461: [redacted] SC QW In OLTP 4, all patients will receive high-dose REGN4461 ([redacted] SC QW in Tier 1 or [redacted] SC QW in Tier 2). After week 52, the REGN4461 dose may be adjusted downward based upon the safety, tolerability, PK, or PD data obtained during the study. During OLTP 5, all eligible patients will receive [redacted] IV loading dose, followed

[redacted] SC QW for [redacted]. During OLTP 5, the REGN4461 dose may be adjusted downward to [redacted] SC QW based upon the safety, tolerability, PK, or PD data obtained during the study.

Endpoint(s)

Primary: The primary endpoints of the study are:

- In patients with elevated baseline HbA1c (HbA1c ≥7%), absolute change from baseline to the end of the double-blind treatment period 1 (DBTP 1) in:
  - HbA1c (week 8)
  - Fasting glucose (week 8)
  - Weighted mean glucose (WMG) (week 8)
- In patients with elevated baseline fasting TG (fasting TG ≥250 mg/dL), percent change from baseline to the end of the DBTP 1 (week 8) in fasting TGs

Secondary: The secondary endpoints of the study are:

- Change from baseline to week 8 in composite endpoint comprising absolute change in either HbA1c or percent change in fasting TG for all patients.
- Absolute change from baseline in fasting glucose over time for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Percent change from baseline in fasting TG over time in all patients and in patients with elevated baseline fasting TG (TG ≥250 mg/dL)
- Absolute change from baseline in HbA1c over time for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Absolute change from baseline in WMG over time for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Change from baseline in glucose AUC_{0-4} during a mixed meal tolerance test (MMTT) at weeks 8, 16, and 24 for all patients and in patients with elevated baseline HbA1c (HbA1c ≥7%)
- Change from baseline in glucose infusion rate per kilogram body mass during hyperinsulinemia-euglycemic clamp (clamp study) at week 8 and week 52, for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)

	• Change from baseline in glucose clearance rate (k_{ITT}) during insulin-tolerance test (ITT) at week 8 and week 52 for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%) • Treatment-emergent adverse events (TEAEs) • Concentrations of total REGN4461 in serum over time • To assess the incidence of treatment emergent anti-drug antibodies to REGN4461 and titer over time
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, HIV serology, and hepatitis testing (HBsAg, HCV), menstrual history, and pregnancy status. Safety procedures include: vital signs, physical examination, body weight, height, Tanner staging, Menstrual history/pregnancy status reporting/ confirmation of contraception and hypoglycemia monitoring and electrocardiogram. Laboratory procedures include: hematology, blood chemistry, urinalysis, pregnancy testing, lipid panel, endocrine hormones and other laboratory testing. Efficacy procedures include: fasting glucose assessment, fasting TG assessment, hemoglobin A1C, fructosamine, insulin/C-peptide, lipid panel, lipoprotein analysis by NMR, urine protein/urine creatinine, WMG, MMTT, liver volume and fat content by MRI and MRI-Proton Density Fat Fraction (MRI-PDFF), respectively, whole body composition by DXA, vibration-controlled transient elastography (VCTE), and patient-reported outcomes.
Statistical Plan	No formal statistical hypothesis testing will be conducted. The size of the study is determined by study feasibility constraints due to the limited number of GLD patients in the world not being treated with metreleptin. It is determined that up to 26 patients will be enrolled for the study with approximately a 20% dropout rate. The primary objective is to estimate the treatment effect of REGN4461 on glycemic and lipid parameters. With 20 patients (10 patients per study arm) completing the study, the study has a minimal detectable change (MDC) of 1% absolute value reduction in HbA1c (standard deviation [SD]=1.5%, within-group comparison) and a 28% reduction in fasting TG (SD=40%, within-group comparison). For within-group comparison, the study would have 80% power to detect a 1.5% reduction in HbA1c absolute value from baseline to week 8 for a 2-sided alpha of 0.05 test (standard deviation =1.5%). For most primary continuous endpoints, the study assesses the treatment effect of REGN4461 from baseline to the end of the double-blind period 1

(week 8) (within-group and between-group comparison). Summary statistics, including mean change from baseline, standard error (SE), corresponding 95% confidence interval, and nominal p-value will be provided for within- and between-group comparison, using a mixed effect model repeated measurement model (MMRM). Mean changes (+/- SE) will be plotted over time by treatment arm.

For secondary endpoints, summary statistics, including mean change from baseline, SE, 95% confidence interval, and nominal p-value will be provided using a similar MMRM. The treatment effect of REGN4461 changes from baseline over time will be provided based on each scheduled assessment time point.

Summary statistics will be provided comparing the effects of REGN4461 low-dose and high-dose regimens on HbA1c, fasting glucose, WMG, fasting TG, and MMTT.

As a secondary objective, the REGN4461 treatment effect will be evaluated using a composite "Z score" of HbA1c and TG. MMRM will be used to evaluate the effects of REGN4461 on both between-group and within-group comparisons. Mean, SE, and 95% confidence interval will be provided.

Change from baseline to week 8 for patients in Treatment Arm A will be provided. If there is no significant change in HbA1c or TG, defined as change in HbA1c (absolute value change) ≤0.4% or TG change (percent change) ≤20%, then those patients' changes from week 8 to week 16 will be pooled together with patients' changes in Treatment Arm B from baseline to week 8, to evaluate the treatment effect of the low-dose regimen. Similarly, if there is no significant change from baseline to week 8 for patients in Treatment Arm A, data from patients in Treatment Arm A (change from week 16 to week 24) will be pooled together with data from patients in Treatment Arm B (change from week 8 to week 16), to estimate the treatment effect of increasing the dose from low-dose regimen to high-dose regimen.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

mAb	Monoclonal antibody
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
DBTP	Double blind treatment period
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray absorptiometry
EC	Ethics Committee
eCOA	Electronic clinical outcome assessment
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLD	Generalized lipodystrophy
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HRQoL	health-related quality of life

IA	Interim Analysis
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational product
IRB	Institutional Review Board
ITT	insulin-tolerance test
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LEPR	Leptin receptors
MDC	Minimal detectable change
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MMRM	Mixed effect repeated measurement model
MMTT	Mixed meal tolerance test
NAS	Non-alcoholic fatty liver disease activity score
NASH	Non-alcoholic steatohepatitis
NMR	Nuclear magnetic resonance
NOAEL	No observed adverse effect level
OLTP	Open-Label Treatment Period
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PDFF	Proton Density Fat Fraction
PedsQL™	The Pediatric Quality of Life Inventory
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
QW	Once a week
PK	Pharmacokinetic
PRO	Patient reported outcomes
PT	Preferred term
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
REMS	Risk evaluation and mitigation strategy

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36 survey
sLEPR	Soluble form of the leptin receptor
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TP	Treatment period
ULN	Upper limit of normal
US	United States
VCTE	Vibration-controlled transient elastography
WBC	White blood cell
WMG	Weighted mean glucose
WOCBP	Women of Childbearing Potential

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1. INTRODUCTION

REGN4461, a leptin receptor (LEPR) agonist, is a fully human monoclonal antibody (mAb) that is being investigated for the treatment of conditions associated with leptin deficiency, including lipodystrophy. Generalized lipodystrophy (GLD) is an ultra-rare condition characterized by near-complete loss of adipose tissue (lipoatrophy). There are an estimated 300 to 400 patients with GLD identified worldwide and an estimated prevalence of approximately 0.23 to 0.96 cases per million (Chiquette, 2017). Adipose tissue functions to store energy and signal the status of energy stores by secreting hormones (adipokines) such as leptin, which regulates energy intake, energy expenditure, and reproductive function. Severe lipoatrophy and leptin deficiency in GLD manifest as hyperphagia, insulin resistance, diabetes, hypertriglyceridemia, pancreatitis, infertility, and hepatic steatosis (progressing to non-alcoholic steatohepatitis [NASH] and advanced liver disease).

Recombinant methionyl human leptin (rhLeptin) (metreleptin, Myalept®) is the only approved treatment option to treat the complications of leptin deficiency in patients with GLD. Currently, rhLeptin is approved in the United States (US) for GLD, and in Japan and Europe for lipodystrophy (both general and partial). However, immunogenicity (>80% of patients develop anti-drug antibodies and ~6% develop neutralizing antibodies) (Myalept, 2015) and the requirement for once daily injections can limit the effectiveness of metreleptin in some patients. In the US, metreleptin carries a black box warning noting that anti-metreleptin antibodies might cross react to endogenous leptin. In the US, metreleptin is only available through a risk evaluation and mitigation strategy (REMS) program in order to restrict prescribing to only trained, certified physicians, to reserve access for eligible patients, and to ensure that the benefits of the therapy outweigh risks. There is thus an unmet need in GLD for effective therapies that are safer, administered less frequently, and can treat patients with neutralizing antibodies to the only approved therapy, metreleptin.

REGN4461 binds and activates leptin receptors (LEPR) signaling. REGN4461 is not related to endogenous leptin, and therefore should not have elevated risks of anti-drug antibodies cross-reacting with endogenous leptin. Once-weekly administration of REGN4461 improved glycemic control, insulin sensitivity, hypertriglyceridemia, food intake, body weight, hepatic mass, and steatosis in lipodystrophic humanized LEPR mice. In toxicology studies (a non-GLP single- and repeated-dose pilot study and a GLP 13-week toxicology study in monkeys), REGN4461 administration resulted in either reduction in body weight gain or body weight loss. These effects are consistent with a role of leptin in regulation of body weight. No adverse reactions of treatment have been identified to date. A first-in-human (FIH), double-blind, placebo-controlled study of REGN4461 in healthy volunteers (R4461-HV-1794) is completed. In the initial (Part A) single-ascending dose portion of the study, participants were randomized 3:1 to REGN4461 vs. placebo in 1 of 7 cohorts to receive doses [redacted] intravenously (IV) up to [redacted] IV, and [redacted] subcutaneously (SC) and [redacted] SC. In Part B of the study, participants were randomized to 4 distinct cohorts defined by sex, baseline leptin levels and BMI to receive [redacted]. Results of the R4461-HV-1794 study indicate that REGN4461 was well tolerated by healthy volunteers when administered via IV and SC routes at the doses tested. There were no safety signals identified from the TEAEs observed in the REGN4461-treated groups compared to placebo group in either part of the study.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are to:

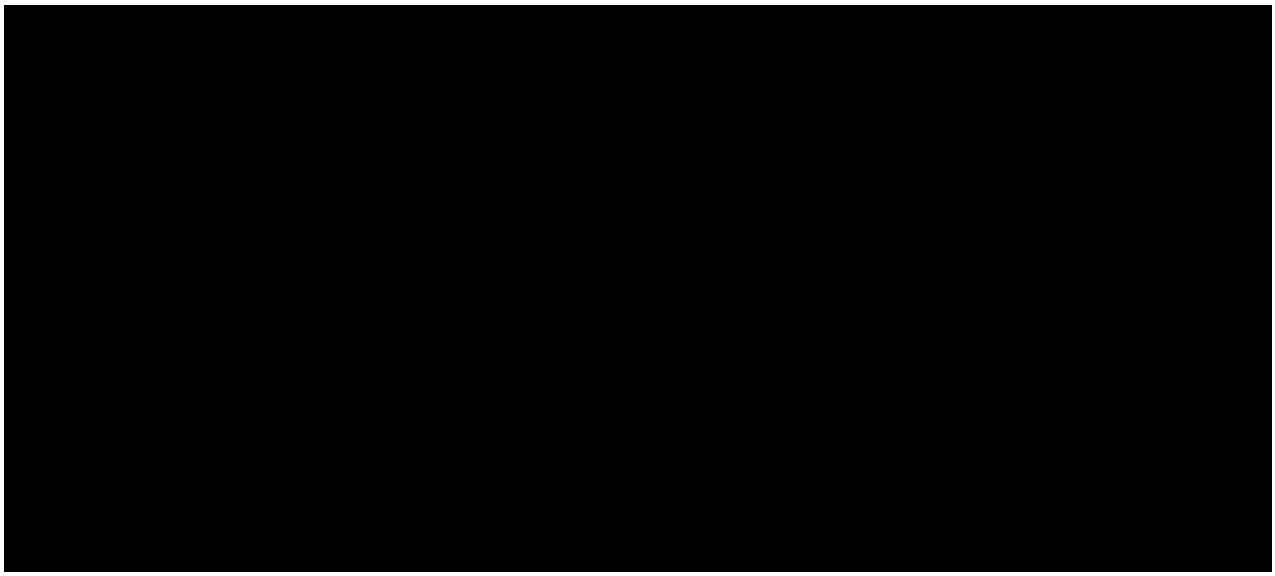
- Estimate the effects of REGN4461 on glycemic parameters in the subset of patients with elevated baseline hemoglobin A1c levels (HbA1c ≥7%)
- Estimate the effects of REGN4461 on fasting triglyceride levels in the subset of patients with elevated baseline fasting triglycerides (TG ≥250 mg/dL)

2.2. Secondary Objectives

The secondary objectives are to:

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

2.3. Exploratory Objectives



3. HYPOTHESIS AND RATIONALE

3.1. Rationale

3.1.1. Rationale for Study Population

The patient population for this study is patients with a clinical diagnosis of congenital or acquired GLD who are not currently treated with metreleptin. The majority of patients with GLD have marked improvements in metabolic parameters with leptin replacement. These results closely mirror preclinical data with REGN4461 and recombinant leptin in a murine model of lipodystrophy. Some GLD patients are untreated with metreleptin because metreleptin is not approved in their country, because they are unwilling or unable to perform daily SC administration of metreleptin, or because they have experienced an adverse effect from metreleptin or developed neutralizing antibodies to metreleptin. The treatment effect of metreleptin was greater and more directionally consistent in patients with GLD and baseline levels of HbA1c ≥7% or TG ≥250 mg/dL (FDA, 2013). Therefore, the patient population in this study is limited to patients with GLD with baseline HbA1c ≥7% or TG ≥250 mg/dL, in order to reduce variability and more clearly evaluate the effects of REGN4461 in the small subset of patients available that are not being treated with metreleptin. Acquired and congenital forms of GLD are included, as both groups of patients experience clinical benefit from metreleptin (Myalept, 2015).

