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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A THREE-PART, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF EVINACUMAB IN PEDIATRIC PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	REGN1500 (Evinacumab)
Clinical Phase:	1b/3
Protocol Number:	R1500-CL-17100
Protocol Version:	R1500-CL-17100 Amendment 2
Amendment 2 Date of Issue:	*See appended electronic signature page*
Amendment 1 Date of Issue:	07 May 2020
Original Date of Issue	11 Dec 2019
Medical /Study Director:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Overall Rationale for Amendment 2

The overall rationale of the amendment is to allow patients who enter into the compassionate use program (CUP) or early access program (EAP) to forgo the follow-up period of the study. The follow-up period was intended to be an off-drug follow-up period. For patients entering EAP, there may be no off-drug follow-up period. In addition, due to difficulties in recruitment, the overall study participant target population is being reduced from 24 to 20, and the part B target is being reduced from 18 to 14.

The following table shows the changes made to the protocol and the affected sections:

Change	Rationale	Sections Changed
Decreased the target sample size in part B from 18 to 14	Despite rigorous efforts, recruitment of additional pediatric Homozygous Familial Hypercholesterolemia (HoFH) patients has been challenging. Therefore, the sample size has been reduced from 18 to 14.	Clinical Study Protocol Synopsis, Study Design, Part B Clinical Study Protocol Synopsis, Population, Sample Size, Statistical Plan Section 1 Introduction Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Allowed patients who enter the CUP or EAP to forgo the 24-week follow-up period in this study after the last dose	The 24-week follow-up period was intended to be an off-drug period. With many physicians and Principal Investigators (PIs) applying for or expressing interest in CUP or EAP for evinacumab, the sponsor is amending the protocol to allow patients to forgo the off-drug follow-up period if they are acquiring early access to evinacumab. This is to avoid the patients having a 24-week period off drug with uncontrolled Low-density lipoprotein cholesterol (LDL-C) levels.	Clinical Study Protocol Synopsis, Study Design, Part C Synopsis, Study Duration Section 6.1 Study Description and Duration Figure 3 Study Flow Diagram - Extension Section 9.1 Schedule of Events, Part C Section 9.1.1.3 Footnotes for the Schedule of Events Table – Part C, footnote #14, and new footnote #17 Section 9.1.2 Early Termination Visit Section 10.1.2 Data Collection Period
Editorial changes/typographical errors	Revised for accuracy, consistency, and clarity	Throughout the protocol

Amendment 1

The following table shows the changes made to the protocol and the affected sections:

Change	Rationale	Sections Changed
The study design has been revised. The treatment period of Part	The primary objective of Part B is to demonstrate efficacy, and the primary	Synopsis – Site Location(s), Study Design, Study Duration, and Population - Sample

Change	Rationale	Sections Changed
B has been reduced from 48 weeks to 24 weeks. The treatment period of Part C has been reduced from up to 3 years to 48 weeks.	efficacy endpoint is percent change from baseline in calculated LDL-C at week 24. As such, the treatment period of Part B now matches the timing of the efficacy endpoint. Part C has been reduced to allow the study to complete in a timely manner, but still provide sufficient exposure to assess long-term safety and tolerability(inclusive of the 24-week follow-up period).	Size, Treatment(s) – Background, Endpoints - Secondary Section 2.3 Exploratory Objectives Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 6.1.1 Description of Dose Selection Section 7.1 Number of Patients Planned Section 7.2.2 Exclusion Criteria #4 Section 8.3 Background Treatments Section 8.4.2 Study Drug Discontinuation Section 8.9.1 Prohibited Medications Section 8.9.2 Permitted Medications Table 1 Schedule of Events – Part A, PK and PD Portion Table 2 Schedule of Events – Part B, 24-week Efficacy and Safety Portion Table 3 Schedule of Events – Part C Section 11.4.3.2 Secondary Efficacy Analysis for Part B Section 11.5.3 Third Step: Final Safety Analysis
Removed the use of acceptable methods of contraception (double barrier), updated the contraception requirements to only include highly effective contraception, and added the duration that highly effective contraception should be used in case a patient becomes sexually active during the study and initiates contraception use.	Highly effective contraception should be used for 24 weeks after the last dose of evinacumab because that is generally the duration evinacumab concentrations remain above the lower limit of quantitation	Section 7.2.2 Exclusion Criteria, #15 and #16
Added absolute change in LDL-C at week 24 as an endpoint.	This was an omission from the original protocol	Section 4.1.2 Secondary Endpoints
Added an exclusion criterion for patients who are accommodated in an institution by official or court order.	Requested by an Ethics Committee	Section 7.2.2 Exclusion Criteria, #17

Change	Rationale	Sections Changed
Added neurocognitive events, new onset of diabetes, pancreatitis, and moderate or severe infusion reactions to list of AESIs	Additions made in response to FDA comments.	Section 10.1.4 Events that Require Expedited reporting to Sponsor
Clarifications and corrections: Clarified rationale for dose selection Provided more detailed safety data for risk benefit assessment Clarified inclusion criterion for informed consent and assent Clarified exclusion criterion for hypersensitivity to mAbs Infusion of evinacumab over 65 minutes instead of 1 hour Clarified weight measure to be used to calculate dose of evinacumab. Removed serum pregnancy tests throughout. Only urine pregnancy tests will be done. Updated visits and timing of some laboratory assessments, Tanner stage, and PK, Updated footnotes for schedule of events tables. Removed assessments at visit 1 of Part C, and added imaging at Visit 7 of Part C. Clarified early termination visit. Removed "long term extension" and OLTP.	Changes made to clarify protocol, make corrections, and correct inconsistencies	Section 3.2.2 Rationale for Dose Selection Section 3.3 Risk Benefit Section 4.1.3 Exploratory Endpoints Section 5.6 Ultrasound Imaging Section 7.2.1 Inclusion Criteria #7 Section 7.2.2 Exclusion Criteria, #12, #13 Section 8.1 Investigational and Reference Treatments Table 1 Schedule of Events – Part A, PK and PD portion Table 2 Schedule of Events – Part B, 24-week Efficacy and Safety Portion Table 3 Schedule of Events – Part C Section 9.1.1.1 Footnotes for Schedule of Events Table 1 #8 and #17 Section 9.1.1.2 Footnotes for Schedule of Events Table 2 #16 and #17 Section 9.1.1.3 Footnotes for Schedule of Events Table 3 #13, #15, #16 Section 9.1.2 Early Termination Visit Section 10.2.6 Causality Section 11.3.1 Efficacy Analysis Set for Part B Section 11.3.2 Safety Analysis Set Section 11.4.1 Patient disposition Section 11.4.3.3 Other Efficacy Analyses for Part B Section 11.4.5 Safety Analysis Section 11.4.5.1 Adverse Events Section 11.4.5.2 Other Safety Section 11.4.5.3 Treatment Exposure Section 11.4.5.4 Treatment Compliance Section 11.4.7 Analysis of Immunogenicity Data

Change	Rationale	Sections Changed
Instead, referred to Part C and treatment period.		
Added statements to address the impact of the COVID-19 pandemic on the conduct of the study,	To explain the plan for ensuring continuity of clinical study activities and study oversight activities during the COVID-19 public health emergency.	Section 3.3 Risk-Benefit Section 9 Study Schedule of Events and Procedures

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
Apo	Apolipoprotein
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
cIMT	Carotid intima-media thickness
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CUP	Compassionate use program
CVD	Cardiovascular disease
EAP	Early access program
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
FH	Familial Hypercholesterolemia
GCP	Good Clinical Practice
HDL	High-density lipoprotein
HoFH	Homozygous Familial Hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDLRAP1	Low-density lipoprotein receptor adaptor protein 1
LMT	Lipid-modifying therapy

LOF	Loss of function
mAb	Monoclonal antibody
NAb	Neutralizing antibody
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
QW	Weekly
Q2W	Every 2 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia
Site Location(s)	The study will be conducted globally (eg, Europe, North America, Asia) at approximately 24 sites.
Principal Investigator	To be determined
Objective(s)	**Primary** The primary objective for Part A of the study is to assess the pharmacokinetics (PK) of evinacumab in pediatric patients with homozygous familial hypercholesterolemia (HoFH). The primary objective for Part B of the study is to demonstrate a reduction of low-density lipoprotein (LDL) cholesterol (LDL-C) by evinacumab in pediatric (5 to 11 years of age) patients with HoFH. **Secondary** The secondary objective for Part A of the study is to evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH The secondary objectives for Part B of the study are: • To evaluate the effect of evinacumab on other lipid parameters (ie, Apo B, non-HDL-C, TC, lipoprotein a [Lp(a)]) in pediatric patients with HoFH • To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH • To assess the PK of evinacumab in pediatric patients with HoFH • To assess the immunogenicity of evinacumab in pediatric patients with HoFH over time • To evaluate patient efficacy by mutation status
Study Design	**Part A** is a phase 1B single-dose, open-label study to determine the safety, PK and pharmacodynamics (PD) of evinacumab 15 mg/kg intravenous (IV) in approximately 6 patients ages 5 to 11 years with HoFH. To ensure a distribution of body weight within Part A of the study, every effort will be made to enroll 3 patients <25 kg and 3 patients ≥25 kg. Additionally, to ensure a distribution of ages, every effort will be made to enroll 2 patients <10 years of age. All patients who successfully complete Part A may continue receiving evinacumab in an extension of the study, Part C. Initially, patients from Part A who enter the Part C will receive evinacumab 15 mg/kg IV Q4W. When PK data from all patients in Part A have been sufficiently analyzed, the dose for Part B will be determined using the cumulative data to date with evinacumab and data from Part A. If data from 6 patients is

	insufficient, up to 4 more patients may be enrolled to confirm the dose in Part B. The dose for Part B will also be the final dose in Part C. The dose for Part B (and final dose in Part C) will likely remain at 15 mg/kg IV every 4 weeks (Q4W). However, there is a small possibility that the exposure analysis or the observed PD effect indicate a small increase in the dose is needed for the pediatric population to match the exposure and PD effect observed in adult patients. As such, the dose in Part B (and final dose in Part C) could be between 15-20 mg/kg IV Q4W. A maximum dose of 20 mg/kg is selected as the top dose because it is the highest dose evaluated in the prior evinacumab studies. **Part A** consists of up to 4 periods: run-in, screening, single-dose, open-label treatment, and 16-week observation. Upon completion of Part A, patients will have the opportunity to continue into Part C. **Part B** is a phase 3 single-arm, open-label study to assess the efficacy and safety of evinacumab in pediatric patients (age 5 to 11 years) with HoFH. Part B will begin once dose-selection for Part B has been completed. Part B will enroll approximately 14 pediatric patients. Patients enrolled in Part B will not include patients from Part A. Upon completion of Part B, patients will have the opportunity to continue into the extension, Part C. Part B consists of up to 4 periods: run-in, screening, 24-week open-label treatment, and follow-up (for patients who do not enter the extension, Part C). **Part C** is an extension of the study for patients from both Part A and Part B and consists of 2 periods, a 48-week treatment period and a 24-week follow-up period after the last dose of study drug. All patients from Part A who enter Part C will initially receive open-label evinacumab 15 mg/kg IV Q4W. The final dose in Part C will be the same as the dose in Part B; therefore, the dose in Part C could be adjusted to align with the dose in Part B. Patients who are receiving background LMT or who are undergoing apheresis should make every effort to maintain a stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study to the end of the study. The frequency of apheresis may be reduced during this part of the study based on the investigator's judgement. The Sponsor of this study, consistent with our corporate policy governing access to investigational drugs in confirmatory clinical studies, is committed to provide evinacumab to patients after their participation in this trial has concluded, if permitted per local laws. Agreement to continue treatment beyond this study is a treatment decision that must be made by the investigator, and the patient or their parent/guardian. After completion of the study, investigators interested in continuing treatment with evinacumab in patients considered to have a positive response can discuss post-trial treatment options with the Sponsor, including participation in a CUP or EAP.
Study Duration	For a patient in Part A, the duration of the study is up to approximately 34 weeks, which includes up to an 8-week run-in period, a 2-week screening period, a 16-week open-label treatment and observation period, an 8-week follow-up period (for those patients who decide not to enter Part C). For patients who enter Part C, there will be no follow-up period for Part A and the combined duration of Part A and Part C could be up to 98 weeks, including a 24-week follow-up period after the last dose of study drug in Part C. Although, patients who enter a CUP or EAP may forgo the 24-week follow-up period after the last dose.

	For a patient in Part B, the duration of the study is up to 54 weeks, which includes, up to an 8-week run-in period, a 2-week screening period, a 24-week open-label treatment period, and a 20-week follow-up period (for those patients who decide not to enter Part C). For patients who enter Part C, there will be no follow-up period for Part B and the combined duration of Part B and Part C could be up to 106 weeks, including a 24-week follow-up period after the last dose of study drug in Part C. Although, patients who enter a CUP or EAP may forgo the 24-week follow-up period after the last dose.
End of Study Definition	The end of study is defined as the date of the last visit of the last patient.
Population	
Sample Size:	For Part A, approximately 6 patients are planned. If data from 6 patients is insufficient, up to 4 more patients may be enrolled to confirm the dose in Part B. An additional 14 pediatric patients are planned for Part B and will not include patients from Part A. Patients from both Part A and Part B may enter Part C of the study.
Target Population:	Males and females age 5 through 11 years diagnosed with HoFH receiving any combination of lipid-lowering therapies.
Treatment(s)	
Study Drug	Evinacumab (REGN1500).
Dose/Route/Schedule:	For Part A, a single administration of evinacumab 15 mg/kg IV, given over a 65 minute infusion For Part B, evinacumab with a dose determined by Part A, will be administered IV over a 65 minute infusion Q4W starting at day 1. The last dose will be at week 20. All patients from Part A who enter Part C will initially receive evinacumab 15 mg/kg IV Q4W. The final dose for Part C will be based on data from Part A and all available data from other evinacumab studies. Therefore, the dose for Part C for patients from Part A may be adjusted once the dose selection for Part B is completed.
Background Treatment	Patients should be on a maximally tolerated lipid-modifying therapy (LMT) regimen. Patients in Part B who are receiving background LMT or who are undergoing lipid apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) from screening to the end of treatment visit (week 24) in Part B.
Endpoint(s)	
Primary:	The primary endpoint for Part A is the PK parameters for evinacumab, including C_{max}, AUC, and linear $t_{½}$ following a single administration of evinacumab.

