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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

AN OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF EVINACUMAB IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	Evinacumab (REGN1500)
Clinical Phase:	3
Protocol Number:	R1500-CL-1719
Protocol Version:	R1500-CL-1719 Amendment 7
Amendment 7 Date of Issue:	*See appended electronic signature page*
Amendment 6 FR Admin Date of Issue:	23 Dec 2021
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Amendment 5B FR Admin Date of Issue:	19 Dec 2019
Amendment 5B FR Date of Issue:	01 Nov 2019
Amendment 4B Date of Issue:	11 Oct 2019
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AMENDMENT HISTORY

Overall Rationale for Amendment 7

The overall rationale of the amendment is to allow patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a Compassionate Use Program [CUP], Early Access Program [EAP], or Investigator-Sponsored Study/Trial [ISS/IST]) and thereby may forgo the 24-week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's end-of-treatment visit (EOT) will be their last study visit.

The following table shows the changes made to the protocol with the rationale and the sections changed.

Change	Rationale	Sections Changed
To allow patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a CUP, EAP or ISS/IST) and thereby may forgo the 24-week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's EOT will be their last study visit.	The 24-week follow-up period was intended to be an off-drug follow-up. If clinical trial patients will transition to receive treatment outside of the clinical trial such as through a CUP, EAP or ISS/IST, they will not be required to complete the 24-week follow-up period.	Clinical Study Protocol Synopsis, Study Design Clinical Study Protocol Synopsis, Study Design: Follow-up Period Section 5.1 Study Description and Duration Figure 1: Study Flow DiagramTable 3: Schedule of Events – Open-Label Treatment Period and Follow-Up Section 8.1.3 Footnotes for the Schedule of Events Table 3, footnote #14 , and footnote #15 Section 8.1.4 Early Termination Visit
Minor editorial and administrative changes	To improve consistency and clarity and correct typographical errors	Throughout protocol

Amendment 6 FR Admin

The following table shows the changes made to the protocol with the rationale and the sections changed.

Change	Rationale	Sections Changed
To allow continued access to evinacumab treatment under the protocol in France following regulatory approval	To allow participants in France to continue dosing under the protocol and avoid a lapse in treatment	Clinical Study Protocol Synopsis, Study Design Section 5.1 Study Design and Duration
Editorial change	The confidential statement was updated by Legal	Protocol Title Page

Amendment 6

The following table shows the changes made to the protocol with the rationale and the sections changed.

Change	Rationale	Sections Changed
Added statements to address the impact of the COVID-19 pandemic on 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 3.2.3 Risk/Benefit Assessment. Section 8 Study Schedule of Events and Procedures
Added carotid ultrasound imaging to assess for carotid intima-media thickness. This is only applicable to adolescent patients at sites with the capability to perform the assessment and for whom the sites can obtain images on at least 2 visits separated by 6 months or a year.	This change was made in accordance with a request from the EMA Pediatric Committee to assess the effect of evinacumab on the progression of atherosclerosis in pediatric patients.	Section 2.3 Exploratory Objective Section 4.5 Ultrasound Imaging Table 1 Schedule of Events - Run-in and Screening Table 2 Schedule of Events- Screening for Patients with No Run-in Table 3 Schedule of Events – Open-Label Treatment Period and Follow-up Section 8.1.1 Footnotes to Schedule of Events Table 1 (#11) Section 8.1.2 Footnotes for Schedule of Events Table 2 (#10) Section 8.1.3 Footnotes for Schedule of Events Table 3 (#18) Section 8.2.6 Ultrasound Imaging

Change	Rationale	Sections Changed
Added a provision for patients to receive study drug at home or at an alternative location if the patient is unable to visit the site.	To ensure that patients are able to continue evinacumab treatment despite travel restrictions or challenges as a result of the COVID-19 pandemic.	Synopsis – Study Design Section 5.1 Study Description and Duration
Changed exclusion for LDL-C at screening from <40 mg/dL to <70 mg/dL.	This was changed in response to a health authority request in a country-specific amendment but has been applied to this protocol to align the eligibility criteria across all sites across all regions.	Section 3.2.1 Rationale for Study Design Section 6.2.2 Exclusion Criteria for Evinacumab-Naïve Patients (#16)
Removed the requirement that all males with female partners of child-bearing potential are required to consistently use a condom, even if the male study participant has been vasectomized, which was added as an urgent safety measure (USM) in response to results from an embryofetal development toxicology study in rabbits. Contraception requirements for sexually active males includes both consistent use of a condom or vasectomy.	The USM was added to version 4 of the protocol in response to non-clinical results from an ongoing toxicology study in rabbits showing incomplete ossification of the 15th vertebra in some fetuses fathered by males receiving evinacumab. In the final report, this finding was considered non-adverse because the underlying cartilage for the vertebra was present, indicating that the unossified caudal vertebra likely represented delayed ossification and not a malformation. An unossified caudal vertebra at birth is a common variation that has no adverse impact on survival.	Section 6.2.2 Exclusion Criteria for Evinacumab-Naïve Patients (#15) Section 6.2.3 Exclusion Criteria for Patients from a Previous Evinacumab Study (#8) Table 1 Schedule of Events - Run-in and Screening Table 2 Schedule of Events- Screening for Patients with No Run-in Table 3 Schedule of Events – Open-Label Treatment Period and Follow-up
Updated introduction and benefit-risk and added moderate-to-severe infusion reactions to list of AESIs.	Updates were made to reflect recent clinical data and to align with safety updates in IB Edition 9.	Section 1 Introduction Section 3.2.3 Risk/Benefit Assessment Section 9.4.3 Other Events that Require Accelerated Reporting
Retired protocol version A (applicable to adult subjects only) and updated the protocol	All regions now allow the inclusion of adolescent patients.	