Data from the REGN4461 first-in-human study (R4461-HV-1794) demonstrate that REGN4461 is pharmacologically active only in low-leptin individuals (≤8.0 ng/ml), consistent with LEPR being saturated in individuals with higher leptin levels. All reported patients with congenital GLD have very low leptin levels and are anticipated to respond to REGN4461. However, rare patients with acquired GLD have higher leptin levels as a result of preserved visceral adiposity, despite generalized subcutaneous lipoatrophy. Therefore, for patients with acquired GLD additional inclusion criteria have been incorporated into this study in order to select patients with a greater likelihood of response to a LEPR agonist antibody. The inclusion criterion for low leptin levels (≤8.0 ng/ml) is based on the responder analyses from study R4461-HV-1794. Alternatively, low body adipose mass (<20% for females, <14% for males, based on the first percentile from the National Health and Nutrition Examination Survey cohort III data) independent of leptin concentrations is also acceptable, as leptin levels are proportionate to body fat mass (Meral, 2018) (Diker-Cohen, 2015).

The metabolic complications of GLD manifest early in life, leading to significant morbidity and mortality among pediatric patients (Lima, 2017). The mean age of death in a large rhLeptin-untreated cohort was 27 years old, with patients dying as young as age 11 from diabetic complications (Lima, 2017). Patients with GLD therefore begin metreleptin early in life, and metreleptin has been demonstrated to be safe and effective in pediatric patients (Brown, 2017). The study includes adolescents (ages 12 to 17 years), as these patients have a high, unmet medical need and the preclinical toxicology studies support inclusion of these patients. In healthy, adolescent monkeys of comparable developmental stage to the proposed patient population (peri-pubescent), no adverse effects of continuous exposure (weekly dosing up to [redacted] via IV infusion) were identified (R4461-TX-17003; 13-week GLP toxicology study). The primary effect REGN4461 exhibited in adolescent monkeys was decreased body weight gain or body weight loss, consistent with the expected pharmacology of a LEPR agonist. Upon cessation of exposure during

a dose-free recovery phase, body weight changes were demonstrated to be reversible and lacked any adverse physiological effects on the animals, including microscopic evaluation of the developing reproductive organs, and functional evaluations of the central nervous system.

3.1.2. Rationale for Study Design

[redacted]

The purpose of the single-blind placebo run-in period is to stabilize diet and metabolic parameters. Because the primary mechanism by which LEPR agonism improves metabolic parameters is through improvement of hyperphagia and reductions in caloric intake, changes in diet and medications that can occur upon enrollment in a clinical study might have a considerable impact on study endpoints. For instance, in the initial study of metreleptin, the effect of study enrollment on improvement of TG was nearly as large as the effect of 1 month of metreleptin therapy (Oral, 2002). In the current study, the randomized, placebo-controlled study period ([redacted]) will evaluate the effects of REGN4461 and assess study effects in patients randomized to placebo. The length of the DBTP 1 (8 weeks) was chosen to provide enough time for metabolic parameters to improve, but also to minimize the length of time some patients are treated with placebo. In GLD patients, initiation of metreleptin can improve, and in some patients even normalize, fasting glucose and fasting TG within days to 1 month (Brown, 2018) (Ebihara, 2007) (Vatier, 2016). Reductions in HbA1c upon metreleptin initiation have been demonstrated within 2 weeks (Brown, 2018). After 4 months of treatment with metreleptin, patients with GLD experienced a mean reduction in HbA1c of ~1.5% from a baseline of 9.2%, and a reduction in median TG of 50% from a median baseline of 580 mg/dL. After 6 months, metreleptin was reported to lower HbA1c by 2.7% in the subgroup of patients with baseline HbA1c >8% (mean baseline of 9.8%), and lower mean fasting TG by 72% in the subgroup of patients with a baseline fasting TG >300 mg/dL (mean baseline of 914 mg/dL (Diker-Cohen, 2015). A [redacted] treatment period is also long enough to see improvements in hepatic steatosis, which has been reported to improve within 2 weeks of initiation (Brown, 2018) (Javor, 2005) (Oral, 2002) (Petersen, 2002).

Two dose levels have been selected for the double-blind portion of this study (DBTP 1-3, Section 3.1.3). There is uncertainty regarding the optimal dose of REGN4461 in GLD because: (1) PK in healthy volunteers might differ from PK in GLD patients due to potentially different levels of the target receptor (LEPR); (2) very high doses of REGN4461 were associated with diminished efficacy in cellular reporter assays of LEPR activity, in a LEPR humanized mouse model of lipodystrophy, and in healthy cynomolgus monkeys (ie, an inverse U-shaped dose-response or 'hook effect' was observed); and (3) REGN4461 is an agonist antibody and therefore might not need to saturate the target receptor for maximal efficacy. Therefore, the study design involves an intra-patient dose escalation in DBTP 2 and DBTP 3 to maximize information from each patient enrolled, and to allow for intra-patient comparisons between the 2 dose levels. Exploration of 2 dose levels in the DBTPs will help to minimize bias and leverage objective measures. The low-dose and high-dose treatment regimens will be defined by body weight tiers, as described in Section 3.1.3, in order to ensure equivalent exposure in all patients.

The Open-Label Treatment Period (OLTP) 4 (from week 24 through at least week 52) will explore the durability of treatment effects of the [redacted] doses. Long-term effects of REGN4461 on HbA1c, TG, insulin sensitivity, liver disease, and body composition will be assessed at week 52 by serum studies, insulin sensitivity assessment (clamp or insulin-tolerance test [ITT]), liver volume and fat content (by magnetic resonance imaging [MRI] and MRI-Proton Density Fat Fraction [PDFF], respectively), whole body composition (by Dual-energy X-ray absorptiometry [DXA]), vibration-controlled transient elastography (VCTE), and [redacted].

A pre-specified interim analysis (IA) was performed when the last enrolled patient reached the week 8 primary endpoint. The IA revealed that GLD patients had lower than predicted REGN4461 concentrations and no significant treatment effects on glycemic and lipid parameters at week 8. A population PK analysis was performed and indicated faster clearance of REGN4461 in this GLD population. As the study progressed to week 36, clinically meaningful treatment effects were observed for HbA1c and triglycerides in these patients. Therefore, a higher dose (ie, [redacted] SC QW) is predicted to achieve the target trough concentrations in GLD patients and to increase the likelihood of rapidly achieving optimal treatment effects. REGN4461 appears to be generally well tolerated for the doses observed, with no safety concerns identified with regards to TEAEs, AESIs, and laboratory parameters. As such, an additional treatment period at a dose of [redacted] SC QW (OLTP 5) has been added in order to assess the safety [redacted] that is proposed to be used in future studies of REGN4461 in the GLD population. To rapidly achieve desired concentrations quickly, [redacted] IV is required at the start of this higher-dose treatment period (OLTP 5).

The OLTP 5 [redacted] with dose reduction as described in Section 3.1.3. Long-term effects of REGN4461 on HbA1c, TG, liver disease, and body composition will be assessed at week 52 by serum studies, liver volume and fat content (by magnetic resonance imaging [MRI] and MRI-Proton Density Fat Fraction [PDFF], respectively), whole body composition (by Dual-energy X-ray absorptiometry [DXA]), vibration-controlled transient elastography (VCTE), and [redacted]

Conditions that will mark the end of OLTP 4 and the beginning of OLTP 5 are detailed in Section 6.1.

After the last dose of study drug, patients enter a 16-week follow-up period to assess the efficacy, safety, and PK after discontinuation of REGN4461. The duration of off-drug follow-up (16-weeks) is sufficient to allow concentrations to fall below the limit of quantitation. Patients who complete the EOT visit associated with OLTP 5 and secure access to REGN4461 treatment outside of the study are not required to complete follow-up period visits, and may instead complete the EOS visit and complete the study. This design element was instituted to allow patients experiencing improvements in metabolic parameters to seek continued treatment with REGN4461, should they choose to do so.

3.1.3. Rationale for Dose Selection

REGN4461 dose levels and dosing frequency have been selected based on tolerability and PK data from a single ascending dose (Part A) FIH study in healthy volunteers (R4461-HV-1794), PK-PD

analyses of glucose control and body weight effects in a mouse model of lipodystrophy, and body-weight effect data in healthy cynomolgus monkeys. A 2-tiered dosing paradigm for fixed SC dose considers the wide range of body weights for adult and adolescent patients planned for the current study.

In preclinical species, PD effects were associated with a wide range of exposures to REGN4461, while the sustainability of the effects was observed under dosing conditions where target-mediated clearance (TMC) of REGN4461 was saturated. Transgenic mice expressing nuclear sterol regulatory element-binding protein 1c (nSrebp1c) in adipose tissue through the aP2 promoter (aP2-nSrebp1c$^{Tg/+}$) are reported to develop a syndrome with characteristic features of GLD (Shimomura, 1999). aP2-nSrebp1c^{Tg} mice have a near-absence of white adipose tissue and are severely insulin-resistant, hyperglycemic, and dyslipidemic. aP2-nSrebp1c$^{Tg/+}$ mice also develop an enlarged fatty liver. This mouse model provided the first evidence that leptin resolves the metabolic complications of GLD (Shimomura, 1999). Since aP2-nSrebp1c$^{Tg/+}$ mice recapitulate the clinical manifestations of GLD, they represent a useful model for pharmacological testing of REGN4461. Considering REGN4461 does not bind mouse LEPR (REGN4461-PH-17036), aP2-nSrebp1c$^{Tg/+}$ mice were crossed with mice expressing a humanized ectodomain of LEPR (Lepr$^{hu/hu}$) as described in REGN4461-PH-17041, to generate an aP2-nSrebp1c$^{Tg/+}$Lepr$^{hu/hu}$ line. In this mouse model of lipodystrophy, single doses of REGN4461 resulted in normalization of glucose concentrations and loss of body weight. These effects were evident at concentrations of REGN4461 [redacted] but were notably more sustained at concentrations that saturated the TMC pathway. In monkey studies, sustained body-weight effects (either body weight loss or reduced body weight gain compared to control animals) were observed at steady-state concentrations [redacted]. However, greater overall effects [redacted]. Given that leptin-binding receptors are widely expressed, but that target (signaling) receptors are limited to the central nervous system, it is presumed that the preclinical PK/PD data reflect the need to saturate TMC associated with binding to peripheral LEPR to achieve adequate exposures in the brain. In addition, the interspecies differences in concentration required to saturate TMC and deliver sustained PD effects may be a consequence of differences in peripheral target burden.

[redacted]

Because patients with GLD lack adipose tissue and may therefore have a lower peripheral target burden and altered PK profiles compared to healthy volunteers, it is important to explore a lower dose level in this study. The low dose level, [redacted] SC, [redacted], thereby maximizing the opportunity to observe intra-patient comparisons between low- and high-dose levels. [redacted]

REGN4461 was well-tolerated in healthy adult volunteers in R4461-HV-1794 when administered as single doses [redacted] IV and [redacted] SC. Maximal concentration of

[redacted] IV dose, which is more [redacted] current study. Predicted AUC_{inf} over the entire 52-week study period for each tier is expected to be at least 10-fold lower than 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. Therefore, considering both maximal concentration and total exposure following repeated dosing, the proposed high dose is expected to be well tolerated.

The current study includes both adult and adolescent patients with body weight potentially much lower than a typical adult of 70 kg. The effect of weight on the PK of REGN4461 was examined based [redacted] respectively. Though this magnitude of between-patient variability is typical and reflects inter-individual differences not only in body weight/volume of distribution but also in absorption and elimination, the impact of body weight over the larger range of patient weights expected in this study could necessitate dose adjustment. [redacted] As discussed above, these exposure levels are believed to be efficacious and well-tolerated and to adequately differentiate between the low and high doses. Therefore, the selected doses for patients with weights of less than 50 kg are considered appropriate. No dose changes will be made during the study if the weight tier for a patient changes during treatment.

Table 1: Planned Tiered Weight-Based Dosing Regimen of REGN4461

[redacted] to assess whether the doses selected achieved the expected drug levels and PK profiles and effects on glycemic and lipid parameters. The dose levels in the current study may be adjusted down after the IA.

During the Open-Label Treatment Period 4 (OLTP 4), patients will receive [redacted] REGN4461 SC QW [redacted] REGN4461 SC QW [redacted]. After week 52, dose reduction may occur if deemed necessary based on the IA of safety, tolerability, PK, or PD data.

The pre-specified IA was performed when the last enrolled patient reached the week 8 primary endpoint [redacted]

An additional treatment period at a dose of [redacted] SC QW (OLTP 5) has been added in order to assess the safety of the [redacted] SC QW dose regimen, the proposed regimen for future studies of REGN4461 in the GLD population.

[redacted]

- Patient that has lost excessive weight. For the purposes of this study, excessive weight loss is defined as >10% change from baseline and/or is considered as excessive in the opinion of the investigator and in consultation with the study's medical monitor.

  and/or

- Patient has experienced clinically significant (in the opinion of the investigator) spontaneous hypoglycemia (<70 mg/dL), defined as hypoglycemia that occurs in the absence of exogenous insulin or insulin secretagogues.

[redacted]

Predicted area under the curve at steady state (AUC_{tau}) for the [redacted] SC QW dosing regimen administered to GLD patients is approximately [redacted]

Based on the above observations, a fifth treatment period (OLTP 5) was introduced with Amendment 3 in which all eligible patients [redacted].