	The primary endpoint for Part B is the percent change in calculated LDL-C from baseline to week 24 (intent-to-treat [ITT] estimand) in Part B. The primary endpoint is defined as: 100x (calculated LDL-C value at week 24 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline.
Secondary:	The secondary endpoint for Part A is: • Incidence of treatment-emergent adverse events (TEAE) and other safety variables over time The secondary endpoints in Part B are: • The percent change in Apo B from baseline to week 24 (ITT estimand) • The percent change in non-HDL-C from baseline to week 24 (ITT estimand) • The percent change in total cholesterol (TC) from baseline to week 24 (ITT estimand) • The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand) • The percent change in calculated LDL-C from baseline to week 24 in patients who have negative/negative and null/null mutations (ITT estimand) • The percent change in lipoprotein a [Lp(a)] from baseline to week 24 (ITT estimand) • The absolute change in LDL-C at week 24 (ITT estimand) • Incidence of treatment-emergent adverse events (TEAE) and other safety variables over time • Concentrations of total evinacumab over time • Incidence and titer of treatment-emergent anti-drug antibodies over time
Procedures and Assessments	The efficacy of evinacumab in this population will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Overall safety will be assessed by monitoring and evaluation of TEAEs, physical examinations, pulse rate, blood pressure, electrocardiogram (ECG), and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated.
Statistical Plan	Since this is an open-label, single treatment arm study, formal statistical testing is not planned, therefore, a calculation for patient sample size is not applicable. Six patients are planned to be enrolled for Part A and 14 pediatric patients are planned to be enrolled for Part B. **Primary Efficacy Analysis for Part B**. The percent change from baseline in calculated LDL-C at week 24 will be analyzed in the ITT population using

a pattern mixture model (PMM) approach as described below (see Appendix 1 for more details).

In the PMM approach, different imputation strategies will be applied to calculated LDL-C values missing during the on-treatment period (ie, within the time period from the first study treatment administration up to the day of last study treatment administration +35 days in Part B) versus calculated LDL-C values missing due to treatment discontinuation after the on-treatment period (ie, after the day of last study treatment administration +35 days in Part B) based on the following assumptions:

- Patients within 35 days of their last study treatment administration in Part B would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, calculated LDL-C values missing during the on-treatment period (eg, samples obtained outside the specified window, no blood sample available although visit was performed, etc.) should be considered "Missing at Random" and imputed based on other observed measurements in the on-treatment period.
- Patients who stopped taking their study treatment in Part B no longer benefited from it after discontinuation, and thus tended to have calculated LDL-C values returning to baseline. Therefore, calculated LDL-C values missing after the on-treatment period should be imputed based on patient's own baseline value.

Missing data from the ITT population will be imputed 100 times to generate 100 complete data sets, using the SAS MI procedure (using Markov Chain Monte Carlo). The 100 completed datasets of observed and imputed calculated LDL-C data will be used for the primary analysis.

For the percent change from baseline calculated LDL-C endpoint, the 100 complete datasets of observed and imputed calculated LDL-C data at week 24 will be analyzed using the SAS MEANS procedure. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae. Combined estimate for mean at Week 24 will be provided with the standard error (SE) and 95% confidence interval (CI). Formal statistical testing is not planned.

1. INTRODUCTION

Familial hypercholesterolemia (FH), a primary hyperlipidemia driven by genetic mutation(s) primarily in the low-density lipoprotein (LDL) receptor (LDLR), is the most common monogenic hypercholesterolemia condition in children. The most rare and severe form of FH is homozygous familial hypercholesterolemia (HoFH). It is an inherited autosomal dominant disorder primarily resulting from mutations in the LDLR or, less frequently, from mutations in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB), and LDL receptor adaptor protein 1 (LDLRAP1). Depending on the genes affected and the mutations that are present, patients are categorized as either true homozygotes, compound heterozygotes, or double heterozygotes. True homozygotes have the same mutation on both alleles. Compound heterozygotes have different mutations on the 2 alleles. Double heterozygotes have mutations in 2 different genes. The resulting phenotype includes deficient or defective LDL receptors on the surface of hepatocytes causing impaired clearance of circulating low-density lipoprotein cholesterol (LDL-C). This leads to severe hypercholesterolemia, often 3 to 6 times normal (≥500 mg/dL), starting in infancy, which results in an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis.

The etiology of the hypercholesterolemia observed in patients with HoFH is the same for both adult and pediatric patients. It is a consequence of the above mentioned abnormal lipoprotein metabolism due to mutations in the key genes listed above, and the markedly diminished hepatic LDL-C clearance from plasma (Goldstein, 2001)(Kolansky, 2008)(Macchiaiolo, 2012) (Rader, 2003). These high plasma levels lead to vascular damage starting from birth and morphological and functional vascular changes by 8 years of age or earlier. Children as young as 7 years of age can present with coronary atherosclerosis even without any clinically apparent coronary artery disease. This accelerated atherosclerosis results in premature cardiovascular disease (CVD) and an increased risk of CV events at a young age. Evidence of accelerated atherosclerosis include children with increased carotid intima-media thickness (cIMT) and cIMT progression at a rate approximately double that of unaffected siblings. An observational study of HoFH patients showed that the mean age for first major CV event was 20 years (Goldstein, 2001)(Kolansky, 2008)(Macchiaiolo, 2012)(Rader, 2003). Indeed, if left untreated, children and adolescents with HoFH, have an extremely high risk for premature CVD and reduced life expectancy. For example, in a longitudinal study of 39 pediatric patients with HoFH followed for up to 8 years, 88% of patients >16 years of age and 9% <16 years of age developed CVD. Further, during follow-up, 7 patients developed progression of coronary and/or aortic valvular disease and 4 required surgical intervention (Kolansky, 2008), demonstrating the need for early aggressive lipid-lowering therapy in pediatric subjects with HoFH.

The frequency of HoFH in the general population is historically reported as 1/1,000,000. This estimate is based on a heterozygous familial hypercholesterolemia (HeFH) prevalence of 1/500 and the application of the Hardy-Weinberg equilibrium (1/1,000,000 = 1/500 mother * 1/500 father * 1/4 risk for child). However, based on more recent data, HoFH has an estimated prevalence of 1/300,000, which would be the same in children. Populations with a founder effect have higher prevalence rates.

Diagnosis of HoFH can be made based on clinical criteria or genetic criteria (Section 7.2.1). An LDL-C level ≥13 mmol/L (≥500 mg/dL) is consistent with phenotypic HoFH. However, the LDL-C criteria could be lower depending on the presence of positive family history and age of

screening. Additional phenotypic characteristics include premature coronary heart disease, aortic valve disease, and tendon xanthomas in the hands and Achilles tendons. Clinically identified patients could undergo genetic testing to confirm diagnosis.

Patients with HoFH can be further classified based on the phenotype of the LDLR mutation(s), ranging from defective mutations (where the LDLR retains some LDL-binding functionality) to null or negative mutations where no functioning LDLR is expressed. Patients who have LDLR activity <15% are considered null and patients whose LDLR activity is impaired but >15% are LDLR defective (Banerjee, 2019). Another method that could be used to categorize these mutations is to define a negative mutation status as having mutations in stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations (CNVs) predicted to result in the loss of function of the LDLR. The most extreme cases are those patients who are LDL-receptor negative or null in both alleles. These patients tend to have LDL-C levels at the highest end of the range and experience very little efficacy from existing therapies such as statins and PCSK9 inhibitors. As such, significantly accelerated atherosclerosis and worse clinical outcomes are observed in these patients compared to those who are LDLR defective (Kolansky, 2008) (Moorjani, 1993). Patients who are LDLR null or negative develop xanthomas sooner than patients who are LDLR receptor defective, and untreated patients who are LDLR null or negative rarely live past the second decade of life (Kolansky, 2008) (Moorjani, 1993).

Current approved therapies for patients with HoFH include statins, lomitapide, ezetimibe, evolocumab, and lipoprotein apheresis. All but lomitapide are approved for use in pediatric patients ≥12 years of age. Some of the statins are approved in younger patients (rosuvastatin approved in ages ≥6 years; atorvastatin and simvastatin approved for ages ≥10 years). Because the etiology of the disease is the same for both adult and pediatric patients, the overarching goal of therapy is also the same, to lower LDL-C. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the European Atherosclerosis Society (EAS) recommend at least a 50% reduction in LDL-C in all patients with FH to reduce the risk of CVD (Gidding, 2015)(Grundy, 2019)(Wiegman, 2015). The EAS further recommends a target LDL-C <130 mg/dl (3.5 mmol/L) in patients >10 years (Wiegman, 2015). Lipid-lowering therapy should be started as early as possible (Cuchel, 2014) (France, 2016) (Wiegman, 2015).

Angiopoietin-like protein 3 (ANGPTL3) has recently emerged as a target for treatment of elevated levels of LDL-C. Individuals who are homozygous for loss of function (LOF) mutations in ANGPTL3 have lower levels of LDL-C (mean difference of >50% versus control subjects (Minicocci, 2012)). The mechanism by which ANGPTL3 LOF mutations result in lowering LDL-C is not fully understood but appears to be independent of the LDLR. These data suggest that inhibiting ANGPTL3 may be a meaningful and well-tolerated strategy for lowering serum LDL-C in patients with HoFH, especially those considered to have LDLR negative mutations in both alleles.

Evinacumab (REGN1500) is a fully human monoclonal antibody (mAb), created with Regeneron's VelocImmune® technology platform, which specifically binds to and inhibits ANGPTL3. In an open-label, single-arm, proof-of-concept study in patients with HoFH (R1500-CL-1331), evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, 2 weeks after a single dose of 15 mg/kg IV, with a duration of effect of at least

10 weeks (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients in the study had null/null mutations in the LDLR. Treatment with evinacumab in these difficult-to-treat patients reduced LDL-C by an average of 37.3% at week 4 with peak reductions up to 59.5%.

The LDL-C lowering effect observed with evinacumab in the R1500-CL-1331 study was confirmed in study R1500-CL-1629, a large randomized, double-blind, placebo-controlled study consisting of adult and adolescent patients with HoFH. On average, patients entered the trial with a mean baseline LDL-C of 255 mg/dL, despite treatment with other lipid-lowering therapies, including maximally-tolerated statins, PCSK9 inhibitors, ezetimibe, LDL apheresis and lomitapide. The trial met its primary endpoint, showing that adding evinacumab to other lipid-lowering therapies decreased LDL-C by a mean of 49% from baseline to week 24, compared to lipid-lowering therapies alone (47% reduction for evinacumab compared to a 2% increase for placebo, $p<0.0001$). This reduction translates to a mean absolute change in LDL-C of 132 mg/dL from baseline, compared to placebo (135 mg/dL reduction for evinacumab compared to a 3 mg/dL reduction for placebo, $p<0.0001$). The decreases in LDL-C were observed from the first lipid assessment at week 2 and were maintained throughout the 24-week double-blind treatment period. Importantly, similar levels of LDL-C lowering were observed in the most difficult-to-treat null/null or negative/negative patients. The dramatic reduction in LDL-C led to the achievement of LDL-C levels <100 mg/dL in 47% of the patients treated with evinacumab compared to 23% treated with placebo (nominal $p=0.0203$). Evinacumab also reduced apolipoprotein B (Apo B), non-high-density lipoprotein (HDL) cholesterol (non-HDL-C) and total cholesterol (TC) compared to placebo.

The positive efficacy data in the R1500-CL-1629 study were accompanied by an acceptable safety profile. Evinacumab was generally well-tolerated. During the double-blind treatment period, 66% of evinacumab patients and 81% of placebo patients experienced an adverse event (AE). AEs that occurred in at least 5% of patients and more commonly with evinacumab were influenza-like illness (11% evinacumab, 0% placebo) and rhinorrhea (7% evinacumab, 0% placebo). During the double-blind treatment period there was no difference in the incidence of nausea, abdominal pain or diarrhea between treatment groups, and there were no deaths, major adverse cardiovascular events or findings related to hepatic disorders.

The primary purpose of this current study is to demonstrate the efficacy, safety and tolerability of evinacumab in pediatric patients, aged 5 through 11 years, with HoFH. The study will consist of 3 parts: Part A (phase 1b), Part B (phase 3), and Part C (phase 3). Part A is a single-dose, open-label study to determine the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of evinacumab 15 mg/kg intravenous (IV) in approximately 6 patients ages 5 to 11 years with HoFH. Part B is a 24-week, single-arm, open-label study to assess the efficacy and safety of evinacumab in approximately 14 pediatric patients with HoFH. Part B will begin when PK data from all patients in Part A have been sufficiently analyzed to determine the dose for Part B. Part C is an extension of the study available to patients who complete Part A or Part B to continue to receive evinacumab.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective for Part A of the study is:

- To assess the PK of evinacumab in pediatric patients with HoFH

The primary objective for Part B of the study is:

- To demonstrate a reduction of LDL-C by evinacumab in pediatric (5 to 11 years of age) patients with HoFH

2.2. Secondary Objective(s)

The secondary objective for Part A of the study is:

- To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH

The secondary objectives for Part B of the study are:

- To evaluate the effect of evinacumab on other lipid parameters (ie, Apo B, non-HDL-C, TC, lipoprotein a [Lp(a)]) in pediatric patients with HoFH
- To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH
- To assess the PK of evinacumab in pediatric patients with HoFH
- To assess the immunogenicity of evinacumab in pediatric patients with HoFH over time
- To evaluate patient efficacy by mutation status.