Change	Rationale	Sections Changed
amendment nomenclature to reflect a single, global protocol applicable to adult and adolescent subjects.		
Editorial revisions	To make minor edits	Throughout

Amendment 5B FR Admin

This is a non-substantial amendment to correct typographical errors referencing footnotes in Table 3 of the Schedule of Events.

Change	Sections Changed
The reference to footnote 12 was removed for some visits where PK sampling was limited to adolescents (footnote 17).	Table 3 Schedule of Events – Open-Label Treatment Period and Follow-Up.

Amendment 5B FR

The primary purpose for this amendment is to increase the number of patients from 100 to 120 and to add objectives to assess efficacy and safety in adolescent patients with HoFH. As a result, there are also changes to the statistical analyses.

Change	Section Changed
Study objectives were added to specifically assess efficacy and safety of evinacumab in adolescent patients with HoFH. As such, the number of patients was increased from 100 to approximately 120 to allow additional evinacumab-naïve adolescents to enter the study and gain experience with evinacumab in a subpopulation of adolescent patients. As a result, the analyses were also revised.	Synopsis–Objectives Synopsis – Population Synopsis –Statistical Plan Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 5.2 Planned Interim Analysis Section 6.1 Number of Patients Planned Section 10.2 Justification of Sample Size Section 10.4 Statistical Methods Section 10.4.1 Patient Disposition Section 10.4.2 Demography and Baseline Characteristics Section 10.4.3 Efficacy Analyses Section 10.4.4.1 Adverse Events
Added topline data from a phase 3, double-blind, placebo-controlled study in patients with HoFH (R1500-CL-1629).	Section 1 Introduction Section 3.2.3 Risk/Benefit Assessment
Added a provision for re-screening of patients	Section 6.5 Re-screening of Patients (section added)
Increased the window from ±5 days to ±7 days for evinacumab administration every 4 weeks to ease patient burden and provide flexibility in this long-term safety study without impacting the consistency of drug exposure to evinacumab	Section 5.1 Study Description and Duration Section 7.1 Investigational and Reference Treatments Table 3 Schedule of Events - Open-Label Treatment Period and Follow-Up

Change	Section Changed
Flexibility was added in terms of timing of study drug administration in relation to apheresis, because Regeneron has collected data showing apheresis has a minor effect on drug concentrations, which most likely does not impact efficacy. The PK sampling frequency was reduced for most patients because of the amount of PK data collected to date in adult patients with HoFH. New PK sampling time points were added for the additional evinacumab-naïve adolescents who will enter this study as well as any patients who might undergo plasma exchange.	Synopsis – Study Design Section 5.1 Study Description and Duration Table 3 Schedule of Events - Open-Label Treatment Period and Follow-Up Section 8.1.3 Footnotes for Schedule of Events Table 3 (#3, #12, #16, #17)
Removed plasma exchange from the list of prohibited procedures to allow assessment of the impact of plasma exchange on the PK of evinacumab.	Synopsis – Study Design Section 5.1 Study Description and Duration Section 7.7 Concomitant Medications and Procedures Section 7.7.1 Permitted Medications and Procedures Section 7.7.2 Prohibited Medications and Procedures Section 8.1.3 Footnotes for Schedule of Events Table 3 (#3, #12)
Although bilateral tubal ligation is considered a method of highly effective contraception, it does not eliminate the need for routine pregnancy testing in the study. This was incorrectly described in the protocol and corrected in this amendment.	Section 6.2.2 Exclusion Criteria for Evinacumab-Naïve Patients Section 6.2.3 Exclusion Criteria for Patients from a Previous Evinacumab Study
Editorial revisions	Throughout the protocol

Amendment 4B

After completion of the 2A and 2B versions of the protocol, a country-specific version was required, which became R1500-CL-1719 2B FR. Subsequently, the R1500-CL-1719 2B FR was amended to become R1500-CL-1719 3B FR. Consequently, to avoid confusion and maintain the sequence, the numbering of the present amendment becomes R1500-CL-1719 4B.