3.1.4. Rationale for Endpoints

Clinical studies of metreleptin in lipodystrophy patients demonstrated improvement in HbA1c, fasting TG, and fasting glucose (FDA, 2013). Regulators globally have approved metreleptin based on changes seen in these parameters, and therefore these endpoints have been chosen for this study. Due to the variability of TG and HbA1c endpoints, several design elements have been utilized to reduce variability and enhance the ability to observe a treatment effect in this small study of metreleptin-untreated patients. The averaging of multiple, fasting TG observations will improve the accuracy of the fasting TG estimate in the baseline and treatment periods, compared to only single values. Since fasting and blood draws can be burdensome on patients with lipodystrophy, particularly in metreleptin-untreated patients with hyperphagia, measurements of fasting TG will be limited to the end of the study periods. Since effects on HbA1c are delayed and quite variable, mixed meal tolerance test (MMTT), weighted mean glucose (WMG), and fasting blood glucose will also be assessed as a short-term measure of glycemic control.

A secondary composite endpoint comprising change in HbA1c or change in TG will be calculated to assess the overall effects of REGN4461 on metabolic parameters in the enrolled population. There is significant heterogeneity in baseline metabolic abnormalities among patients with GLD, and the treatment effect on a given endpoint (eg, HbA1c, TG) is expected to vary according to the baseline abnormality. For example, estimates suggest that only ~one-third of patients have abnormalities in both HbA1c and fasting TG. This observation is consistent with prior studies in GLD patients (FDA, 2013). Most patients identified have elevated TG, while a smaller fraction of patients have uncontrolled HbA1c (<40%). Significant inter-patient differences in diet, medication adherence, and underlying disease pathology are possible contributors to this heterogeneity in metabolic manifestations of lipodystrophy. The composite endpoint will assess the overall impact of REGN4461 in this heterogeneous population, by assessing the effects on glycemic parameters among patients with abnormal baseline glycemic control and effects on fasting TG among patients with elevated baseline fasting TG, in a single composite endpoint.

REGN4461 improved insulin sensitivity in a mouse model of lipodystrophy and is expected to improve insulin sensitivity in patients with GLD. The gold-standard assessment of insulin sensitivity is the hyperinsulinemic-euglycemic clamp study (clamp study). Patients with metreleptin-untreated GLD are insulin-resistant and require high insulin infusion rates (120 $mU/m^2 \cdot min$) to suppress endogenous glucose production and stimulate glucose uptake. In a recent study of 14 lipodystrophy patients, a statistically significant 30% increase in insulin sensitivity, as measured by glucose infusion rate to maintain euglycemia, was observed within 2 weeks of metreleptin administration to previously untreated patients (Brown, 2018). Inclusion of a clamp study at baseline, week 8, and week 52 will provide a sensitive assessment of metabolic effects of REGN4461. At clinical sites that do not have the capability to perform a clamp study, an ITT will be used instead.

REGN4461 is expected to reduce hepatic steatosis, similar to what has been observed with metreleptin therapy (Brown, 2018) (Javor, 2005) (Oral, 2002) (Petersen, 2002). REGN4461 reduced hepatic fat in a mouse model of lipodystrophy. Patients will undergo baseline and on-treatment MRI (weeks 8, 24, and 52 for all patients, and at the start and at the end of OLTP 5 for all eligible patients) to evaluate the effects of REGN4461 on hepatic volume and fat content. Liver fat content and liver volume assessment by MRI-PDFF and MRI, respectively, will be performed only at sites with the requisite technical capability. Baseline, week 52, and at the start

and at the end of OLTP 5 VCTE evaluation will assess long-term impact of REGN4461 on liver fibrosis. Liver fibrosis assessment will be performed only at sites with VCTE capability. Since hepatic steatosis can progress to NASH, cirrhosis, and liver failure in patients with lipodystrophy, an [redacted] may be performed (in adult patients who have consented to participate in this sub-study) at baseline and after treatment to evaluate the effects on the non-alcoholic fatty liver disease activity score (NAS) and fibrosis.

It is expected that REGN4461 will decrease appetite, a therapeutic effect in GLD patients with hyperphagia. In order to quantify these effects, hunger and eating behaviors will be assessed during the study by a daily de novo lipodystrophy-specific PRO measure. To ensure the measure is fit for purpose under the context of use, we will also conduct exit interviews between weeks 6 and 8 (or at the early termination visit before week 8, if applicable). The qualitative data from the exit interviews will also be used to interpret trial results and to further understand whether the observed changes were meaningful from the perspective of the patient.

Excessive appetite suppression could have an impact on muscle mass. Therefore, body weight will be monitored throughout the study. In addition, whole body DXA imaging will be performed at baseline and during the treatment period to quantify the short- and long-term effects of REGN4461 on fat and lean tissue mass. Whole body DXA will be performed only at sites with these capabilities.

3.2. Hypothesis

REGN4461 will improve the metabolic complications of leptin deficiency in patients with GLD who are untreated with metreleptin.

3.3. Benefit-Risk

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 for REGN4461

For patients with generalized lipodystrophy, REGN4461 has the potential to be a better alternative than metreleptin to reduce metabolic complications of lipodystrophy (as discussed in the most current version of the Investigators' Brochure). In addition, because the structure of REGN4461, a monoclonal antibody, is distinct from leptin, there is no expected risk of REGN4461-treated patients developing neutralizing antibodies that cross-react to endogenous leptin. To date, no important identified risks have been established with REGN4461. Important potential risks have been established based on observations from nonclinical studies, the mechanism of action of REGN4461 (including class effects), and risks associated with mAbs in general. These potential risks include:

- Decreased lymphocytes

- Hypoglycemia in patients with concomitant use of insulin and insulin secretagogues
- Systemic hypersensitivity reactions
- Clinical consequences of immunogenicity (ADA formation)

REGN4461 has not been administered to pregnant humans, and embryofetal toxicity studies have not been conducted. As such, embryofetal toxicity remains a potential risk.

A risk-benefit statement with respect to the overall development program is provided in the Investigators' Brochure.

4. ENDPOINTS

4.1. Primary Endpoints

The primary endpoints of the study are:

- In patients with elevated baseline HBA1c (HbA1c ≥7%), absolute change from baseline to the end of the DBTP 1 in:
  - HbA1c (week 8)
  - Fasting glucose (week 8)
  - WMG (week 8)
- In patients with elevated baseline fasting TG (fasting TG ≥250 mg/dL), percent change from baseline to the end of the DBTP 1 in fasting TGs

4.2. Secondary Endpoints

The secondary endpoints of the study are:

- Change from baseline to week 8 in composite endpoint comprising absolute change in either HbA1c or percent change in fasting TG for all patients
- Absolute change from baseline in fasting glucose over time for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Percent change from baseline in fasting TG over time in all patients and in patients with elevated baseline fasting TG (TG ≥250 mg/dL)
- Absolute change from baseline in HbA1c over time for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Absolute change from baseline in WMG over time for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Change from baseline in glucose $AUC_{0\text{-}4}$ during an MMTT at weeks 8, 16, and 24 for all patients and patients with elevated baseline HbA1c (HbA1c≥7%)

- Change from baseline in glucose infusion rate per kg body mass during hyperinsulinemia-euglycemic clamp at week 8 and week 52, for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Change from baseline in glucose clearance rate (k_{ITT}) during ITT at week 8 and week 52 for all patients and patients with elevated baseline HbA1c (HbA1c ≥7%)
- Treatment-emergent adverse events
- Concentrations of total REGN4461 in serum over time
- Assessment of incidence of anti-drug antibodies to REGN4461 and titer over time

4.3. Exploratory Endpoints

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics include standard demography (eg, age, race, weight, height, etc.), disease specific-characteristics including fasting glucose, HbA1c, WMG, MMTT, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting TG, disease characteristics including detailed GLD history (medical history, and medication history including previous lipid-modifying therapies and control of diabetes) for each patient.

5.2. Efficacy Variables

Efficacy variables include HbA1c, fasting glucose, WMG, fasting TG, $AUC_{0\text{-}4h}$ from MMTT, glucose infusion rate per kg body mass from clamp, and glucose clearance rate (k_{ITT}) from ITT, liver volume as measured by MRI, and liver fat content as measured by MRI-PDFF.

5.3. Safety Variables

Safety variables include adverse events, body weight, vital signs, 12-lead-ECG, physical examination, and laboratory safety tests.

5.4. Pharmacokinetic Variables

Concentrations of total REGN4461 and soluble leptin receptor (sLEPR) will be measured at prespecified sampling times.

5.5. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include ADA status and titer over time.

5.6. Pharmacodynamic, Other Biomarker, and Research Variables

Pharmacodynamic, other biomarker and research variables include:

- Liver stiffness from VCTE
- Urine protein, creatinine, albumin
- Angiopoietin-like 3 (ANGPTL3)
- Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- Endocrine hormone panel (eg, luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol [E2], and testosterone)
- Immunophenotyping studies (T cell subsets)
- NAS score from histologic assessment of liver core needle biopsy (in patients who consent)
- Transcriptomic profiling studies on RNA extracted from liver biopsies
- Biomarkers of insulin resistance, appetite control, liver fibrosis.
- Biomarkers of lipid parameters (lipid panel, lipoprotein analysis by NMR)
- Patient-reported outcomes measuring quality of life (as measured by the SF-36 and PedsQL^{TM}),
- Patient-reported outcomes measuring impacts on hunger and eating behaviors
- Patient-reported outcomes measuring impact on sensation of body temperature

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 GLD who are not receiving recombinant methionyl human leptin (rhLeptin, metreleptin) therapy.

The study comprises [redacted] Patients who complete the EOT visit associated with OLTP 5 and have secured access to continued REGN4461 treatment through other means, (eg, another Regeneron-sponsored clinical trial, compassionate use, or an expanded access program), may forgo any or all of the off-drug follow-up visits 119-121 and proceed to the EOS visit. These patients will be considered study completers.

Patients who are ≥12 years of age, (or lower limit of age approved by Health Authority, EC, and IRB) at the screening visit with a clinical diagnosis of GLD, will undergo screening, including measurement of HbA1c and fasting TG. Eligible patients will then begin the single-blind placebo run-in period within 4-weeks of screening.

The 24-week DBTP consists of the following:

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

[redacted]

[redacted]

Figure 1: Study Flow Diagram

[redacted]

4-Week Screening Period

The screening period will last for up to 4 weeks (days -56 to -29). Patients will undergo screening assessments as per the schedule outlined in Table 3 to determine their eligibility for study participation. Patients may be re-screened if they fail the screening for reasons related to incidental or transitory conditions (eg, medication use, concomitant illness, medical condition). If patients

are re-screened within the original 4-week screening period, only screening test(s) (eg, an out-of-range laboratory value) that resulted in initial screen failure should be repeated.

4-Week Single-Blind Placebo Run-in Period (Week -4 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 injections of placebo, administered once weekly for 3 weeks. After the first administration of placebo at the study site, subsequent administration may either be continued at the clinical site, or by the site personnel or another healthcare professional at a remote location (eg, the patient's home, school, or place of work).

Blood samples will be collected to measure fasting lipid and glucose levels during the run-in period. These blood samples may be collected at a clinical unit, at home by a visiting nurse, or at an outpatient clinic visit. Patients will also receive training on a clinical outcome assessment (COA), if available, which they will use to record patient-reported outcome (PRO) measures.

At the end of the placebo run-in period, patients will undergo MMTT assessment, WMG assessment, insulin-sensitivity assessment, and VCTE assessment. The insulin-sensitivity assessment will be a clamp study for patients who visit qualified sites where a qualified clamp research unit and experienced investigator are available. Patients presenting to sites without a qualified clamp research unit will undergo an ITT in lieu of a clamp study. The patients who present to sites that are not qualified and experienced to perform clamp (and additionally are not qualified and experienced to perform ITT testing) will not undergo insulin-sensitivity assessment. Additionally, patients will undergo baseline liver volume and fat content by MRI, and whole-body composition by DXA imaging (at sites with the requisite capability). Adult patients will have the [redacted] during the placebo run-in period. Baseline efficacy labs (eg, HbA1c, fasting glucose, and fasting TG) will be collected on study day 1 prior to study drug administration.

[redacted]

After baseline testing, patients will be randomized 1:1 to placebo (Treatment Arm A), or REGN4461 (low-dose regimen) (Treatment Arm B), stratified based on screening HbA1c (HbA1c ≤8% or HbA1c >8%) to ensure equal representation of patients with very elevated HbA1c in each study arm. On study day 1, patients in Treatment Arm A will receive an IV infusion of placebo and patients in Treatment Arm B will receive an IV [redacted] REGN4461. Starting on day [redacted] and continuing weekly through days [redacted] patients will receive weekly SC injections of either placebo or [redacted], administered by either a trained visiting nurse at a remote location or by trained study staff at a study site (see Table 2 for details of dosing schedule). At the end of DBTP 1, patients will undergo in-clinic assessments including laboratory assessments for PD, MMTT, WMG, and insulin sensitivity (clamp or ITT), liver volume and fat content by MRI, and whole body composition by DXA imaging (at sites with the requisite capability) (see Table 4 for details). The primary endpoints are assessed at the end of DBTP 1 (week 8).

Double-Blind Treatment Periods 2 and 3 (Weeks 8 to 16 and 16 to 24)

The DBTP 2 begins at week 8 and will continue until week 16. On week 8, patients in Treatment Arm A will begin the REGN4461 low-dose regimen, and patients in Treatment Arm B will transition to the REGN4461 high-dose regimen (Table 2).

During the [redacted]

[redacted]

At the end of DBTP 2, patients will undergo in-clinic assessments including laboratory assessments for PD, MMTT, and WMG (see Table 5 for details).

The DBTP 3 begins [redacted], patients will undergo in-clinic assessments including laboratory assessments for PD, MMTT, WMG, liver volume and fat content by MRI, and whole body composition by DXA imaging (see Table 6 for details).