2.3. Exploratory Objective(s)

The exploratory objectives of the study are:

- To evaluate the efficacy of evinacumab in the extension of the study (Part C) in patients with HoFH
- To explore vascular changes using imaging techniques

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Blockade of ANGPTL3 with evinacumab will reduce LDL-C in pediatric patients with HoFH.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is intended to demonstrate the efficacy and safety of evinacumab in the treatment of pediatric patients with HoFH. Diagnosis of HoFH will be based on either genotyping or clinical criteria. The genetic definition will include all individuals considered to be

- Homozygotes: presence of the same mutation(s) in both alleles for LDLR, Apo B, PCSK9 or LDLRAP1 (autosomal recessive hypercholesterolemia),
- Compound heterozygotes: presence of different mutations in the same allele
- Double heterozygotes: presence of mutations in different genes

The study will be conducted in 3 parts:

Part A is a single-dose, open-label study to assess the safety, PK, and PD of evinacumab. The purpose of this part of the study is to confirm the dose for Part B and Part C. To address this objective, patients will only receive a single dose of evinacumab, followed by semi-dense PK sampling to adequately assess the PK profile in these patients. To ensure a distribution of body weight within Part A of the study, every effort will be made to enroll 3 patients <25 kg and 3 patients ≥25 kg. Additionally, to ensure a distribution of ages, every effort will be made to enroll 2 patients <10 years of age.

Part B is a 24-week multiple-dose, single-arm, open-label study to assess the efficacy and safety of evinacumab. The purpose of this part of the study is to evaluate the LDL-C lowering effects of evinacumab in pediatric patients with HoFH

Part C is an extension of the study for patients completing Part A and Part B. The purpose of this part of the study is to evaluate the long-term safety of evinacumab in pediatric patients with HoFH. Initially, patients from Part A who enter Part C will receive evinacumab 15 mg/kg Q4W. When all patients complete the PK/PD portion (Part A), the dose for Part B will be determined using the cumulative data to date with evinacumab from prior studies and data from Part A. The dose for Part B will also be the final dose in Part C.

The duration of the study for the study participants will be up to approximately 2 years for patients in Part A (98 weeks) and for patients in Part B (106 weeks), assuming all patients participate in the extension (Part C). This duration was selected to sufficiently assess long-term safety and tolerability, including growth and development.

The primary endpoint of Part B is the percent change in LDL-C from baseline to week 24. LDL-C is an accepted surrogate endpoint for CV risk and has repeatedly been used as the primary endpoint for approval of other HoFH treatments. This study is designed as an open-label trial with the addition of evinacumab on top of patients' existing treatment regimens of maximally tolerated lipid-modifying therapy (LMT), including lipoprotein apheresis. This study

will utilize a run-in period for those patients whose LMT regimen is not stable. This "add-on" design is appropriate because removal of any therapy from patients' existing treatment regimen may lead to an increase in LDL-C and possibly contribute to the serious CV sequelae seen in this severe disease with high CV risk.

3.2.2. Rationale for Dose Selection

The initial dose selected for this study is 15 mg/kg IV Q4W, but could be adjusted to up to a maximum of 20 mg/kg IV Q4W. Evinacumab exhibits marked target-mediated drug disposition (TMDD), on which the impact of age and body-weight has not been thoroughly evaluated. Body weight, in general, has an effect on the linear clearance of mAbs, where mAbs exhibit decreasing exposure with decreasing body weight. This trend is due to the over-correction effect when the dose is scaled down linearly with body weight, while clearance is scaled down in a less-than-linear manner (Zhang, 2015) (Xu, 2019). For this reason, it is possible a dose higher than 15 mg/kg may be needed in pediatric patients so that similar exposures seen in the adult population are achieved. In addition, the similarity or difference in the PK/PD relationship in LDL-C lowering between children younger than 12 years old and adults has not been evaluated. To address these uncertainties, Part A, a single dose PK/PD study will be conducted for pediatric patients with HoFH (5 to 11 years of age). Based on current data collected from adult patients with HoFH, an effect on lowering LDL-C is expected in most patients following a single IV dose of evinacumab. Semi-dense PK samples will be collected to characterize PK of evinacumab in the pediatric population. Total ANGPTL3 concentrations, a target engagement marker, and LDL-C reduction, the efficacy measurement, will be evaluated to characterize the PK/PD relationship. These data will be compared to those observed in adults and adolescents and data analysis will be facilitated by PK/PD modeling and simulation.

A single dose of 15 mg/kg IV is selected for Part A. It is the dose tested in adolescents (age ≥12 to <18 years) and adults (age ≥18 years) with HoFH in the on-going phase 3, double-blind, placebo-controlled study, R1500-CL-1629 and the phase 3 open-label, long-term safety study, R1500-CL-1719. Based on the current PK/PD profile, exposures in Part A are not expected to be higher than those observed in adults and adolescents who received the same dose. A similar degree of LDL-C lowering is also anticipated to those observed in the ongoing studies. The final dose selection will be based on PK/PD data analysis from Part A and all other available data in the evinacumab program. The goals of the dose selection are to: 1) achieve exposure levels in the intended pediatric patients within the range observed in the adult and adolescent patients in phase 3 studies; 2) achieve a similar magnitude of LDL-C reduction as adult patients with HoFH, or to have a magnitude of LDL-C reduction considered adequate for the intended pediatric population; 3) maintain an adequate duration of efficacy during the proposed dosing interval.

The dose for Part B (and final dose in Part C) will likely remain at 15 mg/kg IV every 4 weeks (Q4W). However, there is a small possibility that the exposure analysis or the observed PD effect indicate a small increase in the dose is needed for the pediatric population. As such, the dose in Part B (and final dose in Part C) could be between 15 and 20 mg/kg IV Q4W. A maximum dose of 20 mg/kg is selected as the top dose because it is the highest dose evaluated in the prior evinacumab studies. Preclinical studies in adult cynomolgus monkeys, adult rat, and juvenile rats concluded the no-observed-adverse-effect-level (NOAEL) in those studies was considered to be 100 mg/kg/dose via IV or subcutaneous (SC). The dose range of 15 to 20 mg/kg IV Q4W proposed in the present study is expected to generate steady-state exposure that falls within the

range of systemic exposure measured at the NOAEL levels identified during these nonclinical toxicology studies.

A treatment and observation period up to 16 weeks should be an adequate duration to characterize the full PK/PD profile in this pediatric population and to allow comparisons with the profile observed in the adult patients and the limited number of adolescent patients in the ongoing studies.

3.3. Risk-Benefit

Patients with HoFH have extremely high LDL-C levels are far from their target level and will require significant reductions to get to their treatment goal. Statins are the only pharmacological LMT approved for use in pediatric patients below the age of 10. Unfortunately, they are unable to lower LDL-C sufficiently, even when used in the highest doses and in combination with other therapies. Moreover, the unmet need is greatest in patients with null/null mutations of the LDLR who typically have the highest levels of LDL-C and in whom statins have minimum to no effects. In addition to pharmacologic treatment, lipoprotein apheresis is the standard of care for pediatric patients with HoFH. However, the availability of lipoprotein apheresis is limited, and the procedure is expensive, invasive and burdensome for young children and their caregivers. Therefore, there is a high unmet need for additional therapeutic options for pediatric patients with HoFH. Evinacumab could be a new addition to the armamentarium of LMT that could contribute to lowering the LDL-C of HoFH pediatric patients, including patients with null/null mutations.

In study R1500-CL-1331, evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, 2 weeks after a single dose of 15 mg/kg IV, with a duration of effect of at least 10 weeks (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients in the study had null/null mutations in the LDLR. Treatment with evinacumab in these difficult-to-treat patients reduced LDL-C by an average of 37.3% at week 4 with peak reductions up to 59.5%. The LDL-C lowering effect observed with evinacumab in the R1500-CL-1331 study was confirmed in study R1500-CL-1629, a large randomized, double-blind, placebo-controlled study consisting of adult and adolescent patients with HoFH. On average, patients entered the trial with a mean baseline LDL-C of 255 mg/dL, despite treatment with other lipid-lowering therapies, including maximally-tolerated statins, PCSK9 inhibitors, ezetimibe, LDL apheresis and lomitapide. The trial met its primary endpoint, showing that adding evinacumab to other lipid-lowering therapies decreased LDL-C by a mean of 49% from baseline to week 24, compared to lipid-lowering therapies alone (47% reduction for evinacumab compared to a 2% increase for placebo, $p<0.0001$). This reduction translated in this study to a mean absolute change in LDL-C of 132 mg/dL from baseline, compared to placebo (135 mg/dL reduction for evinacumab compared to a 3 mg/dL reduction for placebo, $p<0.0001$). The decreases in LDL-C were observed from the first lipid assessment at week 2 and were maintained throughout the 24-week double-blind treatment period. Importantly, similar levels of LDL-C lowering were observed in the most difficult-to-treat null/null or negative/negative patients. The dramatic reduction in LDL-C led to the achievement of LDL-C levels <100 mg/dL in 47% of the patients treated with evinacumab compared to 23% treated with placebo (nominal $p=0.0203$). Evinacumab also reduced Apo B, non-HDL-C and TC compared to placebo. Based

on these data in adults, it is expected that the addition of evinacumab to existing treatments will lead to significant LDL-C reductions in the pediatric HoFH population.

In non-FH populations, numerous epidemiological studies and CV outcomes studies with lipid-lowering therapies have continually demonstrated that lowering LDL-C reduces the risk of CV events. In fact, the body of evidence from the statin literature shows that the relationship between LDL-C reduction and CV event reduction is approximately linear and for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C there is a corresponding 22% risk reduction in CV events (Baigent, 2010). Moreover, results from recent outcomes trials with ezetimibe (IMPROVE-IT (Cannon, 2015)), alirocumab (ODYSSEY OUTCOMES (Schwartz, 2018)) and evolocumab (FOURIER (Sabatine, 2017)) reinforce this concept, providing additional evidence for the relationship between LDL-C lowering through diverse mechanisms and reductions in CV events. Within the context of this study in the HoFH pediatric patient population, additional reductions in LDL-C at an early age may get patients closer to their LDL-C target and maintaining these levels could translate into significant benefit in reducing CV risk.

It is also expected that treatment with evinacumab will be well tolerated and have an acceptable safety profile. The accumulated safety information from the most recent phase 2 and phase 3 studies where evinacumab was given IV in patients with HoFH (R1500-CL-1629, R1500-CL-1719) or persistent hypercholesterolemia (R1500-CL-1643) shows that the more common adverse events across all the studies include Nasopharyngitis, Rhinorrhoea, Upper respiratory tract infection, Influenza-like illness, Back pain, Pain in extremity, Dizziness, Headache, Nausea, Abdominal pain, and Fatigue.

A review of all available safety data shows there is one identified risk of Systemic hypersensitivity reactions, including Infusion reactions, and rarely Anaphylaxis. In most cases, the allergic reactions were mild to moderate in intensity, nonserious and, in the case of infusion reactions, did not lead to interruption or discontinuation of the evinacumab infusion. One event of Anaphylaxis was observed in the phase 2 dose ranging study in patients with severe hypercholesterolemia (R1500-CL-1643). Briefly, the anaphylactic reaction was reported in a single patient randomized to the evinacumab 15 mg/kg IV treatment group. This patient with relevant medical history of syncope, palpitations, asthma, obesity, and seasonal allergy experienced an anaphylactic reaction during the second infusion of evinacumab on study day 28. Within 5 minutes of initiating the infusion, the patient felt dizzy with a racing heart, followed by chest pressure, arms and legs tingling, shortness of breath, itchiness, and feeling warm and lethargic. The patient was noticeably flushed with face and chest redness. The infusion was stopped. The patient was treated with diphenhydramine orally due to continued itching. The event was considered resolved on the same day. The investigator assessed the event as moderate in severity and related to study treatment. Study treatment was permanently discontinued. Further details of this event are provided in the Investigator's Brochure.

The important potential risks include immunogenicity and embryofetal toxicity. These risks will be managed through careful patient selection and monitoring. Additionally, any potential effects of evinacumab on a child's development during childhood and early adolescence will be monitored via Tanner staging, sex hormones, and overall growth by tracking weight and height.

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

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.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint for Part A is:

- The PK parameters for evinacumab, including C_{max}, AUC, and linear $t_{1/2}$, following a single administration of evinacumab

The primary endpoint for Part B is:

- The percent change in calculated LDL-C from baseline to week 24 (intent-to-treat [ITT] estimand) in Part B. The primary endpoint is defined as: 100x (calculated LDL-C value at week 24 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

The baseline LDL-C value is defined as the last calculated LDL-C value obtained before the first dose of study treatment in Part B. The calculated LDL-C at week 24 will be the LDL-C value obtained within the week 24 analysis window, regardless of adherence to treatment and subsequent therapies (intent-to-treat [ITT] estimand).

All calculated LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary efficacy endpoint, if appropriate, according to the above definition. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

4.1.2. Secondary Endpoints

The secondary endpoint in Part A is:

- Incidence of treatment-emergent adverse events (TEAE) and other safety variables over time

The secondary endpoints in Part B are:

- The percent change in Apo B from baseline to week 24 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 24 (ITT estimand)
- The percent change in TC from baseline to week 24 (ITT estimand)
- The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand)
- The percent change in calculated LDL-C from baseline to week 24 in patients who have negative/negative and null/null mutations (ITT estimand)
- The percent change in Lp(a) from baseline to week 24 (ITT estimand)
- The absolute change in LDL-C at week 24 (ITT estimand)
- Incidence of TEAEs and other safety variables over time
- Concentrations of total evinacumab over time

- PK parameters including $C_{max,ss}$, $AUC_{tau.ss}$, $C_{trough\cdot ss}$,
- Incidence and titer of treatment-emergent anti-drug antibodies (ADA) over time

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Vascular changes via carotid intima-media thickness at baseline and at 6 month intervals, as clinically indicated (for intra-patient comparison)

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics, medical history, and medication history for each patient.