Open-Label Treatment Period 4 (OLTP 4)

The open-label period begins at week 24 through at least week 52 during which time all patients will initially continue to receive weekly SC administration of [redacted]. REGN4461 may be administered at the clinical site, by the site personnel or another healthcare professional at a remote location (eg, satellite site, patient's home, school, or place of work), or self-administered/administered by the patient or designated person, respectively. For patients who choose to self-administer REGN4461, training on self-administration must be performed by qualified study personnel, and the first occurrence of self-administration must be observed by same. In-clinic assessments including physical examination and laboratory assessments for PK, PD, and safety parameters will occur every 3 months during the entire length of the OLTP 4 or as-needed based on study staff assessment via monthly phone contacts. Study personnel contact with patient via either phone or in-person assessments must occur at least once monthly throughout the study.

The final insulin sensitivity assessment (clamp or ITT), evaluation will occur at the week 52 visit (see Table 6 for details). [redacted]. Additional week 52 assessments include VCTE examination, liver volume and fat content by MRI, and whole body composition by DXA imaging. Following the [redacted] until the end of OLTP 4 is reached. During the cycling visits, at "each" [redacted], patients will only undergo sample collections for safety (hematology, blood chemistry, pregnancy testing, urinalysis, fasting TG, glucose, and HbA1c) and PK. When cycling, patients will not undergo sample collections for fructosamine, insulin/C-peptide, lipid panel, urine protein, creatinine, or albumin.

OLTP 4 will end at the earliest when all 4 of the following criteria are fulfilled: (1) all active patients have completed the week 52 visit, (2) all data have been collected and validated through

the time when the last active patient randomized into the study completes the week 24 visit, (3) results of the primary analyses of safety and efficacy are available to the sponsor, and (4) Protocol Amendment 3 has been approved at the site. Once all four of these criteria are met, the OLTP 4 will end at the latest four weeks after approval of Protocol Amendment 3 at each site. Based on these factors, the sponsor will determine the end of OLTP 4 for each patient.

Open-Label Treatment Period 5 (OLTP 5)

[redacted] after the end of OLTP 4 (defined above), patients will enter OLTP 5. At the onset of OLTP 5 all patients will receive [redacted] SC QW for [redacted]. The following conditions would exempt a patient from [redacted]: patients that have lost excess weight and/or experience significant spontaneous hypoglycemia previously in the study. Excess weight loss is defined for this protocol as >10% change from baseline and/or considered as excessive in the opinion of the investigator and in consultation with the study's medical monitor. Furthermore, any patient that experiences excess weight loss and/or significant spontaneous hypoglycemia as described above during OLTP 5 will undergo a dose reduction to [redacted] SC QW. After 52 weeks in OLTP 5, study drug will be discontinued.

The REGN4461 [redacted] SC QW maintenance doses may be administered at the clinical site, by the site personnel or another healthcare professional at a remote location (eg, satellite site, patient's home, school, or place of work), or self-administered/administered by the patient or designated person, respectively. For patients who choose to self-administer REGN4461, training on self-administration must be performed by qualified study personnel, and the first occurrence of self-administration must be observed by the same study personnel. In-clinic assessments including physical examination and laboratory assessments for PK, PD, and safety parameters will occur at a frequency depicted in Table 7. Study personnel contact with the patient via either phone or in-person assessments must occur at least once monthly throughout the study.

Patients who complete the EOT visit associated with OLTP 5 and have secured access to continued REGN4461 treatment through other means, (eg, another Regeneron-sponsored clinical trial, compassionate use, or an expanded access program), may forgo any or all of the off-drug follow-up visits 119-121 and proceed to the EOS visit. These patients will be considered study completers.

Off-Drug Follow-up Period

When study drug is discontinued, patients will enter the 16-week off-drug follow-up period. The off-drug follow-up period will be used for safety monitoring, to assess REGN4461 PK, ADA, and explore PD effects at varying drug levels (Table 7).

6.1.1. Sub-Studies

[redacted]

6.1.2. End of Study Definition

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

6.2. Planned Interim Analysis

No formal IA is planned. An unblinded team within Regeneron Pharmaceuticals, Inc., consisting of Regeneron staff not responsible for direct site interactions, will review the PK, PD, efficacy, and safety data to confirm the adequacy of the dose. The investigator, Regeneron study team responsible for site interactions, and patients will remain blinded to individual patient allocation throughout the study.

6.3. Study Committees

6.3.1. Steering Committee

The complexity of this study requires a close partnership with the lipodystrophy experts. A steering committee will be formed to advise the sponsor on the strategic direction, goals, and execution of the study.

6.3.2. Data Monitoring Committee

An internal Data Monitoring Committee (DMC) will monitor patient safety by conducting reviews of individual and aggregate patient data. The DMC charter will be provided with DMC operational details. The DMC charter activities will align with the study protocol and statistical analysis plan (SAP).

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Up to 26 patients will be enrolled.

7.2. Study Population

The target population is patients with a clinical diagnosis of GLD who are at least 12 years of age (or lower limit of age approved by Health Authority, EC, and IRB) and are not currently treated with metreleptin.

7.2.1. Inclusion Criteria

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

1. Male or female patients, ≥12 years of age at the screening visit (or lower limit of age approved by Health Authority, EC, and IRB)
2. Diagnosis of congenital or acquired GLD defined as follows:

Evidence of generalized lipoatrophy of subcutaneous fat by physical examination *AND one of the following (based on historical records):*

a. History of congenital generalized lipodystrophy (ie, onset at birth) based on patient's history or documented pathogenic mutation in GLD associated gene (eg, AGPAT2, BSCL2, CAV1, PTRF)

OR

b. Objective evidence of low total body fat mass as demonstrated by DXA, or of low leptin levels as defined below, assessed within 6-months prior to screening visit:

- Less than 20% total body fat by DXA (females), or less than 14% total body fat (males). Note that the quality of historical DXA images should be consistent with the specifications described in the imaging manual.

OR

- Leptin levels ≤8.0 ng/ml

3. Presence of one or both of the following metabolic abnormalities at screening:
   a. HbA1c ≥7%

      OR

   b. Fasting TG ≥250 mg/dL
4. Generally stable diet (based on patient's recall) and medication regimen (that optimizes treatment for their metabolic disease) for at least 3 months prior to the screening visit
5. Willing and able to comply with clinic visits and study-related procedures

   Notes: Patients incapable of completing PRO assessments or unable to undergo MRI will not be excluded from the study. The willingness and ability to comply with clinic visits and study-related procedures applies to those patients associated with the main study (ie, not to the sub-studies included in this protocol).
6. 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 1 month of the screening visit
2. Patients with clinically significant hematologic abnormalities such as neutropenia, lymphopenia, or lymphadenopathy at screening
3. Treatment with over-the-counter or prescription medications for weight loss within 3 months prior to the screening visit
4. Treatment with oral glucocorticoids >7.5 mg prednisone equivalents per day within 3 months prior to screening visit or plans to begin treatment with oral glucocorticoids >7.5 mg prednisone equivalents per day during the study period

5. 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
6. Estimated GFR of <30 mL/min/1.73 m^2 based on CKD-Epi equation at screening
7. History of heart failure hospitalization, diagnosis of a 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
8. Advanced heart failure (New York Heart Association Class 3 to 4) or severe and uncontrolled hypertension at screening
9. History of HIV or HIV seropositivity at screening visit
10. Uncontrolled infection with hepatitis B or hepatitis C infection, or known active tuberculosis at screening
    a. Patients will be tested for hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening.
    b. Patients with hepatitis B (HBVsAg+) who have controlled infection (serum HBV DNA 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.
    c. 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.
11. A history of an anaphylactic reaction to monoclonal antibody therapeutics
12. If a patient has any medical condition which impacts HbA1c levels (eg, hemolytic anemia or blood transfusion), the sponsor should be consulted before the investigator decides whether to enroll the patient.
13. Participation in any clinical research study evaluating an 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 involve procedures (eg, muscle biopsies) or testing (eg, MRI) that will not interfere with the current study is permitted.
14. 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

    NOTE: A patient who has a documented, positive reverse-transcriptase polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or positive serology for SARS-CoV-2 may be enrolled provided the following:

    a. Repeat RT-PRC testing for SARS-CoV-2

A) For patients with a positive test ≤90 days before screening, the patient must have 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**
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

B) For patients with a positive test >90 days before screening, then the patient must have 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)

OR

b. The patient provides documented vaccination for SARS-CoV-2

15. Pregnant or breast-feeding women
16. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include:

    – Stable use of progestogen-containing hormonal contraception, or transdermal estrogen hormonal contraception, associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening

    – Intrauterine device (IUD); intrauterine hormone-releasing system (IUS)

    – Bilateral tubal ligation

    – Vasectomized partner (provided that partner is the sole sexual partner of the WOCBP patient and that the vasectomized partner has received medical assessment of the surgical success)

    – And/or sexual abstinence†, ‡.

    * Women of childbearing potential is defined as women who are fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

    A postmenopausal state is defined as age greater than 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 (LAM) are not

acceptable methods of contraception. Female condom and male condom should not be used together.

17. Sexually active adult or adolescent men who are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period and for 4 months 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 4 months 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 study assessments, as described in Section 9.1.6.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Patients

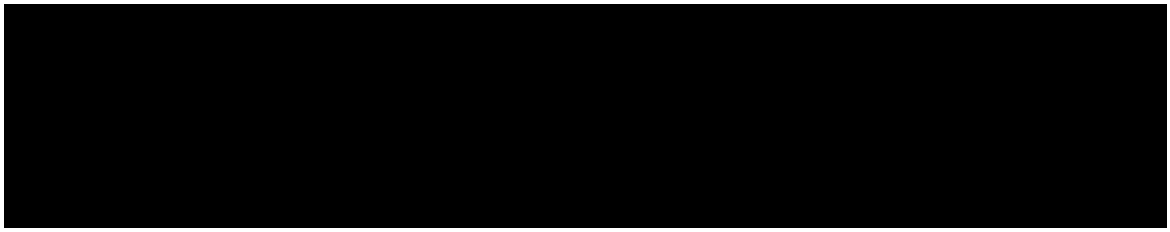
Patients prematurely discontinued from the study will not be replaced. Up to 26 patients will be enrolled to account for an expected 20% dropout rate.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The investigational product is REGN4461, an IgG4 monoclonal antibody agonist to the leptin receptor. REGN4461 will be supplied for IV or SC administration. Placebo-matching REGN4461 is prepared in the same formulation without the addition of protein. Instructions on dose preparation are provided in the Pharmacy Manual and Nursing Manual.

Treatment Arm A will receive the following:



Treatment Arm B will receive the following:

[redacted]

During OLTP 4 ([redacted]), both treatment arms will continue to receive weekly SC administration of high-dose REGN4461 ([redacted]). During OLTP 4, REGN4461 may be administered at the clinical site, by the site personnel or another healthcare professional at a remote location (eg satellite site, patient's home, school, or place of work), or self-administered/administered by a designated person (eg, caregiver), respectively. For patients who choose to self-administer REGN4461, training on self-administration must be performed by qualified study personnel, and the first occurrence of self-administration must be observed by same study personnel. In addition, a medication administration diary will be provided to the patient/designee prior to initiation of self-administration or administration by a designated person such as a parent or caregiver. The diary must be completed upon each study drug administration. For self-administration/administration by a designated person, an Instructions For Use document shall be provided with instructions for reconstitution of IP and administration.

During OLTP 5 (starting no sooner than when the last enrolled patient has reached 52 weeks and Protocol Amendment 3 has been approved at the site, please see detailed description above in the section describing OLTP 4) both treatment arms will receive a[redacted] IV followed a week later by weekly injections of [redacted] SC QW for [redacted]. Exceptions to this include patients who have lost >10% weight loss since baseline and/or in the opinion of the investigator and in consultation with the study's medical monitor the weight loss is considered excessive. In addition, any patient that experiences significant spontaneous hypoglycemia (Section 3.1.3) will not undergo the dose increase. Spontaneous hypoglycemia is defined as hypoglycemia that occurs in the absence of exogenous insulin or insulin secretagogues. Patients that do not undergo the dose increases will not undergo any loading dose at the beginning of OLTP 5 and will continue the dose they were receiving in OLTP 4 during OLTP 5. Those patients that begin the [redacted] in OLTP 5 and experience excessive weight loss or significant hypoglycemia as described above will have their dose reduced to [redacted] SC QW.

Table 2: [redacted]

[redacted]

8.2. Run-in Treatment(s)

There will be a 4-week single-blind placebo run-in period (week -4 through day 1). At the beginning of the placebo run-in period, patients will receive an IV placebo infusion, followed 1 week later by SC injections of placebo, administered once weekly for [redacted]

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

At the beginning of OLTP 5 (at least week 52) patients in both treatment arms will receive a [redacted] IV followed a week later by weekly injections of [redacted] SC QW for [redacted]. Exceptions to this include patients who have lost >10% weight loss since baseline and in the opinion of the investigator, in consultation with the study's medical monitor, are considered to be experiencing excessive weight loss. In addition, any patients that experiences significant spontaneous hypoglycemia that is considered adverse by the investigator will not undergo the dose increase. Spontaneous hypoglycemia (<70 mg/dL) is defined as hypoglycemia that occurs in the absence of exogenous insulin or insulin secretagogues. Patients that do not undergo the dose increases will not undergo any loading dose at the beginning of OLTP 5 and will continue the dose they were receiving in OLTP 4 during OLTP 5. Those patients that begin [redacted] SC QW.

8.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for an early termination visit which consists of assessments performed at the EOT visit and remaining study visits starting with the off-drug follow-up period (Table 6).

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.6.

8.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- 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) >8 x upper limit of normal (ULN) or

  - ALT or AST >5 x ULN for more than 2 weeks or
  - ALT or AST >3 x ULN and total bilirubin >2 x ULN (or international normalized ratio (INR) >1.5)
- For individuals with abnormal baseline transaminase and liver enzyme levels:
  - ALT or AST >3 x over baseline and total bilirubin >2 x over baseline (or international normalized ratio (INR) >1.5)
- Patient withdraws consent
- Investigator's clinical judgment that it is in the best interest of the patient

8.3.2.2. 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 and if this is determined to be in the patient's best interest. However, the Regeneron medical monitor should be contacted as soon as possible in any case of temporary or permanent study drug discontinuation. If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor. Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.4. Management of Acute Reactions

8.4.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available in the treatment unit for immediate use. All infusion reactions must be reported as adverse events (AEs) (as defined in Section 10.4.1) and graded using the grading scales as instructed in Section 10.5.1.

8.4.1.1. Interruption of the Intravenous Infusion

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

- 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.

8.4.1.2. Termination of the Intravenous Infusion

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

- Anaphylaxis*δ
- 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)

δ If anaphylaxis is suspected, all efforts should be made to collect additional blood samples within 30 minutes of the onset of symptoms for measurement of serum tryptase. In case of suspected systemic hypersensitivity or anaphylaxis additional blood samples may also be collected for the assessment of REGN4461 drug concentration and immunogenicity.

8.4.2. Acute Injection Reactions

8.4.2.1. Systemic Injection Reactions

Patients should be observed for 30 minutes after the first SC injection in clinic.

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 10.4.1) and graded using the grading scales as instructed in Section 10.5.1.

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

8.4.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.5.1.

8.5. Method of Treatment Assignment

All eligible patients will begin the single-blind placebo run-in period within 4 weeks of screening. Upon completion of a 4-week run-in period, up to 26 patients will be randomized in a 1:1 ratio in Treatment Arm A or Treatment Arm B. Central randomization scheme will be 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 (HbA1c ≤8% vs HbA1c >8%) at the screening visit.

8.5.1. 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.

An unblinded pharmacist or qualified, unblinded designee will reconstitute study drug (for IV and SC injections) and prepare the IV infusion bags. Further details are provided in the Pharmacy Manual or Nursing Manual.

Investigators will be blinded to specific endpoints, including but not limited to HbA1c, TG, and other lipids, for the entire length of the double-blind treatment period (up to week 24). However, there may be extenuating circumstances (eg, interruptions of biospecimen shipments to the central laboratory due to COVID-19 restrictions, expedited laboratory results needed to assess potential safety finding, etc.) in which laboratory assessments may be performed at a local laboratory. Based on the protocol schedule of events, these assessments are not expected to be unblinding, and this contingency mitigates risk of losing critical study data.

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

Any unblinded analyses used for dose adequacy decisions will be executed with controlled dissemination to ensure the integrity of ongoing data collection. No study personnel involved in the day-to-day conduct of the study will have access to any patient randomization assignments before the database is locked for this study.

8.5.2. 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).

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

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded and open-label 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 (when applicable), these lists will not be accessible to individuals involved in study conduct. Study drug will be stored at a temperature of 2ºC to 8ºC; storage instructions will be provided in the Pharmacy Manual, Nursing Manual, and Instructions for Use document.

8.6.2. 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.

Patients may be allowed to receive study drug from the investigator at regular interval when attending visits at the clinical site for administration by a nurse, caregiver, and/or self-use. Patients will be provided with an appropriate transport container and instructions for use. Study drug, opened and unopened, must be returned to the site for appropriate reconciliation and destruction by the sponsor or designee.

8.6.3. 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.

8.6.4. Treatment Compliance

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

8.7. Concomitant Medications and Procedures

Any treatment administered or procedure performed (eg, vaccination) from the time of informed consent to final study visit will be considered concomitant medication or procedure. This includes medications that were started before the study and are ongoing during the study.

8.7.1. Prohibited Medications

Prohibited medications are:

- Recombinant human leptin (metreleptin, Myalept®), starting 1 month prior to study start and throughout the duration of the study
- All over-the-counter and prescription weight loss medications eg orlistat (Xenical®, Alli®), lorcaserin (Belviq®), phentermine-topiramate (Qsymia®), naltrexone-bupropion (Contrave®) starting 1 month before the study start and throughout the duration of the study

8.7.2. Permitted Medications

All medications except those listed in Section 8.7.1, are permitted.

Every attempt should be made to keep concomitant medications, permitted 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: Documentation of concomitant medications, doses of medications, and other medical treatments (eg, apheresis) will occur according to the schedule of assessments in Table 3, Table 4, Table 5, Table 6, and Table 7. **All concomitant medication changes that occur during the course of the study must be recorded.**

Diabetes medications: If a patient is taking diabetes medications at the beginning of the study, REGN4461 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 (glucose <100 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 10.3.3. New hyperglycemia requiring treatment is defined as follows: Fasting glucose ≥250 mg/dL (13.9 mmol/L) 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, REGN4461 will be added to existing therapy. No changes to lipid lowering medications (medication addition, discontinuation, or dose adjustments) should be made during the course of the study, unless as needed for safety.

Antidepressant medications: concomitant antidepressant medications should continue at current doses throughout the course of the study. Additions, discontinuations, or dose modifications of anti-depressant medications may occur only if a safety concern necessitates.

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 3, Table 4, Table 5, Table 6, and Table 7.

Table 3: Screening and Placebo Run-In

Study Period	**Screening**	**Placebo Run-In**			
	In-Clinic Outpatient Visit[1,2]	**In-Clinic Outpatient Visit[2]**	**In-Clinic Outpatient Visit or Remote Visit[3]**		
Visit Number:	[redacted]				
Day:					
±Visit Window (d):					
Week:					
Screening/Baseline					
Informed Consent	X				
Inclusion/Exclusion	X	X			
Medical History[4]	X				
Demographics	X				
HIV Serology and Hepatitis Testing (HBsAg, HCV)	X				
Treatment and Medications					
[redacted]					
Safety[6]					
Vital Signs	X	X	X	X	X
Height[7]	X				
Weight	X	X			
Physical Examination[8]	X	X			
Tanner Staging	X				
Electrocardiogram[9]	X				
Adverse Events	X	X	X	X	X

Study Period	**Screening**	**Placebo Run-In**			
	In-Clinic Outpatient Visit[1,2]	**In-Clinic Outpatient Visit[2]**	**In-Clinic Outpatient Visit or Remote Visit[3]**		
Visit Number:					
Day:					
±Visit Window (d):					
Week:					
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[10]	X	X	X	X	X
Laboratory Testing[11]					
Hematology	X	X[12]			
Blood Chemistry	X	X[12]			
Pregnancy Test (WOCBP)[10]	Serum	Urine			
Urinalysis	X				
Leptin		X			
Efficacy[11]					
Fasting Triglycerides and Glucose[2]	X[2]	X[2]			X
HbA1c, Fructosamine	X	X			
Insulin/C-peptide[2]	X[2]	X[2]			
Urine Protein, Creatinine, Albumin		X			
COA Training[13]		X			
Daily Appetite Hunger and Eating Behavior PRO[13]		X ←	→		X
Sensation of Body Temperature PRO		X			
SF-36 Questionnaire/PedsQL™ [14]		X			
Patient Global Impression of Severity		X			
Liver MRI (volume/fat content)[15]		X			
VCTE[15]		X			

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

9.1.1. Footnotes for the Schedule of Events Table 3: Screening and Placebo Run-In

1. Patients may be re-screened if they fail the screening for reasons related to incidental or transitory conditions (eg, medication use, concomitant illness, medical condition). If patients are re-screened within the original 4-week screening period, only screening test(s) (eg, an out-of-range lab value) that resulted in initial screen failure should be repeated.
2. Procedures may be conducted on different days during the screening/baseline period, if needed. Blood draws for laboratory testing at the screening visit and visit 2 will be collected in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
3. Procedures may be conducted by trained study staff at a remote location (ie, at home visits, work, and/or school).
4. Medical history should include detailed lipodystrophy history including prior medication/investigational products, genetic diagnosis (if known), imaging results, leptin levels (if known) and results of any previous anti-metreleptin antibody testing (if applicable).
5. [redacted]
6. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
7. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least approximately every 3 months until patient reaches Tanner stage 5.
8. Complete physical examination will be performed at screening (visit 1) and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.
9. The electrocardiogram (ECG) can be performed up to 24 hours prior to study drug administration.
10. Menstrual events and pregnancy status of WOCBP will be monitored throughout the study. A serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed locally (eg, point-of-care) at subsequent visits. A positive urine pregnancy test should be confirmed with a serum test.

11. Study assessments should be performed, and blood samples are to be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure.
12. Samples for hematology and blood chemistry analysis do not need to be collected at visit 2 if visits 1 and 2 occur within 48 hours of each other.
13. Patients must receive eCOA training at the time they receive the eCOA device. Additionally, patients must be trained on the Daily Appetite Hunger and Eating Behavior PRO prior to completion of PRO assessments. Patients will be instructed to fill out the Daily Appetite Hunger and Eating Behavior PRO on a daily basis. The site will check the patient's adherence to completion of all study questionnaires at each designated visit.
14. SF-36 is to be completed by patients 18 years or older, and PedsQL™ is to be completed by patients 12 to 17 years of age. The PedsQL™ will be a PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
15. Liver fat content and liver volume MRI scans, VCTE, and whole body DXA will be performed only at sites where these techniques are available. Liver MRI scans, VCTE, and whole body DXA can be performed from day -28 to day 1 prior to dosing of study drug.
16. Biomarker blood draw samples will be collected pre-dose.
17. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone (Section 9.2.7.1).
18. [redacted]

Table 4: Double-Blind Treatment Period 1

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

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

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

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

[redacted]

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

1. In-clinic stay can begin within a ±2-day window. [redacted] assessments only needs to occur for patient who have consented to [redacted]. All other patients may choose to be admitted on day -1. Patients will have the option to leave on the same day of study drug administration after being observed for at least 4 hours, provided all required assessments and procedures have been completed on that day.
2. Assessments/procedures other than those occurring during in-clinic stays may be conducted by trained study staff at a remote location (ie, at home visits, work, and/or school).
3. Randomization can occur within 24 hours prior to day 1 study drug administration if necessary.
4. [redacted]
5. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
6. [redacted]
7. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least approximately every 3 months until patient reaches Tanner stage 5.
8. This body weight will be used for dose tier determination. Body weight may be measured up to 24 hours prior to day 1 study drug administration and must be measured prior to randomization.
9. The ECG can be performed up to 24 hours prior to study drug administration.
10. Menstrual events and pregnancy status of WOCBP will be monitored throughout the study. A urine pregnancy test will be performed locally (eg, point-of-care). A positive urine pregnancy test should be confirmed with a serum test.
11. Study assessments should be performed, and blood samples are to be collected before study drug administration unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure.

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

    [redacted]

    For sites that do not have the ability to perform a clamp study but do have a qualified and experienced ITT facility and staff, patients will undergo an ITT. Patients with a history of seizure disorder should not undergo ITT. Blood samples will be collected for the analysis of glucose, insulin, C-peptide timed as follows: 2 baseline samples before starting insulin administration and at 5, 10, 15, 20 and 30 minutes after starting the insulin administration.

    [redacted]
14. Patients presenting to sites without qualified and experienced facility and staff to perform a clamp or ITT will not undergo clamp or ITT evaluation. This procedure can be done within 3 days prior to day 1.
15. Patients must be in a fasted state (after at least approximately a 12-hour fast) prior to MMTT assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Blood samples will be collected on the days of the MMTT for the analysis of glucose, insulin, C-peptide, and TGs. Sampling times are as follows:
    - For glucose analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For insulin analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For C-peptide analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes
    - For TG analysis: -15, 0 (premeal), 30, 60, 90, 120, and 180 minutes

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

16. Additional blood samples will be collected on the days of WMG assessments, timed as follows: (1) less than 30 minutes prior to lunch, (2) 120±10 minutes after lunch, (3) less than 30 minutes prior to dinner, (4) 120±10 minutes after dinner, and (5) 10 PM or bedtime. This procedure must be done on the same day as MMTT. Blood samples will be analyzed for glucose, insulin and for C-peptide.

17. Patients must receive eCOA training at the time they receive the eCOA device. Additionally, patients must be trained on the Daily Appetite Hunger and Eating Behavior PRO prior to completion of PRO assessments. If the patient was previously trained on both the eCOA and the PRO assessments, no additional training is required at this time. Patients will be instructed to fill out the Daily Appetite Hunger and Eating Behavior PRO on a daily basis. The site will check the patient's adherence to completion of all study questionnaires at each designated visit.
18. SF-36 is to be completed by patients 18 years or older, and PedsQL™ is to be completed by patients 12 to 17 years of age. The PedsQL™ will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
19. Collection of blood samples for drug concentration on day 1 will be pre-infusion/injection and at the end of infusion ±15 mins. On other visits, drug concentration and biomarker samples will be collected pre-dose. Samples for sLEPR, ANGPTL3, and PCSK9 should be collected at the time points that drug concentration is measured. On all visits ADA and drug concentration samples should be collected prior to administration of drug.
20. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone (Section 9.2.7.1).
21. [redacted]
22. Complete physical examination will be performed on day 1 (visit 8) and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.