5.2. Efficacy Variables

The efficacy variables include LDL-C, Apo B, non-HDL-C, TC, and Lp(a).

5.3. Safety Variables

The safety variables include AEs, laboratory data, vital signs, Tanner stages, and electrocardiograms (ECG).

5.4. Pharmacokinetic Variables

The PK variables are the concentrations of total evinacumab at each time point. These sampling timepoints are specified in Table 1, Table 2, and Table 3.

Although not a PK variable, total ANGPTL3 concentration in serum is a measure of target engagement by evinacumab and will be determined in the samples obtained to evaluate evinacumab concentration.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and neutralizing antibody (NAb) status and time-point/visit. Neutralizing antibody analysis will be conducted for all phases (Part A, B, and C) of the study. Samples positive in the ADA assay will be analyzed in the NAb assay. Samples in this study will be collected at the clinic visits specified in Table 1, Table 2, and Table 3.

5.6. Ultrasound Imaging

Carotid intima-media thickness (cIMT in mm) will be determined at sites with this capability at visits specified in Table 1, Table 2, and Table 3.

6. STUDY DESIGN

6.1. Study Description and Duration

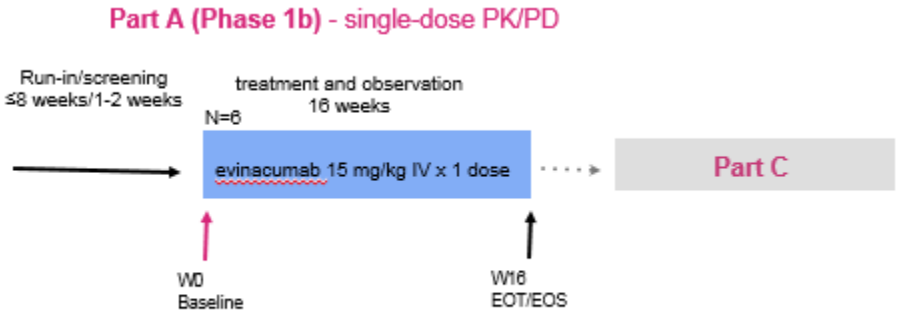
This study consists of 3 parts: Part A, Part B, and Part C

- Part A: phase 1B single arm, single dose PK/PD study
- Part B: phase 3, single-arm, 24-week, open-label efficacy and safety study
- Part C: phase 3, 48-week treatment period and 24-week follow-up period
  - Note, for patients who enter a CUP or EAP, they may forgo the 24-week follow-up period after the last dose. In this situation, the end of treatment (EOT) visit will be their last visit.

Part A is a phase 1B single-dose, open-label study to determine the safety, PK and PD of evinacumab 15 mg/kg IV in approximately 6 patients ages 5 to 11 years with HoFH. To ensure a distribution of body weight within Part A of the study, every effort will be made to enroll 3 patients <25 kg and 3 patients ≥25 kg. Additionally, to ensure a distribution of ages, every effort will be made to enroll 2 patients <10 years of age. All patients who successfully complete Part A may continue receiving evinacumab in Part C. Initially, patients from Part A who enter Part C will receive evinacumab 15 mg/kg IV Q4W. When PK data from all patients in Part A have been sufficiently analyzed, the dose for Part B will be determined using the cumulative data to date with evinacumab and data from Part A. If data from 6 patients is insufficient, up to 4 more patients may be enrolled to confirm the dose in Part B. The dose for Part B will also be the final dose in Part C. The dose for Part B (and final dose in Part C) will likely remain at 15 mg/kg IV Q4W. However, there is a small possibility that the exposure analysis or the observed PD effect indicate a small increase in the dose is needed for the pediatric population to match the exposure and PD effect observed in adult patients. As such, the dose in Part B (and final dose in Part C) could be between 15 and 20 mg/kg IV Q4W. A maximum dose of 20 mg/kg is selected as the top dose because it is the highest dose evaluated in the prior evinacumab studies.

Part A consists of up to 4 periods: run-in; screening; single-dose open-label treatment and 16-week observation, and a follow-up period (for patients who do not enter Part C). Upon completion of Part A, patients will have the opportunity to continue into Part C (Figure 1).

Figure 1: Study Flow Diagram Part A



Run-in

The run-in period is optional and available if a patient requires stabilization of background LMT or requires genotyping to confirm diagnosis of HoFH.

Lipoprotein apheresis therapy - Patients who are undergoing lipoprotein-apheresis with a schedule and/or setting not stable for approximately 8 weeks before the screening visit will enter an 8-week run-in period before the screening period. All patients undergoing apheresis should be on a weekly (every 7±1 days) or every other week (every 14±2 days) schedule. After the 8-week run-in period, patients whose lipoprotein-apheresis schedule remains stable will be eligible to enter the 2-week screening period. The use of plasmapheresis is excluded.

Pharmacological lipid-modifying therapy - Patients who are on background LMT not stable for at least 4 weeks before the screening visit will enter a 4-week run-in period to stabilize their LMT before entering the screening period.

Genotyping - Confirmation of patient's HoFH status can be made by either genetic or clinical criteria. If HoFH diagnosis cannot be confirmed by the clinical criteria listed or from previous genotyping results, patients can enter the run-in period to determine their mutation status in advance of screening, if deemed appropriate by the investigator.

Screening:

Patients on a stable background LMT (as applicable) for at least 4 weeks (8 weeks for apheresis) before the screening visit, will enter a 2-week screening period. Every effort should be made to perform the screening visit immediately before apheresis, if applicable, to ensure an accurate assessment of the lipid parameters.

Open-Label Treatment and Observation

Patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled to receive 1 dose of evinacumab 15 mg/kg IV at the baseline visit.

Patients who are receiving background LMT should maintain stable LMT throughout the duration of the study, from screening to the end of study visit for Part A (week 16). Patients on apheresis will need to temporarily discontinue apheresis from the baseline visit through 4 weeks after the single dose administration of evinacumab. The duration between the apheresis treatment prior to the baseline visit and the baseline visit should be at least either 14 days or 7 days, depending on the frequency of the patient's apheresis treatment regimen. Patients will be allowed to resume their apheresis schedule after completing all Week 4 assessments.

After completion of the 16-week open-label treatment and observation period, all patients who have successfully completed Part A may enter Part C, the extension of the study (see below).

Follow-up Period (if applicable)

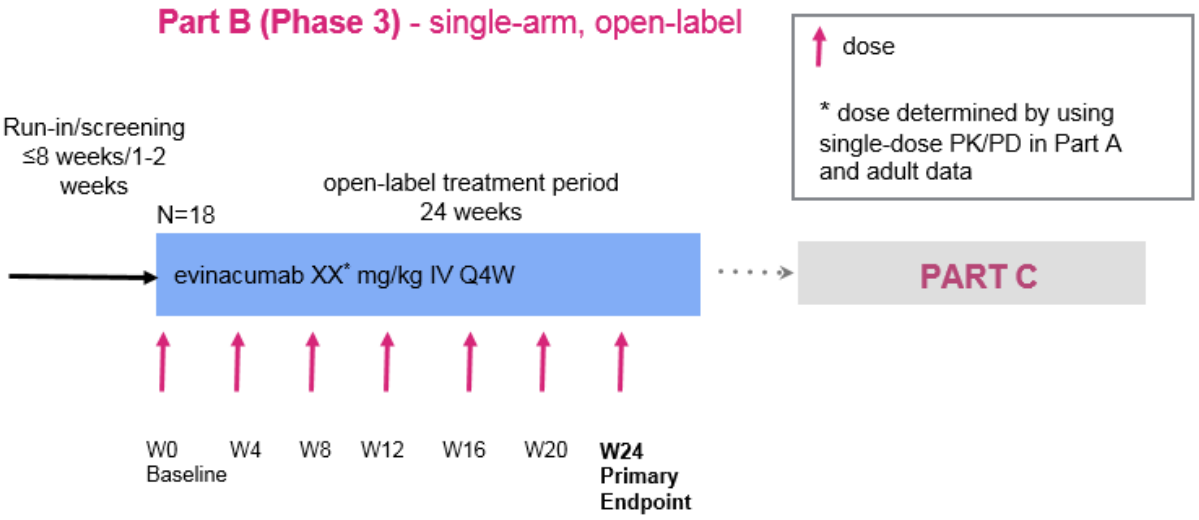
Patients not entering Part C will enter an 8-week follow-up period after receiving the single dose of evinacumab. In general, a follow-up period of 24 weeks after the single dose of study drug will be required for any patient who prematurely discontinues study treatment.

Part B is a phase 3 single-arm, open-label study to assess the efficacy and safety of evinacumab in pediatric patients (age 5 to11 years) with HoFH. Part B will begin once dose-selection for Part B has been completed. Part B will enroll approximately 14 pediatric patients. Patients

enrolled into Part B will not include patients from Part A. Upon completion of Part B, patients will have the opportunity to continue into Part C.

Part B consists of up to 4 periods: run-in; screening; 24-week open-label treatment; follow-up (for patients who do not enter Part C) (Figure 2).

Figure 2: Study Flow Diagram Part B



Run-in

The run-in period is optional and available if a patient requires stabilization of background LMT or requires genotyping to confirm diagnosis of HoFH

Lipoprotein apheresis therapy - Patients who are undergoing lipoprotein-apheresis therapy with a schedule and/or setting not stable for approximately 8 weeks before the screening visit will enter an 8-week run-in period before the screening period. All patients undergoing apheresis should be on a weekly (every 7±1 days) or every other week (every 14±2 days) schedule. After the 8-week run-in period, patients whose lipoprotein-apheresis schedule remains stable will be eligible to enter the 2-week screening period. The use of plasmapheresis is excluded.

Pharmacological lipid-modifying therapy - Patients who are on background medical LMT not stable for at least 4 weeks before the screening visit will enter a 4-week run-in period to stabilize their LMT before entering the screening period.

Genotyping - Confirmation of patient's HoFH status can be made by either genetic or clinical criteria. If HoFH diagnosis cannot be confirmed by the clinical criteria listed or from previous genotyping results, patients can enter the run-in period to determine their mutation status in advance of screening, if deemed appropriate by the investigator.

Open-Label Treatment

Patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled to receive evinacumab IV Q4W. The dose can be between 15 to 20 mg/kg but will likely remain at evinacumab 15 mg/kg. The final dose will be confirmed at a dose selection meeting once sufficient data from Part A are available.

Administration of evinacumab during the treatment period will take place at the study site, starting at the baseline visit (visit 2) through week 20 (visit 10). For patients on apheresis, every effort should be made to administer evinacumab within 1 day of completing apheresis.

Patients who are receiving background LMT or who are undergoing apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of open-label treatment period visit (week 24).

After completion of the 24-week treatment period, all patients may enter Part C (see below). All patients who enter Part C will continue to receive open-label evinacumab at the dose administered in Part B.

Follow-up Period (if applicable)

Patients not entering Part C will enter a 20-week follow-up period after completion of the treatment period. A follow-up period of 24 weeks after the last dose of study drug will be required for any patient who prematurely discontinues study treatment.

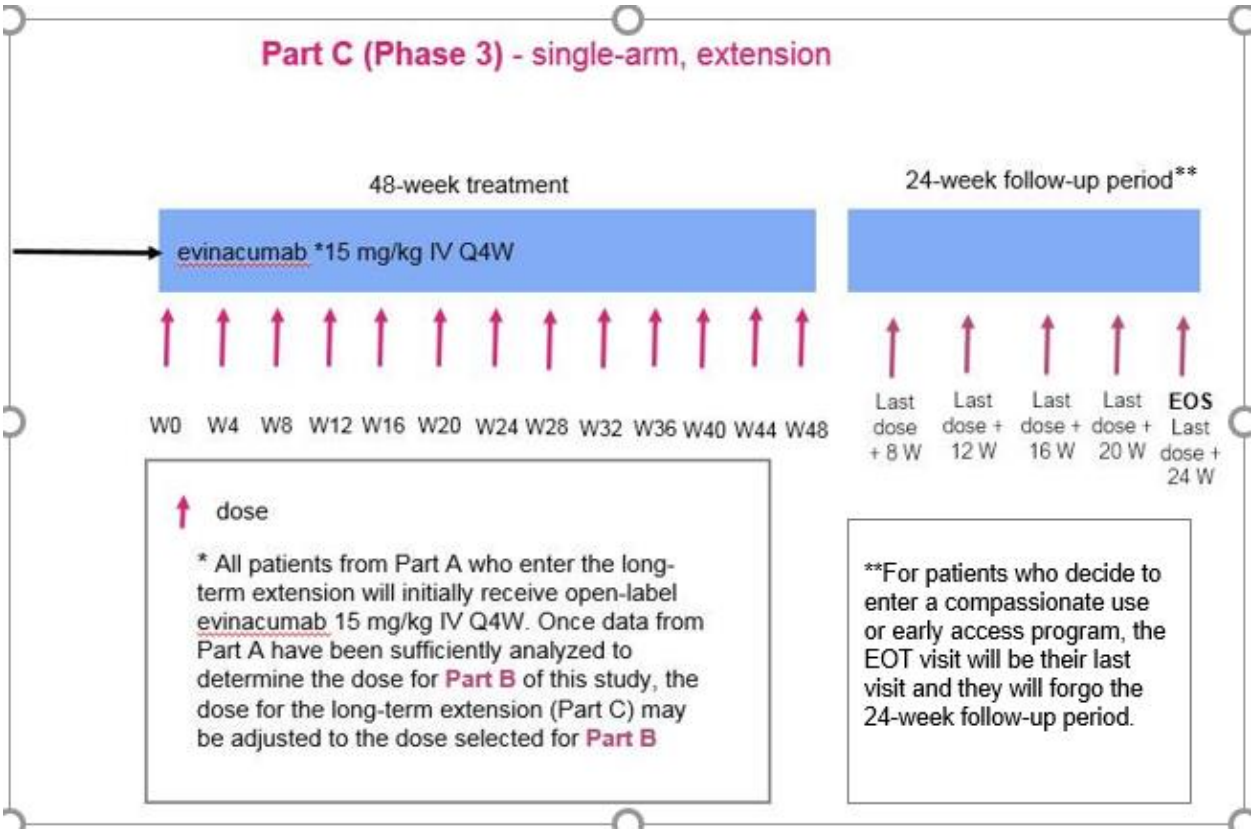
Part C is an extension for patients from both Part A and Part B. It consists of 2 periods: a 48-week treatment period and a 24-week follow-up period after the last dose of study drug (Figure 3). Patients who participate in Part C should enter directly from Part A or Part B. The first visit (visit 1) in Part C can occur on the same day as the EOT visit in Part A (visit 11)/Part B (visit 11). Overlapping assessments completed at the EOT visit do not need to be duplicated during visit 1 in Part C.