Table 5: Double-Blind Treatment Periods 2 and 3

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

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

Study Period	Double-Blind Treatment Period 2										Double-Blind Treatment Period 3								
	In-Clinic Stay[1]			In-Clinic Outpatient Visit or Remote Visit [2]							In-Clinic Stay[1]		In-Clinic Outpatient Visit or Remote Visit[2]						
Visit Number:																			
Day:																			
±Visit Window (d):																			
Week:																			
Urine Protein, Creatinine, Albumin		X										X							
Insulin Sensitivity Measurement[11,12]		X																	
MMTT[13]	X										X								
Weighted Mean Glucose Assessment[14]	X										X								
COA Training[15]	X																		
Daily Appetite Hunger and Eating Behavior PRO[15]	X	←																	X →
Sensation of Body Temperature PRO	X										X								
SF-36 Questionnaire/ PedsQL™ [16]	X										X								
Patient Global Impression of Severity	X										X								
Patient Global Impression of Change	X										X								
Exit Interview	X[17]																		
Liver MRI (volume/fat content) [18]	X																		

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

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

1. In-clinic stay may begin within a ±2-day window. Patients will have the option to leave on the same day of study drug administration after being observed for at least 4 hours, provided all required assessments and procedures on that day have been completed.
2. Assessments/procedures other than those occurring during in-clinic stays may be conducted by trained study staff at a remote location (ie, at home visits, work, and/or school). However, [redacted]
3. [redacted]
4. All safety assessments should be performed before study drug administration, if possible, unless otherwise indicated.
5. Vital signs should be recorded [redacted]
6. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least approximately every 3 months until patient reaches Tanner stage 5.
7. The ECG can be performed up to 24 hours prior to study drug administration.
8. Menstrual events and pregnancy status of WOCBP will be monitored throughout the study. A serum pregnancy test will be performed at the screening and EOS visit and urine pregnancy test performed locally (eg, point-of-care) at subsequent visits. A positive urine pregnancy test should be confirmed with a serum test.
9. Study assessments should be performed, and blood samples are to be collected before study drug administration unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure.
10. Patients must be in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.

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

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

12. Patients presenting to sites without qualified and experienced facility and staff to perform a clamp or ITT will not undergo clamp or ITT evaluation. This procedure can be done [redacted]

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

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

This procedure can be done [redacted]

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

15. Patients must receive eCOA training at the time they receive the eCOA device. Additionally, patients must be trained on the Daily Appetite Hunger and Eating Behavior PRO prior to completion of PRO assessments. If the patient was previously trained on both

the eCOA and the PRO assessments, no additional training is required at this time. Patients will be instructed to fill out the Daily Appetite Hunger and Eating Behavior PRO daily through week 24. The site will check the patient's adherence to completion of all study questionnaires at each designated visit.

16. SF-36 is to be completed by patients 18 years or older and PedsQL™ is to be completed by patients 12 to 17 years of age. The PedsQL™ will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form).
17. Exit interviews will be conducted either during in-clinic stay for DBTP2 [redacted].
18. Liver volume and fat content MRI and whole body DXA scans may be performed [redacted]. These tests will only be performed at sites where these techniques are available. Patients may be required to fast at least 5 hours prior to an MRI scan.
19. Collection of blood samples for drug concentration on [redacted] will be pre-infusion and at the end of infusion ±15 mins. On other visits, drug concentration and biomarker samples will be collected pre-dose. Samples for sLEPR, ANGPTL3, and PCSK9 will be collected at the time points that drug concentration is measured. On all visits ADA and drug concentration samples should be collected prior to administration of drug.
20. Endocrine hormones include but are not limited to luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone (Section 9.2.7.1).

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

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

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

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

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

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

7. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least approximately every 3 months until patient reaches Tanner stage 5.
8. Menstrual events and pregnancy status of WOCBP will be monitored through the EOS visit. A urine pregnancy test will be performed locally (eg, point-of-care). A positive urine pregnancy test should be confirmed with a serum test.
9. Study assessments should be performed, and blood samples are to be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure. At all visits, PK, ADA, and ANGPTL3/PCSK9/sLEPR samples should be collected prior to the administration of drug.
10. Patients must be in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
11. Patients must be in a fasted state (after at least approximately a 12-hour fast) for insulin sensitivity assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.

    Insulin sensitivity will be measured by clamp at sites where a qualified and experienced facility and staff are available. Blood samples for the clamp will be collected for the analysis of glucose, insulin, C-peptide at following times: 2 baseline samples within 30 minutes before starting insulin infusion and up to 4 samples during the 30 minutes long steady state. Additional samples will be analyzed for point of care glucose measures during insulin infusion, as outlined in the study manual. [redacted]

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

days of the MMTT for the analysis of glucose, insulin, C-peptide, and TGs. Sampling times are as follows:

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

This procedure can be done within 3 days prior to day 168.

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

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

	Open-Label Period[1]											Off-Drug Follow-up Period[13]			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:	[redacted]														
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Treatment and Medications															
[redacted]															

	Open-Label Period[1]											Off-Drug Follow-up Period[13]			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:	[redacted]														
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
[redacted]															
Safety[5]															
Vital Signs[6]	X		X		X		X		X		X	X	X	X	X
Height[7]	X		X		X		X		X		X				X
Weight	X		X		X		X		X		X	X	X	X	X
Tanner Staging[7]	X		X		X		X		X		X		X		X
Physical Examination	X				X		X				X[12]				X[12]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Open-Label Period[1]											Off-Drug Follow-up Period[13]			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:															
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Menstrual History, Pregnancy Status Reporting, and Confirmation of Contraception[8]	X				X		X		X		X		X		X
Laboratory Testing[9]															
Hematology	X		X		X		X		X		X	X	X		X
Blood Chemistry	X		X		X		X		X		X	X	X		X
Pregnancy Test (WOCBP)[8]	X				X		X		X		X		X		Serum
Urinalysis	X				X		X		X		X				X

	Open-Label Period[1]											Off-Drug Follow-up Period[13]			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:	[redacted]														
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
Efficacy[9]															
Fasting Triglycerides and Glucose[10]	X		X		X		X		X		X	X	X		X
HbA1c	X				X		X		X		X		X		X
Lipid Panel[10]	X				X		X		X						X
Urine Protein, Creatinine, Albumin	X						X				X				X
Liver MRI (volume/fat content)[11]	X										X				
Whole body DXA[11]	X				X						X				
VCTE[11]	X										X				

	Open-Label Period[1]											Off-Drug Follow-up Period[13]			
	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit[1]	In-Clinic Outpatient Visit	In-Clinic Outpatient Visit or Remote Visit			In-Clinic Outpatient Visit
											EOT				EOS
Visit Number:	[redacted]														
Day of OLTP 5:															
±Visit Window (d):															
Week of OLTP 5:															
PK/Biomarker/ Drug Concentration and ADA Samples[9]															
REGN4461 Concentration Blood Sample	X		X		X		X		X		X				X
ADA Sample	X						X				X				X
ANGPTL3, PCSK9, sLEPR	X		X		X		X				X				X

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

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

7. In individuals under 18 years of age, standing height should be recorded at least approximately every 3 months. Tanner staging for pubertal development should be performed at least every 3 months until patient reaches Tanner stage 5.
8. Menstrual events and pregnancy status of WOCBP will be monitored through the EOS visit. A serum pregnancy test will be performed at the EOS visit a urine pregnancy test will be performed locally (eg, point-of-care). A positive urine pregnancy test should be confirmed with a serum test.
9. Study assessments should be performed, and blood samples are to be collected before study drug administration, unless otherwise indicated. For patients undergoing apheresis, study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure. Study drug will be administered after the apheresis procedure.
10. Patients must be in a fasted state (after at least approximately a 12-hour fast). The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting.
11. Liver volume and fat content MRI and VCTE may be [redacted] Whole body DXA may be [redacted] If the patient had their [redacted] whole body DXA and/or liver MRI within 28 days prior to [redacted], the applicable procedure does not need to be repeated at [redacted]. These tests will only be performed at sites where these techniques are available. Patients may be required to fast at least 5 hours prior to an MRI scan.
12. Complete physical examination will be performed at the EOT and EOS visits and includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. Limited physical examination will be performed on all remaining visits and includes lungs, heart, abdomen, and skin.
13. Patients who complete the EOT visit associated with OLTP 5 and have secured access to continued REGN4461 treatment through other means, (eg, another Regeneron-sponsored clinical trial, compassionate use, or an expanded access program), may forgo any or all of the off-drug follow-up [redacted] and proceed to the EOS visit. These patients will be considered study completers.

9.1.6. Early Termination Visit

Patients who discontinue treatment before the end of the Open-Label Treatment Period 4 at week 52 but who remain in the study will complete the early termination visit consisting of assessments listed for the EOT visit. After completing the early termination visit, patients who have discontinued study drug but who remain in the study will enter the off-drug follow-up period (Table 7). 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. Patients who complete the EOT visit associated with OLTP 5 and have secured access to continued REGN4461 treatment through other means (eg, another Regeneron-sponsored clinical trial, compassionate use, or an expanded access program),

may forgo any or all of the off-drug follow-up visits 119-121 and proceed to the EOS visit. These patients will be considered study completers.

9.1.7. Unscheduled Visits

Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. Additional blood samples may be collected if necessary.

9.2. Study Procedures

In circumstances where clinically indicated (eg, in patients with low body weight, anemia, or significant co-morbid illness), blood sample collections may be reduced or eliminated to maintain patient safety and comply with adequate blood volume considerations. A prioritization list for samples to be collected will be provided in the laboratory manual. For example, safety laboratory and PK samples will be prioritized over other blood sample collections.

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. Safety Procedures

9.2.2.1. Vital Signs

Vital signs, including temperature, blood pressure, pulse, and respiration will be collected after the patient has been sitting or supine position at time points according to Table 3, Table 4, Table 5, Table 6, and Table 7.

9.2.2.2. Physical Examination, Body Weight, Height, and Tanner Stages

A thorough and complete physical examination must be performed at screening (visit 1), day 1 (visit 8), end of the treatment (EOT), and end of study visits (EOS). Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination. Limited physical examination will include lungs, heart, abdomen, and skin and care should be taken to examine and assess any abnormalities that may be present. Physical exam will be performed according to Table 3, Table 4, Table 5, Table 6, and Table 7 and may be limited in scope if appropriate as indicated by the patient's medical history.

Physical exams for the screening visit may be conducted on a different day from the initial screening visit, as long as they are conducted within the screening window.

Body weight will be measured at time points according to Table 3, Table 4, Table 5, Table 6, and Table 7. Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes. The same type/model of scale should be used throughout the study.

In individuals under 18 years of age, standing height should be recorded at least every 3 months using a stadiometer at time points according to Table 3, Table 4, Table 5, Table 6, and Table 7. Patients should be instructed to remove footwear and stand upright with their heels together.

Tanner staging for pubertal development should be performed at least every 3 months at time points according to Table 4, Table 5, Table 6, and Table 7. If the patient reaches Tanner stage 5, this assessment will be no longer performed. Whenever possible, the same trained health care professional will conduct the Tanner staging at each assessment.

9.2.2.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 3, Table 4, Table 5, and Table 6.

Twelve-lead ECGs will be collected after the patient has been in the supine position for at least 10 minutes. The electrodes should be positioned in the same location, as much as possible, for each ECG recording.

The ECG will be interpreted locally by the investigator. If new and/or clinically significant changes in ECG parameters are observed, a repeat ECG should be immediately performed for confirmation before making any decision for the concerned patient. Any clinically significant abnormality should be documented as an AE/SAE, as applicable.

Heart rate will be calculated from the ventricular rate (or RR interval) and recorded. The PR or PQ, QRS, and QT (QTcF) intervals will be recorded. The ECG recordings and reports will be retained with the source.

9.2.2.4. 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 3, Table 4, Table 5, Table 6, and Table 7 to identify any changes in occurrence, frequency, or duration following study drug treatment.

9.2.2.5. 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. Patients who have been instructed by their treating physicians to routinely self-monitor glucose using a glucometer will be asked to enter glucose values into an electronic patient diary. The purpose of the electronic patient diary is to facilitate prompt interaction with their study site if low blood glucose values are recorded. Low blood glucose values will trigger an alert for the patient to call the site and the site will be automatically notified to call the patient. This monitoring is not intended to replace protocol adverse events of special interest and other safety reporting procedures.

9.2.3. 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 3, Table 4, Table 5, Table 6, and Table 7. 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" (ie, fasting TG, fasting lipid panel, and fasting glucose).

For patients undergoing [redacted] INR/PTT and platelets will be done locally. Additional laboratory testing may be performed and analyzed locally, per local standard practice or local regulations [redacted].

Tests will include:

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)	
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	
Magnesium		
Phosphorus		

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urine Studies

Protein	Glucose
pH	Bilirubin
Specific gravity	Leukocytes
Ketones	Nitrite

Endocrine Laboratory Tests

Luteinizing hormone	Estradiol	Testosterone

Follicle-stimulating hormone

Other Laboratory Tests

HbA1c	Pregnancy test (serum/urine)
Fructosamine	
Leptin	
Hepatitis B surface antigen (sAg)	HIV (Ab)
INR	PTT
Total Protein/Creatinine/Albumin (Urine)	
Hepatitis C (Ab)	

Lipid Panel

LDL-C	NMR lipoprotein analysis
HDL-C	Apolipoprotein B
Total Cholesterol	Triglycerides

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 10.4.5.

9.2.4. Efficacy Procedures

9.2.4.1. Fasting Triglycerides

Samples for fasting TG will be collected at visits according to Table 3, Table 4, Table 5, Table 6, and Table 7.

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.

9.2.4.2. Fasting Glucose

Samples for fasting glucose will be collected at visits according to Table 3, Table 4, Table 5, Table 6, and Table 7.

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.

9.2.4.3. Hemoglobin A1C

Hemoglobin A1C will be collected at visits according to Table 3, Table 4, Table 5, Table 6, and Table 7 (see Section 9.2.3).

9.2.4.4. Fructosamine

Samples for fructosamine will be collected at visits according to Table 3, Table 4, Table 5, and Table 6.

9.2.4.5. Insulin/C-peptide

Samples for insulin/C-peptide will be collected at visits according to Table 3, Table 4, Table 5, and Table 6.

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.

9.2.4.6. Lipid Panel

Samples for lipid panel LDL-C, HDL-C, total cholesterol, and Apolipoprotein B will be collected at visits according to Table 3, Table 4, Table 5, Table 6, and Table 7. For patients with TG >400 mg/dL, direct LDL-C measurement will be used. Lipoproteins will be analyzed by NMR.

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.

9.2.4.7. Urine Protein, Creatinine, and Albumin

Samples for urine protein, creatinine, and albumin will be collected at visits according to Table 3, Table 4, Table 5, Table 6, and Table 7.