All patients from Part A who enter Part C will initially receive open-label evinacumab 15 mg/kg IV Q4W. The final dose in Part C will be the same as the dose in Part B; therefore, the dose in Part C for patients entering from Part A may need to be adjusted to align with the dose in Part B.

Extension

Administration of evinacumab during Part C will take place at the study site. For patients on apheresis, every effort should be made to administer evinacumab within 1 day of completing apheresis.

Figure 3: Study Flow Diagram – Extension



Patients who are receiving background LMT or who are undergoing apheresis should make every effort to maintain a stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study to the end of the study. The frequency of apheresis may be reduced during this part of the study based on the investigator's judgement.

The Sponsor of this study, consistent with our corporate policy governing access to investigational drugs in confirmatory clinical studies, is committed to provide evinacumab to patients after their participation in this trial has concluded, if permitted per local laws. Agreement to continue treatment beyond this study is a treatment decision that must be made by the investigator and the patient and/or their parent/guardian. After completion of the study, investigators interested in continuing treatment with evinacumab in patients considered to have a positive response can discuss post-trial access options with the Sponsor.

Follow-up Period

Patients will enter a 24-week follow-up period after the last dose of evinacumab in Part C. However, for patients entering a compassionate use or extended access program, they may forgo the follow-up period. The EOT visit will be their last visit.

Throughout the Study

The efficacy of evinacumab in this population will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. All samples for clinical laboratory evaluation must be obtained prior to evinacumab administration. For patients undergoing apheresis, all samples for clinical laboratory evaluation must be obtained

immediately prior to apheresis. This is to ensure the effect of apheresis on lipid parameters is minimized as much as possible.

Overall safety will be assessed by monitoring and evaluation of TEAEs, physical examinations, vital signs, including blood pressure, ECG, Tanner stages, and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated. Patients who experience an ongoing serious adverse event (SAE) at the pre-specified study end-date should be followed until resolution, stabilization, or collection of outcome and related data.

6.1.1. Description of Dose Selection

Pharmacokinetic, PD, and safety data from Part A of the study will be used to determine the dose for Part B and the final dose for Part C. This will occur when PK, PD, and safety data from Part A have been sufficiently analyzed and reviewed at a Dose Determination Review meeting. This meeting will be led by a designated member of the Regeneron clinical team (generally either the medical director/study director or the clinical study lead) and at a minimum will be attended by the Regeneron Medical Monitor and the Risk Management Lead or designee; other individuals, including the Clinical Pharmacology Lead, may be included. The final dose selected will not exceed evinacumab 20 mg/kg.

6.1.2. End of Study Definition

The end of study is defined as the date of the last visit of the last patient.

6.2. Planned Interim Analysis

No interim analysis is planned.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data; if requested, the IDMC may have access to any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

For Part A, approximately 6 patients are planned. If data from 6 patients is insufficient, up to 4 more patients may be enrolled to confirm the dose in Part B.

For Part B, approximately 14 patients are planned. Patients for Part B will not include patients from Part A. Patients from Part A and Part B may enter Part C.

7.1.1. Rescreening of Patients

Patients who do not meet eligibility criteria during the initial screening may rescreen. Patients who are rescreened after the screening window ends must re-consent for study participation and repeat all screening procedures.

Patients who do not meet all eligibility criteria during the initial screening, and are still within the screening window, may retest those assessments that did not meet eligibility criteria.

7.2. Study Population

Males and females age 5 through 11 years, diagnosed with HoFH receiving any combination of lipid-lowering therapies (additional information on background therapies provided in Section 6.1).

HoFH diagnosis can be confirmed by either the genetic or clinical criteria shown in Section 7.2.1.

7.2.1. Inclusion Criteria

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

1. Males and females ages 5 to 11 years at the time of the screening visit
2. Diagnosis of functional HoFH by either genetic or clinical criteria:

   Genetic Criteria

   a. Documented functional mutation or mutations in both LDLR alleles
      Note: Patients who have null receptor mutations on both LDLR alleles, ie, double null, are eligible
   b. Documented homozygous mutations in LDLRAP1, or homozygous or compound heterozygous mutations in APOB or PCSK9
      Note: Patients who are double heterozygous, i.e. mutations on different genes [LDLR/PCSK9 or LDLR/APOB] are eligible

   Clinical Criteria

   c. Untreated TC >500 mg/dL (>13 mmol/L) and triglycerides (TGs) <300 mg/dL (<7.8 mmol/L)

AND

Both parents with documented TC >250 mg/dL OR cutaneous or tendinous xanthoma in the study patient before age 10 years

3. LDL-C >130 mg/dL at the screening visit
4. Body weight ≥15 kg
5. Receiving stable maximally tolerated therapy*at the screening visit

   *Maximally tolerated therapy could include a daily statin.

   Note: Patients who are not able to be on a maximum daily statin should be on the appropriate dose for the patient or no statin, according to the investigator's judgment. Some examples of acceptable reasons for a patient taking a lower statin dose include but are not limited to: adverse effects on higher doses, lack of efficacy, regional practices, local prescribing information, concomitant medications. The reason(s) will be documented in the case report form (CRF).
6. Willing and able to comply with clinic visits and study-related procedures
7. Parent(s) or legal guardian(s) must provide the signed informed consent form (ICF). Patients ≥5 years of age (or above age determined by the IRB/EC and in accordance with the local regulations and requirements) must also provide informed assent forms (IAFs) to enroll in the study, and sign and date a separate IAF or ICF signed by the parent(s)/legal guardian(s) (as appropriate based on local regulations and requirements)

7.2.2. Exclusion Criteria

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

1. Background pharmacologic LMT, nutraceuticals or over-the-counter (OTC) therapies known to affect lipids, at a dose/regimen that has not been stable for at least 4 weeks (8 weeks for PCSK9 inhibitors) before the screening visit and patient is unwilling to enter the run-in period
2. For patients entering Part A, unable to temporarily discontinue apheresis from the baseline visit through the week 4 visit
3. Receiving lipid apheresis, a setting (if applicable) and schedule that has not been stable for approximately 8 weeks before the screening visit or an apheresis schedule that is not anticipated to be stable over the duration of the treatment period (48 weeks). A stable schedule is defined as a weekly (every 7±1 days) or every other week (every 14±2 days) schedule
4. Plasmapheresis within 8 weeks of the screening visit, or plans to undergo plasmapheresis during Part A or Part B
5. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
6. Newly diagnosed (within 3 months prior to randomization visit [week 0/day 1]) diabetes mellitus or poorly controlled (hemoglobin A1c [HbA1c] >9%) diabetes

7. Chronic use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization

   Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed

8. History of a myocardial infarction (MI), percutaneous coronary intervention (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack (TIA), valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit
9. History of cancer within the past 5 years
10. Use of any active investigational drugs within 1 month or 5 half-lives, whichever is longer
11. Conditions/situations such as:
    a. Any clinically significant abnormality identified at the time of screening that, in the judgment of the investigator or any sub-investigator, would preclude safe completion of the study or constrain endpoints assessment; eg, major systemic diseases, patients with short life expectancy
    b. Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, eg:
       - Deemed unable to meet specific protocol requirements, such as scheduled visits
       - Investigator or any sub-investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.
       - Presence of any other conditions (eg, geographic or social), either actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
12. Laboratory findings during screening period (not including randomization labs):
    - Positive urine pregnancy test in females of childbearing potential
    - Triglycerides >300 mg/dL (>4.52 mmol/L) (1 repeat lab is allowed)
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) (1 repeat lab is allowed)
    - CPK >3 x ULN (1 repeat lab is allowed)
13. Known hypersensitivity to monoclonal antibodies or any excipient in the evinacumab solution for infusion
14. Sexually active males, and sexually active females of childbearing potential at screening
15. Female patients who have commenced menstruating at any time during the study and are either:
    - Found to have a positive urine pregnancy test, or

- Sexually active, not using or not willing to use an established highly effective contraception method prior to subsequent dosing of study treatment, during the study, and for at least 24 weeks after the last dose of study drug. Highly effective contraceptive measures include:
  - Stable use of combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening: oral, intravaginal, transdermal
  - Stable use of progestogen-only hormonal contraception associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening: oral, injectable, implantable
  - Intrauterine device or intrauterine hormone-releasing system
  - Bilateral tubal ligation
  - Vasectomized partner. Note: vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success
  - only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments. True abstinence: When this is in line with 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.

16. Male patients who become sexually active at any time during the study and do not use an established acceptable contraception method of consistent use of barrier contraception with spermicide during the study and for up to 24 weeks after the last infusion of study drug.
17. Individuals who are accommodated in an institution by official or court order.

7.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

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

7.4. Replacement of Patients

Patients prematurely discontinued from study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

In Part A, patients will receive 1 dose of evinacumab 15 mg/kg IV infusion over 65 minutes at the baseline visit (day 1).

In Part B, patients will receive evinacumab at a dose assessed from Part A and will be administered IV over a 65-minute infusion Q4W starting at the baseline visit (day 1). The last dose of evinacumab will be at week 20.

In Part C, patients from Part A will initially receive evinacumab at 15 mg/kg IV Q4W. The final dose selection in Part C will be based on data from Part A and data in adults from other studies. Therefore, the dose for patients from Part A entering Part C may be adjusted once the dose selection for Part B is completed.

The IV dose should be prepared using the patient's most recent weight. The most recent weight is either the current visit's weight or, if the current visit's weight is not available when preparing the dose, the weight from the previous visit. Further instructions on dose preparation are provided in the pharmacy manual.

Dosing should fall within a window of ±7 days; if >14 days have passed, skip the dose and return to the original schedule.

8.2. Run-in Treatment(s)

Patients who are undergoing apheresis therapy should be on a stable weekly (every 7±1 days) or every other week (every 14±2 days) schedule and/or stable settings for approximately 8 weeks prior to screening. Patients with a schedule and/or apheresis settings not stable for approximately 8 weeks before the screening visit will enter an 8-week run-in period before the screening period.

Patients who are on background LMT that has not been stable for at least 4 weeks (4 weeks for statins and ezetimibe, 8 weeks for PCSK9 inhibitors) before the screening visit will enter a run-in period to stabilize their LMT before entering the screening period.

8.3. Background Treatment(s)

Patients who are receiving background LMT or who are undergoing apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of the treatment period visit (week 24) of Part B. For patients who enter Part C of the study, and are receiving lipid apheresis, the frequency of apheresis may be reduced based on the investigator's judgement.

Patients should be on a maximally tolerated LMT regimen. Whether or not a patient is considered to be on a maximum tolerated regimen of LMT (statin, PCSK9 inhibitor, etc), reasons why or why not (eg, due to intolerance, lack of efficacy) the patient is taking/not taking the various treatments will need to be documented in the CRF.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.4.2. Study Drug Discontinuation

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

Patients in Part B and Part C who prematurely discontinue study drug and agree to remain in the study should undergo all study visits and procedures with the exception of study drug dosing. At the time of study drug discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at the week 24 EOT visit (Part B patients) or the week 48 visit (Part C patients) and then resume the original study schedule until the end of study (EOS) visit.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments (EOS/early termination [ET]), per Section 9.1.2.

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

An individual will permanently discontinue study drug dosing in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met ([Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA 2009])
- Patient withdraws consent

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest.

8.5. Management of Acute Reactions

8.5.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

8.5.1.1. Interruption of the Intravenous Infusion

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

- 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 per investigator discretion.

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

8.5.1.2. Termination of the Intravenous Infusion

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

- anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- severe 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 BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.6. Method of Treatment Assignment

This is an open-label study in which all patients receive evinacumab.

8.7. Blinding

This study is not blinded as it is a single-arm, open-label study.

To reduce bias, a central lab will be used.

8.8. Treatment Logistics and Accountability

8.8.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label. A medication numbering system will be used in labeling investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups responsible for study drug packaging and labeling.

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

8.8.2. Supply and Disposition of Treatments

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

8.8.3. 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.

8.8.4. Treatment Compliance

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

8.9. Concomitant Medications

Any treatment administered, including apheresis, from the time of informed consent to end of the treatment period/final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.9.1. Prohibited Medications

The following concomitant medications and procedures are prohibited in Part A or Part B:

- Background LMT (if applicable) that has not been stable for at least 4 weeks (eg, statins and ezetimibe) with the exception of PCSK9 inhibitors, which is prohibited unless stable for 8 weeks before the screening visit (week -2) (unless participating in the run-in period to stabilize)
- Recent discontinuation of lomitapide that has not been washed out for at least 8 weeks before the screening visit (week -2)
- Lipid apheresis schedule that is not an approximately every 7 day (±1 day) or an every 14 day (±2 days) regimen or has not been stable for approximately 8 weeks prior to screening (week -2)
- Plasma exchange
- Nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit (week -2)
- Chronic systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to the screening visit (week -2)
- Thyroid replacement therapy, unless the dosage of replacement therapy has been stable for at least 12 weeks prior to the screening visit (week -2)

8.9.2. Permitted Medications

The use of all nutritional supplements and approved medications known to alter serum lipids, including (but not limited to) statins, PCSK9 inhibitors, ezetimibe, fibrates, niacin, bile acid resins, red yeast rice is permitted as long as that therapy has been stable for at least 4 weeks for most LMT with the exception of PCSK9 inhibitors, which is 8 weeks prior to the screening visit (week -2). Patients in Part B should continue taking their background LMT for the duration of the study starting at screening and through visit 10 (week 24). Similarly, patients should maintain their apheresis regimen (if applicable) starting at screening and through the end of visit 10 (week 24).