9.2.4.8. Insulin Sensitivity Measurement

Insulin sensitivity will be assessed using clamp technique or ITT per site's capability, at visits according to Table 3, Table 4, Table 5, and Table 6. Patients with a history of seizure disorder should not undergo ITT. Assessments will be performed in the fasted state. The duration of fasting may be shortened for patients with a documented clinical contraindication to prolonged fasting. Additional details on both procedures are provided in the study manual. The blood samples drawn during insulin sensitivity procedures may be decreased if clinically indicated, eg, in patients with

low body weight, anemia, or significant co-morbid illness. Details for blood sample assessments in at-risk patient populations will be provided in the study manual.

9.2.4.9. Mixed Meal Tolerance Test

An MMTT will be conducted at the time points specified in Table 4, Table 5, and Table 6. Blood samples will be collected by study personnel before and after the morning MMTT for the analysis of glucose, insulin, C-peptide, and TGs according to the sampling schedule as shown in Table 4, Table 5, and Table 6. Patients must be in a fasted state (after at least approximately a 12-hour fast) for insulin sensitivity assessments. The duration of fasting may be shortened for patients with a documented clinical contraindication to fasting. Additional details on procedure are provided in the study manual.

9.2.4.10. Weighted Mean Glucose

Samples for WMG assessment will be collected throughout the day during in-clinic visits according to Table 4, Table 5, and Table 6. Additional details on the WMG assessment procedures are provided in the study manual.

9.2.4.11. Assessment of Body Composition

Patients will undergo whole body DXA scans to examine body composition. DXA is extensively used in clinical whole-body skeletal densitometry. Total examination times are brief (~6 to 7 minutes) and ionizing radiation doses are minimal below 0.05 mSv.

Whole body DXA imaging will be performed per the schedule outlined in Table 3, Table 4, Table 5, Table 6, and Table 7. Whole body DXA scans will be performed only at sites with whole body DXA capability.

9.2.4.12. Assessment of Hepatic Fat Content and Liver Size**

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

MRI imaging will be performed per the schedule outlined in Table 3, Table 4, Table 5, Table 6, and Table 7.

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.

[redacted]

**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. The sponsor will not provide any incidental findings to the study patient, principal investigator, any other physician treating the study patient or any other third party. If a site has a policy regarding return of research findings (incidental or otherwise), or a country has local regulations regarding these findings, or if an Ethics

Committee or Institutional Review Board requires return of said findings, the principal investigator is responsible for complying with these requirements.

9.2.4.13. Assessment of Liver Stiffness by Vibration-Controlled Transient Elastography (VCTE)

Vibration-controlled transient elastography (eg, FibroScan®) uses transient elastography to measure the stiffness of the liver. Some GLD patients with NASH may have increased liver stiffness, reflective of an accumulation of fibrotic scar tissue. VCTE is used for assessing liver cirrhosis and/or advanced-stage liver fibrosis. Liver stiffness will only be assessed at sites with VCTE capability (Table 3, Table 6, and Table 7).

9.2.5. Patient-Reported Outcome Measures

9.2.5.1. Daily Appetite and Eating Behavior PRO

This PRO measure instrument is being developed specifically for this trial in order to assess hunger, cravings, eating behaviors, and emotional aspect of eating among patients with lipodystrophy. The development of the diary is in accordance with the Food and Drug Administration's (FDA's) guidance on PRO development.

Patients will complete the PRO assessments daily, unless otherwise noted in Table 3, Table 4, Table 5, and Table 6. Patients who are enrolled prior to approval and availability of the PRO instrument will complete the daily PRO assessment once it becomes available. Patients who are incapable of completing the PRO (eg, illiteracy) are still eligible to participate in the study but will not complete PRO assessments.

9.2.5.2. Questions Assessing Sensation of Body Temperature

Self-administered questions developed specifically for this trial will assess the patient's sensation of body temperature. Patients will be asked to rate how often they felt uncomfortably cold in the past 24 hours and how often they felt uncomfortably hot in the past 24 hours. Patients will complete this PRO assessments as noted in Table 3, Table 4, Table 5, and Table 6.

9.2.5.3. Short Form – 36 Survey

The Short Form – 36 Survey (SF-36) is a 36-item self-administered PRO measure assessing health-related quality of life (HRQoL) concepts relevant across age, disease, and treatment group. The SF-36 will be completed by patients ages 18 years of age and older. The SF-36 assesses physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Patients answer questions assessing these concepts over the previous week using 3-, 5-, or 6-point Likert scales; scores range from 0 to 100, with higher scores indicating better health. The past-week recall has been compared to the 4-week recall and is shown to have comparable properties (Keller, 1997). The SF-36 is one of the most widely used and studied PRO measures, with good psychometric properties documented across different populations (Table 3, Table 4, Table 5, and Table 6).

9.2.5.4. Pediatric Quality of Life Inventory Generic Core Scales

The Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales is a measure assessing HRQoL in children and adolescents. The PedsQL™ will be used to measure HRQoL in patients ages 12 to 17. The PedsQL™ is a 23-item measure that assesses physical functioning, emotional functioning, social functioning, and school/work/studies functioning. The instructions for PedsQL™ ask how much of a problem each item has been over the past 7 days on a 5-point response scale, ranging from never a problem (0) to almost always a problem (4). The measure will be a self-administered PRO for patients ages 13 to 17 years (teen report) and for patients 12 years of age (child form). The items for each of the teen and child forms for patients are essentially identical, differing primarily in the use of developmentally appropriate language. Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate better HRQoL. The total scale score is computed as the sum of all the items over the number of items answered on individual scales (Table 3, Table 4, Table 5, and Table 6). The PedsQL™ was developed using focus groups, cognitive interviews, pre-testing, and field testing measurement development protocols (Varni, 1999) and has demonstrated validity, reliability, ability to detect change, and responsiveness (Varni, 2001) (Varni, 2002) (Varni, 2003) (Desai, 2014).

9.2.5.5. Patient Global Impression of Severity

Patient Global Impression of Severity (PGIS) items are self-administered PRO questions assessing the patient's perception of the overall severity of the symptoms of their disease and/or of a specific symptom of their disease. At study visits (see Table 3, Table 4, Table 5, and Table 6), patients will be asked to rate the severity of specific symptoms of lipodystrophy (ie hunger, cravings, eating behaviors) on a Likert scale ranging from "not at all" to "very much."

9.2.5.6. Patient Global Impression of Change

Patient Global Impression of Change (PGIC) items are self-administered PRO questions assessing the patient's perception of the change in overall severity of the symptoms of their disease and/or of a specific symptom of their disease, compared to the start of the study (Table 6). At weeks 8, 16 and 24 patients will be asked to rate the severity of specific symptoms of lipodystrophy compared to before the start of the study on a 7-point Likert scale ranging from "much better" to "no change" to "much worse."

9.2.5.7. Exit Interview in Relation to Hunger and Eating Behavior PROs

At the time point of the primary endpoint [redacted] patients will be interviewed to ensure the Hunger PRO is fit-for-purpose under the context of use for GLD patients (Table 6). Results from exit interviews will also be used to contextualize findings on the COA assessments. Each interview will last approximately 60 minutes and will be conducted by trained external interviewers following a semi-structured interview guide.

9.2.6. Pharmacokinetic/Drug Concentration and Immunogenicity Samples

9.2.6.1. REGN4461 Concentration Measurements

Samples for REGN4461 will be collected during DBTP 1 at the visits listed in Table 4, during DBTP 2 and 3 at the visits listed in Table 5, and during OLTP 4 and 5 at the visits listed in Table 6 and Table 7. All samples will be collected prior to dose administrations with the exception of IV loading dose samples, which will be collected both prior to and after dose administrations, as described in table footnotes. Any unused samples may be used for future biomarker research for patients who consent.

9.2.6.2. 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 3, Table 4, Table 5, Table 6, and Table 7.

9.2.6.3. Circulating Biomarkers for Pharmacodynamic Assessments

Angiopoietin-Like Protein 3 (ANGPTL3)

Angiopoietin-like protein 3 is an endogenous inhibitor of lipoprotein lipase, which regulates circulating levels of TG (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 3, Table 4, Table 5, Table 6, and Table 7.

Total Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

Proprotein convertase subtilisin/kexin type 9 is a convertase enzyme that promotes degradation of the LDL receptor, resulting in reduced LDL clearance. Gain-of-function mutations in PCSK9 are associated with elevated LDL-C levels, while loss-of-function mutations are associated with lower serum LDL-C and protection from cardiovascular risk. PCSK9 inhibitors have been approved for treating hypercholesterinemia and have been efficacious at reducing serum cholesterol levels and decreasing the rate of major cardiovascular events. Female GLD patients had a reduction in plasma PCSK9 levels after 4 to 6 months of metreleptin therapy (Levenson, 2016). PCSK9 might be a mechanistic marker indicative of the lipid-lowering effects of REGN4461. Total PCSK9 will therefore be assessed at time points noted in Table 3, Table 4, Table 5, Table 6, and Table 7.

9.2.6.4. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3, Table 4, Table 5, Table 6, and Table 7. [redacted]

9.2.7. Pharmacodynamic and Exploratory Biomarker Procedures

[redacted]

9.2.7.1. Endocrine Hormones

Lipodystrophy patients have disruption in endocrine hormone regulation that can result in amenorrhea and hyperandrogenism. Hyperandrogenism and amenorrhea are corrected in a subset of individuals on metreleptin therapy. Metreleptin therapy resulted in lower testosterone levels within 4 months of therapy and restored regular menstrual cycles in patients with irregular menstrual cycles or primary amenorrhea (Musso, 2005). Endocrine levels will be assessed at time points noted in Table 3, Table 4, Table 5, and Table 6. Endocrine hormones include, but are not necessarily limited to, luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone.

9.2.7.2. Immunophenotyping

In patients with congenital GLD, infections have been described as one of the major causes of mortality, which suggests a compromised immune system (Lima, 2018). As leptin signaling is associated with inducing immune cell activation (Dayakar, 2016), it is possible that REGN4461 treatment in patients with lipodystrophy might affect, in a positive manner, immune cell numbers or function. To explore this possibility, whole blood will be collected for performing flow cytometry analysis of immune cell populations, including T cell subsets (Table 4 and Table 5).

9.2.8. [redacted]

[redacted]

[redacted]

9.2.9. Future Biomedical Research (Optional)

[redacted]

9.2.9.1. Pharmacogenomic Analysis (Optional)

[redacted]

10. SAFETY DEFINITIONS, REPORTING, AND MONITORING

10.1. Obligations of Investigator

The investigator must promptly report to the IRB/EC all unanticipated problems involving risks to patients, according to local regulations. This may include death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, according to local regulations.

10.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IRBs/ECs, as appropriate, and to the investigators in a blinded manner.

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected. Any worsening of or new onset of symptoms related to GLD which occur during the screening/washout period prior to study drug administration will be considered expected.

In addition, the sponsor will report in all other SAEs to the health authorities, according to local regulations.

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 ECs/IRBs as appropriate.

10.3. Definitions

10.3.1. 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.

An AE also includes any 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.

10.3.2. 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 admission to a hospital (any duration), or an

emergency room stay 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)

Note: In addition to the criteria above, a new diagnosis or progression of a malignancy in patients enrolled in the study will also be considered an SAE.

Criteria for reporting SAEs must be followed for these events. See Section 10.4 for more information on recording and reporting SAEs.

10.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern 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. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 10.4.3). AESI for this study include:

- Hypoglycemia, defined as blood glucose <54 mg/dL.
- New onset diabetes mellitus (NODM)

  For patients with no diabetes at baseline:

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

   OR

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

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

- Hyperglycemia requiring treatment: this is 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

10.3.4. Infusion Reactions

[redacted]

10.4. Recording and Reporting Adverse Events

10.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study.

Information on follow-up for AEs is provided in Section 10.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 10.4.5.

10.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study or within 112 days of last study drug administration if the patient early-terminated from the study – the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit – only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

10.4.3. 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:

Symptomatic Overdose of Study Drug: 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.

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 study patient, or female partner of a male study patient, during the study or within 112 days 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.

Adverse Events of Special Interest: All AESIs, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 10.4.2. Adverse events of special interest for this study are detailed in Section 10.3.3.

10.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

10.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- The test result is associated with accompanying symptom(s), and/or
- The test result requires additional diagnostic testing or medical/surgical intervention, and/or
- The test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event that the investigator feels an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 10.5.1.

10.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

10.5. Evaluation of Severity and Causality

10.5.1. Evaluation of Severity

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

Mild: Does not interfere in a significant manner with the patient's 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

10.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the blinded investigator and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug.

Related: There is a reasonable possibility that the event may have been caused by the study drug.

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study drug?

No:

- Due to external causes such as environmental factors or other treatment(s) being administered
- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not reappear or worsen when dosing with study drug is resumed
- Is not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- Could not be explained by environmental factors or other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolves or improves after discontinuation of study drug
- Reappears or worsens when dosing with study drug
- Is known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

Relationship of Adverse Events to Study Conduct:

The relationship of AEs to study conduct will be assessed by the blinded investigator and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct.

Related: There is a reasonable possibility that the event may have been caused by study conduct.

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study conduct?

No:

- Due to external causes such as environmental factors or other treatment(s) being administered
- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the course of the study
- Does not reappear or worsen when dosing with study participation is resumed

Yes:

- Could not be explained by environmental factors or other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follows a reasonable temporal sequence following the course of the study
- Resolves or improves after discontinuation from study participation
- Reappears or worsens when study participation is resumed

10.6. 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; 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.

10.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the reference safety information in the Investigator's Brochure and has a reasonable, suspected causal relationship to the study drug).

11. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP may be revised during 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 database is locked.