Patients on thyroid replacement therapy can be included if the dosage has been stable for at least 12 weeks prior to the screening visit (week -2).

Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as ‘systemic’ and are allowed.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1, Table 2, and Table 3.

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, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

If patients and their physicians decide to enter a compassionate use or early access program, they may forgo the 24-week follow-up period following the last dose of evinacumab. In this case, the EOT visit will be their last visit. There is no need to complete the EOS assessments as they are identical to the EOT assessments other than the testing of high sensitivity C-reactive protein (hs-CRP).

Table 1: Schedule of Events – Part A, PK and PD Portion

	Run-in[13]	Screening	Open-Label Treatment and Observation Period										Follow-up[16]
Study Procedure	**Visit 1**	**Visit 1a**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[17] Visit 11**	**EOS Visit 12**
Day	-70 to -14	-14 to -1	1	8	15	22	29	43	57	71	85	113	169
Week	-10 to -2	-2 to -1	0	1	2	3	4	6	8	10	12	16	24
Visit Window (day)			±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Screening/Baseline:													
Inclusion/Exclusion	X	X											
Informed Consent and Assent	X[14]	X											
Pharmacogenomics consent		X											
Future Biomedical Research Consent		X											
Medical/Surgical History		X											
Medication History		X											
Demographics		X											
Treatment:													
Administer Study Drug			X										
Concomitant Meds and Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:													
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]		X	X	X	X		X		X		X	X	X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]			X				X		X		X	X	X
Safety:													
Vital Signs	X	X	X[15]	X	X	X	X	X	X	X	X	X	X
Physical Examination		X										X	X
Electrocardiogram[2]		X										X	X
Tanner Stage		X										X	

	Run-in[13]	Screening	Open-Label Treatment and Observation Period										Follow-up[16]
Study Procedure	**Visit 1**	**Visit 1a**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[17] Visit 11**	**EOS Visit 12**
Day	-70 to -14	-14 to -1	1	8	15	22	29	43	57	71	85	113	169
Week	-10 to -2	-2 to -1	0	1	2	3	4	6	8	10	12	16	24
Visit Window (day)			±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Height		X										X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[3]:													
Hematology		X	X	X			X		X		X	X	X
Blood Chemistry		X	X	X			X		X		X	X	X
HbA1c			X									X	X
Sex Hormones[4]			X									X	
Urine Pregnancy Test[5]		X	X				X		X		X	X	X
Urinalysis		X	X	X			X		X		X	X	X
TSH		X											
Hs-CRP			X									X	
PK/Drug Concentration and ADA Samples:													
PK/Drug conc. Sample[6,7,8]			X	X	X		X		X		X	X	X
ADA sample[9]			X									X	X
Biomarkers:													
Future Biomedical Research Serum[10]			X		X				X			X	
Future Biomedical Research Plasma[10]			X		X				X			X	
Pharmacogenomics:													
Blood sample for HoFH genotyping (mandatory)		X											
Whole Blood for DNA (optional)[11]		X											
Other													
Review of Diet/ compliance with LMT	X	X	X	X	x	X	X	X	X	X	X	X	X

	Run-in[13]	Screening	Open-Label Treatment and Observation Period										Follow-up[16]
Study Procedure	**Visit 1**	**Visit 1a**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[17] Visit 11**	**EOS Visit 12**
Day	-70 to -14	-14 to -1	1	8	15	22	29	43	57	71	85	113	169
Week	-10 to -2	-2 to -1	0	1	2	3	4	6	8	10	12	16	24
Visit Window (day)			±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Carotid Ultrasound Imaging[12]	X											X	

Table 2: Schedule of Events – Part B, 24-Week Efficacy and Safety Portion

	Run-In[14]	Screening	Baseline	Treatment Period								
Study Procedure	**Visit 1**	**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[16] Visit 11**
Day	-70 to -14	-14 to -1	1	8	15	29	43	57	85	113	141	169
Week	-10 to -2	-2 to -1	0	1	2	4	6	8	12	16	20	24
Visit Window (day)			±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Screening/Baseline:												
Inclusion/Exclusion	X	X										
Informed Consent and Assent	X[17]	X										
Pharmacogenomics consent		X										
Future Biomedical Research Consent		X										
Medical/Surgical History		X										
Medication History		X										
Demographics		X										
Treatment:												
Administer Study Drug			X			X		X	X	X	X	
Concomitant Meds and Treatment	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:												
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]		X	X	X	X	X		X	X	X	X	X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]			X			X		X	X			X
Safety:												
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X										X
Electrocardiogram[3]		X										X
Tanner Stage		X										X

	Run-In[14]	Screening	Baseline	Treatment Period								
Study Procedure	**Visit 1**	**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[16] Visit 11**
Day	-70 to -14	-14 to -1	1	8	15	29	43	57	85	113	141	169
Week	-10 to -2	-2 to -1	0	1	2	4	6	8	12	16	20	24
Visit Window (day)			±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Height		X										X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[4]:												
Hematology		X	X					X	X	X		X
Blood Chemistry		X	X					X	X	X		X
HbA1c			X						X			X
Sex Hormones[5]		X	X									X
Urine Pregnancy Test[6]		X	X			X		X	X	X	X	X
Urinalysis		X	X					X	X	X		X
TSH		X										
Hs-CRP			X									X
PK/Drug Concentration and ADA Samples:												
PK/Drug conc. Sample[7,8,9]			X			X		X	X			X
ADA sample[10]			X									X
Biomarkers:												
Future Biomedical Research Serum[11]			X			X			X			X
Future Biomedical Research Plasma[11]			X			X			X			X
Pharmacogenomics:												
Blood sample for HoFH genotyping (mandatory)			X									
Whole Blood for DNA (optional)[12]			X									
Other												
Review of Diet, compliance with LMT	X	X	X	X	X	X	X	X	X	X	X	X

	Run-In[14]	**Screening**	**Baseline**	**Treatment Period**								
Study Procedure	**Visit 1**	**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[16] Visit 11**
Day	-70 to -14	-14 to -1	1	8	15	29	43	57	85	113	141	169
Week	-10 to -2	-2 to -1	0	1	2	4	6	8	12	16	20	24
Visit Window (day)			±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Carotid Ultrasound Imaging[13]	X											X

Table 2 (contd): Schedule of Events – Part B (cont'd)

	Follow-Up Period[15]			
Study Procedure	**Phone Visit 12**	**Visit 13**	**Phone Visit 14**	**Visit 15 EOS**
Day	225	253	281	309
Week	32	36	40	44
Visit Window (day)	±5	±5	±5	±5
Treatment:				
Administer Study Drug				
Concomitant Meds and Treatment	X	X	X	X
Efficacy:				
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]		X		X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]				
Safety:				
Vital Signs[2]		X		X
Physical Examination				X
Electrocardiogram[3]				X
Height				X
Weight		X		X
Adverse Events	X	X	X	X
Tanner Stage				X
Laboratory Testing[4]:				
Hematology		X		X
Blood Chemistry		X		X
Sex Hormones[5]				X
HbA1c				X
Urine Pregnancy Test[6]	X	X	X	X
Urinalysis		X		X
TSH				
Hs-CRP				
PK/Drug Concentration and ADA Samples:				
PK/Drug conc. Sample[7,8,9]				X
ADA sample[10]				X
Biomarkers:				
Future Biomedical Research Serum				X
Future Biomedical Research Plasma				X
Pharmacogenomics:				
Whole Blood for DNA (optional)[11]				
Other				
Review of Diet, compliance with LMT	X	X	X	X
Carotid Ultrasound Imaging				

Table 3: Schedule of Events – Part C

	Treatment Period													24-Week Follow-up Period[14]			
Study Procedure	**V1[15]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13 EOT[17]**	**PV 14**	**V 15**	**PV 16**	**EOS V17**
														Weeks post last dose			
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	+8	+12	+16	+24
Visit Window (day)		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Treatment:																	
Administer Study Drug	X[16]	X	X	X	X	X	X	X	X	X	X	X					
Concomitant Meds and Treatment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:																	
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]			X		X		X	X	X	X	X	X	X		X		X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]			X		X		X	X	X	X	X	X	X		X		X
Safety:																	
Vital Signs[2]		X	X	X	X	X	X	X	X	X	X	X	X		X		X
Physical Examination													X				X
Electrocardiogram[3]													X				X
Tanner Stage[4]							X						X				X
Height[4]							X						X				X
Weight		X	X	X	X	X	X	X	X	X	X	X	X				X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[5]:																	
Hematology			X		X		X		X		X		X		X		X
Blood Chemistry			X		X		X		X		X		X		X		X
HbA1c				X			X			X			X		X		X
Sex Hormones[4,6]							X						X				X
Urine Pregnancy Test[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis			X		X		X		X		X		X				X
Hs-CRP				X			X										X
PK/Drug Concentration and ADA Samples:																	

	Treatment Period													24-Week Follow-up Period[14]			
Study Procedure	**V1[15]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13 EOT[17]**	**PV 14**	**V 15**	**PV 16**	**EOS V17**
														Weeks post last dose			
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	+8	+12	+16	+24
Visit Window (day)		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
PK/Drug conc. Sample[8,9,10]				X			X			X			X				X
ADA sample[11]							X						X				X
Biomarkers:																	
Future Biomedical Research Serum[12]			X				X						X				X
Future Biomedical Research Plasma[12]			X				X						X				X
Other																	
Review of Diet, compliance with LMT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Carotid Ultrasound Imaging[13]							X						X				

9.1.1. Footnotes for the Schedule of Events Table

9.1.1.1. Table 1 Schedule of Events – Part A, PK and PD Portion

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients.
2. ECG should be performed before blood samples are collected at visits requiring blood draws.
3. All laboratory samples should be collected before administration of study drug.
4. Sex hormones include luteinizing hormone, FSH, estradiol, and total testosterone.
5. Pregnancy test with a local urine pregnancy test should be done on sexually active females who have experienced menarche and are of childbearing potential.
6. Including assay of total ANGPTL3. Extra samples may be used to assess the concentration of concomitant medications, eg, statins.
7. The PK sample should be drawn predose and at the end of the IV infusion on days when study drug is administered
8. If apheresis is administered on a dosing day, it is preferred to administer apheresis before the evinacumab infusion. The PK sample should be collected prior to apheresis and at the end of the evinacumab infusion. In the event apheresis is administered after evinacumab administration, the PK sample should be collected prior to and at the end of evinacumab infusion, prior to apheresis.
9. The ADA sample should be drawn before study drug administration.
10. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent prior to collection of Future Biomedical Research samples. Patients are still eligible to enroll in the study if they do not wish to participate in the Future Biomedical Research.
11. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent to participate in the optional genomics sub-study prior to collection of whole blood DNA samples. Patients are still eligible to enroll in the study if they do not wish to participate in the genomics sub-study
12. Carotid ultrasound imaging will be performed only at sites with this capability. Every effort should be made for patients to undergo 2 carotid ultrasound imaging assessments before the first dose of study drug. The assessments should be separated by at least 1 day.
13. For patients who require stabilization of their background LMT (including apheresis) or need to undergo genotyping to confirm diagnosis of HoFH.
14. If the patient requires a run-in the ICF should be signed at that time; otherwise ICF should be signed at screening visit.
15. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion
16. For patients who do not enter Part C, there will be an 8-week follow-up period (visit 12).

17. If continuing to Part C, this visit can occur on the same day as visit 1 of Part C.

9.1.1.2. Table 2 Schedule of Events – Part B, 48-Week Efficacy and Safety Portion

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected before the apheresis procedure; every effort should be made to administer study drug within 1 day of the apheresis procedure.
2. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. All laboratory samples should be collected before administration of study drug.
5. Sex hormones include luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone.
6. Pregnancy test with a local urine pregnancy test should be done on sexually active females of childbearing potential.
7. Including assay of total ANGPTL3. Extra samples may be used to assess the concentration of concomitant medications, eg, statins.
8. The PK sample should be collected predose and at the end of the IV infusion on days when study drug is administered.
9. For patients who are not undergoing apheresis, the PK sample should be drawn before the administration of study drug. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure if it is performed before the evinacumab infusion.
10. For patients who are not undergoing apheresis, the ADA sample should be drawn before study drug administration. For patients undergoing apheresis, the ADA sample should be drawn before the apheresis procedure if it is performed before the evinacumab infusion.
11. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent prior to collection of Future Biomedical Research samples. Patients are still eligible to enroll in the study if they do not wish to participate in the Future Biomedical Research.
12. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent to participate in the optional genomics sub-study prior to collection of whole blood DNA samples. Patients are still eligible to enroll in the study if they do not wish to participate in the genomics sub-study. One DNA sample for the genomics sub-study should be collected on day 1 (visit 2) but can be collected at any visit after that.

13. Carotid ultrasound imaging will be performed only at sites with this capability. Every effort should be made for patients to undergo 2 carotid ultrasound imaging assessments before the first dose of study drug. The assessments should be separated by at least 1 day.
14. For patients who require stabilization of their background LMT (including apheresis) or need to undergo genotyping to confirm diagnosis of HoFH.
15. Only for patients who do not enter Part C.
16. If continuing to Part C, this visit can occur on the same day as visit 1 of Part C.
17. If the patient requires a run-in, the ICF should be signed at that time; otherwise, the ICF should be signed at the screening visit.