The first-step analysis will be conducted as soon as all patients have been randomized and all data through week 36 has been entered, cleaned and locked. The first-step analysis will be conducted on all randomized patients who receive study treatment. These statistical analyses will include the primary and secondary endpoints collected during the double-blind period, as well as the open-label week 36 visit in OLTP 4.

The second-step analysis will be conducted as soon as all patients have been randomized and all data through week 56 has been entered, cleaned and locked. The second-step analysis will be conducted on all randomized patients who receive study treatment. These statistical analyses will include pharmacokinetic and safety measures.

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

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

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

Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

No formal statistical hypothesis will be tested. This study will assess the effects of REGN4461 on glycemic parameters in a subset of patients with elevated baseline HbA1c (≥7%) and fasting serum TG in a subset of patients with elevated baseline TG (≥250 mg/dL). HbA1c at screening visit (HbA1c ≤8% vs. HbA1c >8%) is the stratification factor for patient randomization.

11.2. Justification of Sample Size

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

Metreleptin demonstrated a 2% drop in HbA1c (standard deviation [SD]=1.5%) and a 50% drop in fasting TG (SD=40%) from baseline to month 4 (Myalepta, 2018) (FDA, 2013). As a conservative treatment effect estimation for 8 weeks, the anticipated drop in HbA1c is 1.5%. The change in fasting TG is expected to be the same at week 8 as at week 16. With 20 patients completing the study (10 patients per study arm, assuming approximately a 20% dropout rate from 26 patients), the minimal detectable change (MDC) and power for the study are provided in Table 8 as below, for a 2-sided alpha of 0.05 test.

Table 8: Minimal Detectable Change and Power for HbA1c, Fasting Glucose, WMG, and Fasting TG Separately (N=20, 10 Treated vs. 10 Placebo, Assuming Approximately 20% Dropout Rate from 26 Patients)

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

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

If the glycemic and lipid subsets for the primary analysis have fewer patients with abnormal TGs or fasting glucose values, the table below (Table 9) provides minimal detectable change and power for the subset analysis.

Table 9: Minimal Detectable Change and Power for HbA1c, Fasting Glucose, WMG, and Fasting TG in the Subset Analyses (N=20, Assuming Approximately 20% Dropout Rate from 26 Patients)

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

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

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 Sets

The PK population includes all treated patients who received any study drug and who had a qualified result for drug concentration on day 1 (baseline) and at least 1 non-missing result following the first dose of study drug.

11.3.4. Anti-Drug Antibody Analysis Sets

The ADA population includes all treated patients who received any study drug and who had at least 1 non-missing ADA result following the first dose of study drug. Patients will be analyzed according to the treatment actually received.

11.3.5. Glycemic Analysis Set

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

11.3.6. Triglyceride Analysis Set

The triglyceride analysis set includes all patients who are in the FAS and have elevated baseline fasting TG (TG ≥250 mg/dL).

11.3.7. MRI Analysis Set

The MRI analysis set includes all patients who are in the FAS and eligible for the MRI test (some patients are not eligible for the MRI due to MRI contraindications or some sites do not have the technical capability to perform liver MRI).

11.3.8. Clamp Analysis Set

The clamp analysis set includes all patients who are in the FAS and eligible for the clamp test (some patients are at the sites where there is no clamp capability).

11.3.9. Clamp Glycemic Analysis Set

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

11.3.10. Insulin-Tolerance Test Analysis Set

The ITT analysis test includes all patients who are in the FAS, are not eligible for the clamp test, and are eligible for the qualified ITT (some patients are at the sites without clamp capability, but which have qualified ITT).

11.3.11. Insulin-Tolerance Test Glycemic Analysis Set

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

11.3.12. [redacted]

[redacted]

11.4. Statistical Methods

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

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of randomized patients: received a randomization number
- The total number of patients who completed OLTP 4 (defined as at least 51 weeks of study treatment exposure and week 52 visit performed)
- The total number of patients who completed OLTP 5 (defined as at least 103 weeks of study treatment exposure and week 104 visit performed)
- 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 patient prematurely discontinued from treatment, along with reasons for discontinuation
- The total number of patients in each analysis set

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment arm (Treatment Arm A or Treatment Arm B), and by all patients combined.

11.4.3. Efficacy Analyses

The goal of the study is to estimate the effect of REGN4461 on metabolic parameters in patients with GLD. Comparisons to baseline and between-group comparison will be provided with nominal p-values. There will be no statistical hypothesis testing and no multiplicity will be applied. Logarithm transformation will be performed to normalize the fasting TG.

11.4.3.1. Primary Efficacy Analysis

The primary objective is estimating the treatment effect of REGN4461 on improving metabolic abnormalities. The glycemic endpoint will be run in the glycemic subset of patients (subset with baseline HbA1c $\geq$7%), and fasting TG endpoint will be run in the TG subset of patients (subset with baseline TG $\geq$250 mg/dL).

For primary endpoints, fasting TG, fasting glucose, HbA1c, and WMG, the study assesses the treatment effect of REGN4461 from baseline to week 8 for patients receiving REGN4461 in the DBTP 1 (within-group comparison) and for all patients (between-group comparison). Published data (Oral, 2002) suggest that fasting glucose and fasting TG had the greatest improvement within the first 2 months following metreleptin initiation.

Summary statistics including mean change from baseline, standard error (SE), corresponding 95% confidence interval, and nominal p-value will be provided by treatment group (REGN4461 or placebo at the DBTP 1), using a mixed effect repeated measurement model (MMRM), which will account for the missing data. The model includes the factors (fixed effects) for treatment, week, and treatment-by-week interaction. Relevant baseline HbA1c and/or TG will be included as a continuous covariate. An unstructured covariance structure will be used (if that does not converge, then structured covariance structures such as autoregressive heterogeneous [ARH] will be assessed). If the model does not converge with the MMRM, analysis of covariance (ANCOVA) will be used to estimate the treatment effect of REGN4461. Additional details will be provided in the SAP.

Mean absolute value changes in WMG (mg/dL), HbA1c (%), fasting glucose (mg/dL), and mean percent change in fasting TG will be summarized by treatment group at the DBTP 1. Mean changes (±SE) will be plotted over time by the treatment group. A spaghetti plot will be provided for primary endpoints by the treatment group.

In addition, posterior probability that the improvement in each of the primary endpoints is greater than zero will be computed at week 8 separately for patients receiving REGN4461. Non-informative prior will be used for the posterior probability. The posterior probability will also be used to assess the treatment effect of REGN4461.

11.4.3.2. Secondary Efficacy Analysis

Most of the secondary endpoints will use the FAS for the analyses. Other secondary endpoints will use a subset of patients, eg, with elevated baseline HbA1c; with elevated baseline TG; qualify to perform the MRI test; at sites with clamp capability, etc, in the FAS.

For secondary endpoints measured in the double-blind period, summary statistics, including mean change from baseline, SE, 95% confidence interval, and nominal p-value will be provided using the MMRM with contrast. For secondary endpoints measured after the double-blind period (after week 24), descriptive statistics will be provided. Unless otherwise specified, all secondary analyses will be considered as within-group comparison. Details will be provided in the SAP.

For HbA1c endpoint:

- [redacted]
- [redacted]

For fasting glucose and fasting TG endpoints:

- [redacted]

- [redacted]

For WMG and MMTT:

- [redacted]
- [redacted]

For clamp and ITT endpoints:

- [redacted]

Change from week 8 to week 16 for patients in Treatment Arm A will be provided as above to estimate the treatment effect of the low dose. If the patients do not have a significant reduction in HbA1c or TG from baseline to week 8, defined as change in HbA1c (absolute value change is less than -0.4%, change in TG [percent change] is less than -20%), then their data from week 8 to week 16, after they have switched to the low dose of REGN4461, will be pooled with data from baseline to week 8 for patients in Treatment Arm B, to evaluate the treatment effect of low dose on fasting glucose, fasting TG, WMG, MMTT, and HbA1c. Similarly, if there is not a significant reduction from baseline to week 8 for patients in Treatment Arm A, data from patients in Treatment Arm A (change from week 16 to week 24) will be pooled together with data from patients in Treatment Arm B (change from week 8 to week 16) to estimate the treatment effect of increasing the dose from a low-dose regime to a high-dose regime. MMRM or ANCOVA will be used.

Mean and/or percent change from baseline will be plotted over time by treatment group based on the DBTP 1.

For the secondary objective, the REGN4461 treatment effect will be evaluated based on a composite "Z score" of HbA1c and TG to see whether REGN4461 can improve the metabolic abnormality. The composite score is constructed as follows:

For every patient, the composite "Z score" is derived based on HbA1c and fasting TG in the placebo run-in period (at baseline) and at the end of DBTP 1 (week 8). The REGN4461 treatment effect for each patient is calculated as:

$$Z_{(HbA1c\_chg)} = \frac{HbA1c_{BL} - HbA1c_{week8}}{SD_{(HbA1c)}}$$

$$Z_{(logTG\_chg)} = \frac{logTG_{BL} - logTG_{week\ 8}}{SD_{(logTG)}}$$

$SD_{(HbA1c)}$ and $SD_{(logTG)}$ will be computed using the baseline data from all patients:

$$Z_{(composit\_chg)} = \begin{cases} Z_{(HbA1c\_chg)}\ if\ baseline\ HbA1c \geq 7\%\ and\ TG < 250\ mg/dL \\ Z_{(logTG\_chg)}, if\ baseline\ HbA1c < 7\%\ and\ TG \geq 250\ mg/dL \\ \frac{Z_{(HbA1c\_chg)} + Z_{(logTG\_chg)}}{2}, if\ baseline\ HbA1c \geq 7\% \text{ and } \mathrm{TG} \geq 250\ \mathrm{mg/dL} \end{cases}$$

MMRM will be used to evaluate the REGN4461 effect for both between-group and within-group comparison, mean, SE, and 95% confidence interval at week 8 will be provided.

More details of the analysis plan will be described in the SAP.

11.4.4. Safety Analysis

11.4.4.1. Adverse Events

Definitions

For safety variables, 7 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 blinded treatment period 1 is defined as the day from first dose of study drug to [redacted]
- The blinded treatment period 2 is defined as the time from [redacted]
- The blinded treatment period 3 is defined as the time from [redacted]
- The Open-Label Treatment Period 4 is defined as [redacted]
- The Open-Label Treatment Period 5 is defined as [redacted]
- Combined OLTP (period 4 + period 5)
- The posttreatment period is defined as the time after the last dose of study drug.
- The all-treatment period is defined as the day from the first dose of the study drug to EOT.

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

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

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

11.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) and weight 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.

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.

Listings will be provided with flags indicating the out-of-laboratory-range values.

Electrocardiogram

Electrocardiogram parameters, including QTc, will be summarized over time. Abnormal ECG status will be summarized.

Number and percentage of patients with a PCSV for vital signs or ECG parameters, at any post-randomization time point, will be summarized. The PCSV criteria will be defined before database lock.

11.4.4.3. Treatment Exposure

Treatment exposure during the study will be summarized by treatment arm. Details will be provided in the SAP.

11.4.4.4. Treatment Compliance

Treatment compliance will be summarized. Details will be provided in the SAP.

11.4.5. Pharmacokinetics

11.4.5.1. Analysis of Drug Concentration Data

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

11.4.5.2. Analysis of Pharmacokinetic Parameters

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

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

Parameters will be summarized by standard descriptive statistics and may be suitably normalized by dose and/or body weight.

11.4.6. Analysis of Anti-Drug Antibody 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 less than 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
  - The treatment-emergent responses will be further characterized as persistent, indeterminate, or transient.
    - 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 [redacted] 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 ADA positivity, treatment-emergent ADA, and titers presented by patient, time point, and dose tier will be provided. Prevalence 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.

11.4.7. Analysis of Pharmacodynamic and Exploratory Biomarker Data

[redacted]

11.5. Interim Analysis

No formal IA is planned. Details of other analyses are described in Section 6.2. An unblinded team within Regeneron will review PK, PD, efficacy, and safety data to confirm the adequacy of the dose.

11.6. Statistical Considerations Surrounding the Premature Termination of the 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 17.1.

12. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

12.1. 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 case report form (CRF) data for this study will be collected with an electronic data capture (EDC) tool, Medidata Rave.

12.2. Electronic Systems

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

- IWRS system – randomization, study drug supply

- EDC system – data capture: Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

13. STUDY MONITORING

13.1. 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 methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. Risk-based quality monitoring strategies include: reduced source data verification, targeted source data review, 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.

13.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

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.

13.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. 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.

14. 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.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. 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.

Informed Consent

ADULT PATIENTS:

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 the 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, 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.

PEDIATRIC PATIENTS:

The principles of informed consent are described in ICH guidelines for Good Clinical Practice.

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 and his/her parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents'/guardians' consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the 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's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the patient 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's parent(s) or legal guardian(s).

15.2. 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.

15.3. 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 approval letter with a current list of the IRB 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 review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

16. PROTOCOL AMENDMENTS

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

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

17.1. 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.

17.2. 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.

18. STUDY DOCUMENTATION

18.1. 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 eCRFs that will be provided to the sponsor.

18.2. 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. \

19. DATA 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 summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 12.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 13.1, Section 13.2, and Section 14).

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 (Section 13.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRFs (Section 13.3 and Section 18.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 13.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 18.2).

20. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

21. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

22. PUBLICATION POLICY

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

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24. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-Blind, Placebo-Controlled Study of REGN4461, A Leptin Receptor Agonist Antibody, in Patients with Generalized 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. 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)

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 conduct of the study.

Study Title: A Randomized, Double-Blind, Placebo-Controlled Study of REGN4461, A Leptin Receptor Agonist Antibody, in Patients with Generalized Lipodystrophy

Protocol Number: R4461-GLD-1875

Protocol Version: R4461-GLD-1875 Amendment 4

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-00328257 v1.0

Approval/eSignature	[redacted] 06-Dec-2023 15:44:20 GMT+0000

Approval/eSignature	[redacted] 06-Dec-2023 15:45:02 GMT+0000

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