9.1.1.3. Table 3 Schedule of Events – Part C

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected before the apheresis procedure; every effort should be made to administer study drug within 1 day of the apheresis procedure.
2. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
5. All laboratory samples should be collected before administration of study drug.
6. Sex hormones include luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone.
7. Pregnancy test with a local urine pregnancy test should be done on sexually active females of childbearing potential.
8. Including assay of total ANGPTL3. Extra samples may be used to assess the concentration of concomitant medications, eg, statins.
9. The PK sample should be collected predose and at the end of the IV infusion on days when study drug is administered.
10. For patients who are not undergoing apheresis, the PK sample should be drawn before the dose of study drug. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure if it is performed before the evinacumab infusion.
11. For patients who are not undergoing apheresis, the ADA sample should be drawn before study drug administration. For patients undergoing apheresis, the ADA sample should be drawn immediately before the apheresis procedure if it is performed before the evinacumab infusion.

12. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent prior to collection of Future Biomedical Research samples. Patients are still eligible to enroll in the study if they do not wish to participate in the Future Biomedical Research
13. Carotid ultrasound imaging will be performed only at sites with this capability. The assessment should be performed approximately every 6 months at every other Visit F.
14. At weeks 8 and 16 of the follow-up period all patients will be contacted by phone to query LMT compliance, to inquire about AEs or changes to concomitant medications, confirm required contraception use, and remind patients of pregnancy reporting. Sexually active females of childbearing potential will report the results of their home pregnancy test. For patients who decide to enter a compassionate use or early access program, the EOT visit will be their last visit and they will forgo the 24-week follow-up period.
15. Overlapping assessments completed at the EOT visit of Part A or Part B do not need to be duplicated during visit 1 of Part C. Part C visit 1 should occur on the same day as Part A visit 11 or Part B visit 11. All necessary assessments are listed in the applicable SOE (Part A or Part B) column for visit 11.
16. Patient can only receive the dose once all assessments from Part A or Part B Visit 11 are completed.
17. For patients who decide to enter a CUP or EAP, the EOT visit will be their last visit and they will forgo the 24-week follow-up period.

9.1.2. Early Termination Visit

For patients in Part A who are withdrawn from the study early, an ET should occur as soon as possible with assessments normally planned at the Part A, EOT visit.

For patients in Part B who permanently discontinue study drug before week 24, an ET visit should occur as soon as possible with assessments normally planned at the Part B, EOT visit (week 24).

For patients in Part C who permanently discontinue study drug before the week 48 visit, an ET visit should occur as soon as possible with assessments normally planned at the Part C, EOT visit (week 48).

If the patient agrees to continue in the study, after completing the ET visit, the patient should resume the original study schedule (except for study treatment administration) until the EOS. Specifically, for patients in Part B, all efforts should be made to perform the week 24 assessments (regardless of study treatment administration).

If the patient does not agree to continue in the study after completing the ET visit, patients should enter the follow-up period and be followed for at least 24 weeks from the last dose of study drug, and a final end of study visit can take place with assessments as specified in the end of study visit.

If a patient enters a CUP or EAP, they may forgo the 24-week follow-up period.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: Demographics, medical/surgical history, medication history, and thyroid-stimulating hormone (TSH).

9.2.2. Efficacy Procedures

All laboratory samples will be collected before the dose of study drug is administered.

Blood samples for lipid panels should be collected in the morning, in fasting conditions (ie, overnight, at least 8 hours fast, only water) for all clinic visits. Intense physical exercise within 24 hours, preceding blood sampling is discouraged.

Total-C, HDL-C, Apo B, Apo A-1, TG, and Lp(a) will be directly measured by the central laboratory. LDL-C will be calculated using the Friedewald formula. If TG values exceed 400 mg/dL (4.52 mmol/L) or if calculated LDL-C values are below 25 mg/dL (0.65 mmol/L), LDL-C will be measured via the beta quantification method (rather than via the Friedewald formula). Non-HDL-C will be calculated by subtracting HDL-C from the TC.

Detailed procedures of sample preparation, storage, and shipment are provided in the laboratory manual.

9.2.2.1. Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Section 9.1 for assessment of the lipid profile, comprising calculated LDL-C, HDL-C, non-HDL C, TC, and TGs. These samples will also be used for specialty lipid panel assessment when it is scheduled at the same time as the lipid panel assessment.

9.2.2.2. Specialty Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Section 9.1 for assessment of the specialty lipid profile, comprising Apo B, Apo A-1, ratio of Apo B/Apo A-1, ApoCIII, ApoE, and Lp(a). The specialty lipid panels will be assessed in the same sample that is collected for the lipid panel.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration rate, will be collected predose at time points according to Table 1, Table 2, and Table 3.

On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion.

Blood pressure should be measured in the same arm throughout the study after the patient has been resting quietly for at least 5 minutes. Pulse rate will be measured at the time of the measurement of blood pressure.

9.2.3.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1, Table 2, and Table 3.

Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.3. Tanner Stages

The Tanner stages will be assessed throughout the study for all patients according to Table 1, Table 2, and Table 3.

If possible, for each patient, the Tanner stages assessment should be performed by the same investigator/designee trained to assess pubertal development.

9.2.3.4. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Table 1, Table 2, and Table 3.

The ECG strips or reports will be retained with the source.

9.2.3.5. Laboratory Testing

All laboratory samples will be collected before the dose of study drug is administered.

Samples for laboratory testing will be collected at visits according to Table 1, Table 2, and Table 3 and analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites and specific tests are listed below.

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)	

Hematology

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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Other laboratory tests will be performed at time points shown in Table 1, Table 2, and Table 3 and are as follows: TSH, hs-CRP, HbA1c, sex hormones (luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone), and urine pregnancy test.

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

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

9.2.4. Drug Concentration and Measurements

Samples for assessment of evinacumab and total ANGPTL3 concentrations (marker of target engagement) will be collected at time points listed in Table 1, Table 2, and Table 3. They will be collected predose and at the end of the IV infusion on days when study drug is administered.

Any unused samples collected for drug concentration measurements may be used to assess the concentration of concomitant medications, eg, statins, and for exploratory biomarker research or other investigations.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 1, Table 2, and Table 3.

Samples positive in the ADA assay will be analyzed in the NAb assay.

In case of a suspected SAE such as hypersensitivity or anaphylactic reaction, additional samples may be collected at or near the time of the event.

Any unused samples collected for ADA assessments may be used for exploratory research or bioanalytical investigations.

9.2.6. Ultrasound Imaging

Carotid ultrasound is a reliable method to measure carotid intima-media thickness (cIMT; in mm), which has been shown to be increased in children with HoFH (Kusters, 2014). The technique has shown reliable results with an interobserver coefficient of variation of 7.3% (Doyon, 2013).

9.2.7. Other Assessments

9.2.7.1. Review of Diet and Compliance with LMT

Patients should maintain a stable and exercise routine. Patients will be queried on compliance with their diet and compliance with LMT during the study, at time points according to Section 9.1.

9.2.7.2. DNA Sample for HoFH Genotyping

A required blood sample for DNA extraction will be collected from all patients to identify or confirm known mutations in PCSK9, LDLR, APOB, and LDLRAP1 genes.

9.2.7.3. Future Biomedical Research (Optional)

Research samples (serum/plasma) will be collected at time points listed in Table 1, Table 2, and Table 3.

Parents or legal guardians of patients who agree to participate in the future biomedical research sub-study will be required to consent and patients required to assent to this optional sub-study before samples are banked in long-term storage. The unused biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical

research of FH and related diseases, evinacumab (safety and/or efficacy) or ANGPTL3. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the Clinical Study Report.

9.2.7.4. Pharmacogenomic Analysis (Optional)

Parents or legal guardians of patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) and patients must sign a separate informed assent form before collection of the samples. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study. Samples for DNA extraction should be collected on day 1/baseline (predose) but may be collected at any study visit.

DNA samples for the genomics sub-study will be coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of HoFH as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or HoFH and other diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole genome sequencing, DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

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

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

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

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

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

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

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

All AEs, serious adverse events (SAEs), AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.4.

10.1.2. Data Collection Period

The investigator will record all events, serious and non-serious, that occur from the time of signing the informed consent and for 24 weeks after the last dose of study drug (ie, the follow-up/post treatment period). The follow-up/post treatment period applies to all patients who complete the study or terminate early (excludes those who withdraw consent). However, for those patients entering a CUP or EAP, they may forgo the 24-week follow-up period.

From the time of signing the informed consent and prior to first dose of study drug, the investigator will report the following types of events on the AE CRF:

- SAEs
- Events, serious and non-serious, attributed to study conduct, such as a protocol-mandated procedure or intervention (eg, events related to an invasive procedure such as a biopsy)

Other events that occur prior to the first dose of study drug should be reported on the medical history CRF.

From first dose of study drug, report all AEs on the AE CRF until EOS visit, which includes the follow-up/post treatment period after last dose.

10.1.3. Reporting Procedure

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

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

10.1.4. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Anaphylactic reactions

- Allergic reactions that require consultation with another physician for further evaluation or requiring medical treatment
- Moderate or severe infusion reactions
- Increase in ALT or AST: ≥3 x ULN (if baseline <ULN), or ≥2 times the baseline value (if baseline ≥ ULN)
- Symptomatic overdose with investigational medicinal product
- Neurocognitive events
- Pancreatitis
- New onset of diabetes (NOD) in patients without diabetes at baseline. New onset of diabetes is defined as either:
  - At least 2 HbA1c measurements ≥6.5% during the TEAE period (NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥6.5% will qualify the patient as NOD by default)
  - At least 2 fasting glucose measurements ≥126 mg/dL (7.0 mmol/L). For patients with several fasting glucose measurements but with only the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD)
- NOTE: Diabetes at baseline is based on documented medical history, baseline fasting glucose ≥126 mg/dL (7.0 mmol/L), or baseline HbA1c ≥6.5%

- **Pregnancy:** It is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 24 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

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

10.2.2. Serious Adverse Event

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

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

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

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

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed.

10.2.5. Severity

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

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

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

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject'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.

10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

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

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

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

  or

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

Causality to the study conduct (protocol specified procedure):

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

10.3. 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, Pharmacovigilance; Risk Management; 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.

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

During the study, the sponsor and/or the CRO will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN1500), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

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

Event expectedness for study drug (REGN1500) is assessed against the Reference Safety Information section of the current Investigator's Brochure that is effective for expedited safety reporting.

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

11. STATISTICAL PLAN

This section provides the basis for the 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 first database lock.

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

11.1. Statistical Hypothesis

No formal statistical testing will be performed for this open-label study.

11.2. Justification of Sample Size

Since this is an open-label single treatment arm study, formal statistical testing is not planned, Therefore, a calculation for patient sample size is not applicable.

Six patients are planned to be enrolled for Part A and 14 pediatric patients are planned to be enrolled for Part B, considering the recruitment constraints in this rare patient population.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Set for Part B

Intent-to Treat

The intent-to-treat (ITT) population is defined as all patients who received at least 1 dose or part of a dose of study drug in Part B.

Modified Intent-to-Treat

The modified ITT (mITT) population is defined as all patients who received at least 1 dose or part of a dose of open-label study drug in Part B and have an evaluable primary efficacy endpoint. The endpoint is considered as evaluable when both of the following conditions are met:

1. Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline).
2 Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within one of the analysis windows up to week 24. The efficacy treatment period is defined as the time from the first study drug administration up to 35 days after the last study drug administration in Part B.

11.3.2. Safety Analysis Set

Safety Analysis Set: The safety analysis set (SAF) includes all patients who received at least 1 dose or part of a dose of study drug.

Part C Safety Analysis Set: The Part C safety analysis set includes all patients who received at least 1 dose or part of a dose of study drug in Part C.

11.3.3. Pharmacokinetic Analysis Sets

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

The total target analysis population includes all patients who received any study drug and who had a at least 1 non-missing result for concentration of total ANGPTL3 following the first dose of study drug.

11.3.4. Immunogenicity Analysis Sets

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

Samples positive in the ADA assay may be analyzed in neutralizing antibody assay.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay following the first dose of the study drug. Patients who are ADA negative are set to negative in the NAb analysis set.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

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

Data for patients in Part A and patients in Part B will be summarized and listed separately. Similar analyses will be performed for patients in Part A and patients in Part B, respectively, unless otherwise specified.

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 ICF
- The total number of patients in each analysis set (eg, ITT, SAF, provided in Section 11.3)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who prematurely discontinued study treatment in Part B, and the reasons for discontinuation
- The total number of patients who entered Part C
- The total number of patients who prematurely discontinued study treatment in Part C and the reasons for discontinuation
- A listing of patients prematurely discontinued from study treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for patients in the SAF for Part A, and for patients in the ITT population for Part B.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis for Part B

The percent change from baseline in calculated LDL-C at week 24 will be analyzed in the ITT population using a pattern mixture model (PMM) approach as described below (see Appendix 1 for more details).

In the PMM approach, different imputation strategies will be applied to calculated LDL-C values missing during the on-treatment period (ie, within the time period from the first study treatment administration up to the day of last study treatment administration +35 days in Part B) versus calculated LDL-C values missing due to treatment discontinuation after the on-treatment period (ie, after the day of last study treatment administration +35 days in Part B) based on the following assumptions:

- Patients within 35 days of their last study treatment administration in Part B would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, calculated LDL-C values missing during the on-treatment period (eg, samples obtained out-side the specified window, no blood sample available although visit was performed, etc.) should be considered "Missing at Random" and imputed based on other observed measurements in the on-treatment period.
- Patients who stopped taking their study treatment in Part B no longer benefited from it after discontinuation, and thus tended to have calculated LDL-C values returning to baseline. Therefore, calculated LDL-C values missing after the on-treatment period should be imputed based on patient's own baseline value.

Missing data from the ITT population will be imputed 100 times to generate 100 complete data sets, using the SAS MI procedure (using Markov Chain Monte Carlo). The 100 completed datasets of observed and imputed calculated LDL-C data will be used for the primary analysis.

For the percent change from baseline calculated LDL-C endpoint, the 100 complete datasets of observed and imputed calculated LDL-C data at week 24 will be analyzed using the SAS MEANS procedure. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae. Combined estimate for mean at Week 24 will be provided with the standard error (SE) and 95% confidence interval (CI). Formal statistical testing is not planned.

Robustness of this statistical method will be assessed through sensitivity analyses detailed in the SAP, including an ITT analysis and an on-treatment analysis of the percent change in calculated LDL-C from baseline to week 24 using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within the week 1 to week 24 analysis windows will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effect of time point, as well as the continuous fixed covariate of baseline LDL-C value.

11.4.3.2. Secondary Efficacy Analysis for Part B

For the secondary efficacy endpoints (defined in Section 4.1.2), descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand).

For descriptive summaries, percent change, and when appropriate change from baseline, in calculated LDL-C, total-C, non-HDL-C, Apo B, and Lp(a) will be provided at each time point during the 24-week open-label treatment period. All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. The time profile of each parameter will be plotted with the corresponding SEs.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (eg, percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution [eg, Lp(a)], and binary measurements (eg, proportion of patients with ≥50% reduction in calculated LDL-C).

I Continuous endpoints anticipated to have a normal distribution

Continuous secondary efficacy endpoints anticipated to have a normal distribution (ie, lipids other than Lp(a)) will be analyzed using the same PMM approach as for the primary endpoint. In addition, the same sensitivity analyses using MMRM approach as for the primary endpoint will be conducted in the ITT population and mITT population.

II Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy endpoints anticipated to have a non-normal distribution (ie, Lp(a)), will be analyzed using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with baseline value as a covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The combined means will be provided with respective SE estimates and 95% CI.

III Binary Endpoints

Binary secondary efficacy endpoints will be analyzed with multiple imputation approach for handling of missing values, which will be described in the SAP. Combined proportions will be provided with corresponding 95% CI.

11.4.3.3. Other Efficacy Analyses for Part B

For patients who entered Part C, a combined summary including both the Part B and Part C assessments will be considered, referencing the Part B baseline for variable calculations. Prolonged time between last dose of study treatment in Part B and first dose of study treatment in Part C will need to be taken into consideration when combining longitudinal efficacy data.

11.4.4. Control of Multiplicity

Not applicable.

11.4.5. Safety Analysis

The summary of safety results will be presented for patients in the SAF analysis set. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the following common rule:

- The baseline value is defined as the last available value before the first dose of study treatment.

Safety analyses for the Part C treatment period in the Part C safety analysis set of Part A patients will be performed separately for the period pre- versus post-switch to adjusted dose if applicable.

Safety analyses for the combined treatment period of Part B and Part C will be performed in the Part C safety analysis set of Part B patients.

11.4.5.1. Adverse Events

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

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined from the day the ICF is signed to the day before the first dose of study treatment.
- The TEAE observation period (Part A or Part B) is defined from the day of the first study treatment administration to the day of the last study treatment administration + 168 days (24 weeks). For patients entering Part C, the TEAE period was truncated at the day before the first study treatment administration in Part C.
- The Part C TEAE observation period is defined from the day of the first study treatment administration in Part C to the day of the last study treatment administration in Part C + 168 days (24 weeks).
- The Part B/Part C combined TEAE observation period is defined from the day of the first study treatment administration in Part B to the day of the last study treatment administration in Part C or to the last study treatment administration in Part B for patients not entering into Part C + 168 days (24 weeks).
- The post-treatment period is defined as the time from the day after the end of the respective TEAE period to the last study visit.

Treatment-emergent adverse events are defined as those events that developed, worsened, or became serious during the respective TEAE period.

Analysis

Adverse event incidence tables will present data by SOC sorted alphabetically and PT sorted by decreasing frequency, and summarize the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. Data conventions for missing or partial AE dates will be addressed in the

SAP. The denominator for computation of percentages is the respective SAF analysis sets (ie, SAF or Part C SAF).

Summaries of TEAEs incidences will include:

- All TEAEs (and patient listing)
- All treatment-emergent SAEs, including patient deaths (and patient listing)
- All TEAEs of special interest
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), depicting the worse TEAE severity for those patients with multiple occurrences of the same event
- All TEAEs leading to permanent treatment discontinuation (and patient listing)

An AE patient listing will be provided for all patient deaths occurring during the respective TEAE period and the post-treatment period.

11.4.5.2. Other Safety

Definitions

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant value (PCSV) criteria are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests and vital signs. PCSV criteria will be provided in the SAP.
- PCSV criteria will determine which patients had at least 1 PCSV during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSV percentage.
- Treatment period (Part A or Part B): the treatment period used for quantitative analysis of laboratory and vital signs data is defined from the day after the first study treatment administration to the day of the last study treatment administration + 28 days for those patients not proceeding into Part C, or up to the day of the first study treatment administration in Part C for those patients proceeding into Part C.
- Part C treatment period: the treatment period used for quantitative analysis of laboratory and vital signs data is defined from the day after the first study treatment administration in Part C to the day of the last study treatment administration in Part C + 28 days.
- Part B/Part C combined treatment period: the treatment period used for quantitative analysis of laboratory and vital signs data is defined from the day after the first study treatment administration in Part B to the day of the last study treatment administration in Part C or to last study treatment administration in Part B for patients not entering into the Part C + 28 days.

Analysis

Summary statistics of all laboratory variables and all vital signs parameters (raw data and changes from baseline) will be calculated for each protocol scheduled visit assessed during the respective treatment period. For selected parameters, mean changes from baseline with the corresponding SE may be plotted over time (at same time points).

The incidence of PCSVs at any time during the respective treatment period will be summarized regardless of the baseline level, and again according to the following baseline categories:

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

For laboratory parameters for which a PCSV criterion is not defined, similar table(s) using the normal range will be provided.

Listings will be provided with flags indicating the laboratory values meeting PCSV criteria.

11.4.5.3. Treatment Exposure

The Part A or Part B duration of study treatment will be calculated as:

- Patient duration of study treatment exposure in weeks: (last study treatment administration date + 28 – first study treatment administration date +1 day)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence.
- The total number of treatment infusions by patient.

The Part C duration of study treatment exposure will be calculated as:

- Patient duration of Part C study treatment exposure in weeks: (last study treatment administration date in Part C + 28 – first study treatment administration date in Part C +1 day)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence.
- The total number of Part C treatment infusions by patient.

The combined Part B/Part C duration of study treatment exposure will be calculated as:

- Combined patient duration of study treatment exposure in weeks: Part B treatment duration + Part C treatment duration.
- Combined total number of treatment infusions by patient defined as: total number of Part B study treatment infusions + total number of Part C treatment infusions.

The durations of study treatment exposure measured in weeks, will be summarized by at least; mean, median, SD, and minimum/maximum. The categorical data for number of study treatment infusions will be summarized by patient counts and percentages.

11.4.5.4. Treatment Compliance

Compliance will be assessed by infusion frequency for the Part A treatment period, the Part B treatment period, and the combined Part B/Part C treatment period, specifically:

- Defined for each patient as the average number of days between 2 infusions during the respective period: (last dose date – first dose date) / (number of infusions -1), for patients receiving at least 2 infusions.

Infusion frequency will be summarized by at least; mean, median, SD, and minimum/maximum.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The PK parameters for Part A may include, but are not limited to:

- C_{max}
- AUC_{last}
- AUC_{inf}
- CL
- Linear $t_{1/2}$
- Vss
- MRT

The PK parameters for Part B include:

- $C_{max.ss}$
- $AUC_{tau.ss}$
- $C_{trough.ss}$

The concentrations of total evinacumab over time and selected PK parameters for Part A will be summarized by descriptive statistics for the purpose of estimating exposures. This descriptive statistical assessment will include the geometric means for selected PK parameters, as deemed appropriate.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-first dose ADA results negative, or a positive assay response at baseline, with all post-first dose ADA assay responses less than 9-fold of baseline titer levels
- Treatment-emergent ADA response, defined as any post-first dose positive ADA assay response when the baseline results are negative
  - For Part B and Part C of the study, treatment-emergent ADA response will be further characterized as persistent, transient, or indeterminate:
  - Persistent Response – Treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points, separated by at least 16-week

period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.

  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate.

- Treatment boosted ADA response, defined as any post-first dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- Samples positive in the ADA assay will be analyzed for neutralizing antibody,
  - NAb status (negative or positive) in the neutralizing antibody assay

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

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

11.5. Timing of Analyses

11.5.1. First Step: PK and Safety Analysis for Part A

The first step will be an analysis of PK data from all patients in Part A when PK data have been collected and validated for these patients.

11.5.2. Second Step: Efficacy and Safety Analysis for Part B

The second analysis will be conducted as soon as all patient data through week 24 in Part B have been collected and validated; this will consist of the final analysis of the primary and secondary efficacy endpoints up to week 24 for Part B patients. The safety analysis will be performed on all safety data collected and validated at the time of the second analysis for Part B patients.

The results of the second analysis will not be used to change the conduct of the ongoing study in any aspect. This second analysis may be used for the submission dossier to health authorities.

11.5.3. Third Step: Final Safety Analysis

The third analysis will be conducted at the end of the study and will consist of the final safety analysis.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

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

12.1.2. Electronic Systems

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

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

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

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

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

12.2.3. Case Report Form Requirements

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

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

12.3. Audits and Inspections

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

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

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for 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 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, or if there are significant changes to the study procedures, 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).

13.3. Patients Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A THREE-PART, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF EVINACUMAB IN PEDIATRIC PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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 Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia

Protocol Number: R1500-CL-17100

Protocol Version: R1500-CL-17100 Amendment 2

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

APPENDIX 1. DETAILED DESCRIPTION OF PATTERN MIXTURE MODEL

As the primary analysis of the primary efficacy endpoint (ie, percent change from baseline to week 24 in calculated LDL-C for Part B), a pattern-mixture model approach will be used with a different imputation strategy applied for missing calculated LDL-C values during the on-treatment period (ie, within the time period from the first study treatment administration up to the day of the last study treatment administration +35 days or to the day before the first long-term extension treatment administration, whichever comes first for Part B) and missing LDL-C values after treatment discontinuation (ie, after the day of last study treatment administration +35 days in Part B) based on the following assumptions:

- Patients within 35 days of their last study treatment administration in Part B would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, calculated LDLC values missing during the on-treatment period will be considered "Missing at Random" and imputed using a model estimated using all samples collected on treatment.
- Patients who stopped taking their study treatment no longer benefited from it in the future, and thus tended to have calculated LDL-C values returning to baseline. Thus calculated LDL-C values missing after treatment discontinuation will be imputed based on patient's own baseline value.

The assumptions for this approach are based on the following considerations:

- Missing values during the on-treatment period are mostly consecutive to:
  - Visits performed outside of the pre-specified time-window
  - No blood sample available although visit was done
  - LDL-C not measurable due to technical reasons

  In addition, these missing data are often intermittent, ie, followed by LDL-C values collected at subsequent visits. It is therefore considered reasonable to assume that these missing data were "At Random".

Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to week 24 will be derived from observed and imputed LDL-C at this time point. The completed data sets will be analyzed using the SAS MEANS procedure. The results from the 100 analyses will be combined using Rubin's formulae. If necessary, the number of imputations (100) will be increased until stable estimates are obtained.

Imputation of missing data during the on-treatment period

Missing LDL-C values during the on-treatment period will be imputed from other on-treatment measurements assuming Missing At Random, using SAS® MI procedure.

Only LDL-C values collected during the on-treatment period will be included in the imputation model. This way, missing LDL-C values during the on-treatment period will be imputed based solely on observed on-treatment LDL-C values.

The imputation model will include baseline LDL-C value, and all LDL-C values at pre-specified visits. Since the pattern of missing data will necessarily be non-monotone, a Monte-Carlo Markov Chain (MCMC) method will be used. A minimum value of 0 will be specified in order to avoid negative imputed LDL-C values.

A sample SAS code is provided below:

proc mi data=DATAIN out=DATAOUT nimpute=100 minimum=. 0 0 0 0 0 0 0 0 0 SEED=17100;

ºvar LDL_BASE LDL_W1 LDL_W2 LDL_W4 LDL_W8 LDL_W12 LDL_W16 LDL_W20 LDL_W24;

run;

As stated above, the input dataset DATAIN will include only LDL-C values collected during the on-treatment period. Any LDL-C values collected during the post-treatment period will be excluded from the input dataset. In practice, the MI procedure will generate imputed values for all missing values (whether on-treatment or post-treatment), but only imputed values during the-on-treatment period will be kept in the final datasets that will be analyzed. Imputed values during the post-treatment period will be discarded and replaced by imputed values described in the next paragraph.

Imputation of missing data after treatment discontinuation

Missing LDL-C values during the post-treatment period will be imputed assuming LDL-C values would on average return to baseline values.

For each patient, missing post-treatment LDL-C values will be imputed 100 times, using a random draw from a normal distribution (SEED=34200), with mean equal to patient's own baseline value and variance equal to the conditional variance at the specific time-point, given the baseline value.

Let Y_0 and Y_1 denote the LDL-C at baseline and at the specific time-point respectively. Since Y_0 and Y_1 are assumed to have a bivariate normal distribution, the conditional variance of Y_1 given Y_0 is:

$$Var(Y_1 | Y_0 = y_0) = \sigma_1^2(1-\rho^2)$$

Where σ_1^2 denotes the variance of Y_1 and ρ the coefficient of correlation between Y_0 and Y_1.

The conditional variance will be estimated from observed data at the specific time-point.

During the random generation process, a minimum value of 0 will also be applied in order to avoid negative imputed LDL-C values.

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