The protocol was amended in response to recent non-clinical findings in the rabbit. The table below summarizes the changes and the affected sections:

Change	Sections Changed
In an embryofetal development toxicology study in rabbits, incomplete ossification of the 15th vertebra was observed in some fetuses resulting from the mating of male rabbits exposed to evinacumab with female rabbits not exposed to evinacumab. In male rabbits, there were measurable levels of evinacumab in seminal fluid and, as a safety measure, the current clinical study is amended to require consistent use of a condom for all sexually active males.	Section 3.2.3 Risk/Benefit Assessment Section 6.2.2 Exclusion Criteria for Evinacumab-Naïve Patients (#15) Section 6.2.3 Exclusion Criteria for Patients from a Previous Evinacumab Study (#8) Table 1 Schedule of Events – Run-In and Screening Table 2 Schedule of Events – Screening for Patients with No Run-In Table 3 Schedule of Events – Open-Label Treatment Period and Follow-Up
Updated Medical/Study Director	Title page

Amendment 2B

The primary purpose of this amendment is to revise the patient population to allow patients with HoFH who have not participated in a previous evinacumab study to enter this study. The summary of protocol changes provided below outlines changes from the original protocol dated 12 Sep 2017 because Amendment 1B of this protocol was not finalized. The following table outlines the changes made to the protocol:

Change	Section Changed
Revised the eligibility requirements to allow patients who have not participated in a previous evinacumab study (ie, patients who are evinacumab-treatment naïve) to participate in this study. The reason for this change is to obtain additional long-term safety and tolerability data with evinacumab in patients with HoFH. As such, the sample size was increased to allow up to 100 patients to enroll in the study. Additionally, the following study design changes were made and are only applicable to those patients who did not participate in a previous evinacumab clinical study: – Added inclusion criterion for diagnosis of functional HoFH – Added a requirement for genotyping – Added an exclusion criterion for LDL-C <40 mg/dL at the screening visit – Added other exclusion criteria related to laboratory findings, physical examination, past medical history, and comorbid diseases consistent with those patients who enter this study from a previous evinacumab study – Added an optional run-in period that can be used to stabilize background lipid modifying therapies (LMTs) – Added new Schedule of Events tables for the run-in and screening periods	Synopsis – Study Design Synopsis - Study Duration Synopsis – Population Synopsis –Statistical Plan Section 1 Introduction Section 3.1 Hypothesis Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.1 Number of Patients Planned Section 6.2 Study Population Section 6.2.1 Inclusion Criteria (added #2 and modified inclusion #2 of original protocol and it is now #3) Section 6.2.2 Exclusion Criteria for Evinacumab-Naïve Patients (new) Section 6.2.3 Exclusion Criteria for Patients from a Previous Evinacumab Study (#1, #2, #3, and #7 and section title) Section 7.7 Concomitant Medications and Procedures Table 1 Schedule of Events – Run-In and Screening (new) Table 2 Schedule of Events – Screening for Patients with No Run-In (new) Table 3 Schedule of Events – Open-Label Treatment Period and Follow-Up

Change	Section Changed
	Section 8.1.1 Footnotes for Schedule of Events Table 1 (all new) Section 8.1.2 Footnotes for Schedule of Events Table 2 (new) Section 8.1.3 Footnotes for Schedule of Events Table 3 (new) Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.2.5 Laboratory Testing Section 8.2.9.2 DNA Sample for HoFH Genotyping (new) Section 8.2.9.3 Genomics Sub-Study (Optional) (new) Section 10.2 Justification of Sample Size Section 10.4 Statistical Methods Section 10.4.2 Demography and Baseline Characteristics Section 10.4.3 Efficacy Analyses Section 10.4.4 Safety Analyses Section 10.4.4.1 Adverse Events
Patients allowed to participate in this study could include those who have completed a study evaluating the safety and efficacy of alirocumab in patients with HoFH, but did not participate in a prior evinacumab study. Upon entering the study, these patients may discontinue alirocumab, continue to receive alirocumab provided by the Sponsor, or change to any commercially available PCSK9 inhibitor. This allows patients, the investigator or the patients' health care providers to decide on the best background treatment regimen for the patient prior to entering this study.	Synopsis – Treatment(s) Section 6.2 Study Population Section 7.2 Background Treatment(s)

Change	Section Changed
Added a Risk/Benefit Section that provides an assessment of LDL-C lowering and the potential cardiovascular benefit in patients with LDL-C ≥40 mg/dL and a summary of the safety information with evinacumab. A risk/benefit assessment is also provided for the use of evinacumab with PCSK9 inhibitors (alirocumab or evolocumab) as part of the patient's background LMT.	Section 3.2.3 Risk/Benefit Assessment (new) Section 22 References
Changed the requirement to maintain a stable background LMT regimen for at least 48 weeks to at least 24 weeks, ie, patients are permitted to change the lipoprotein apheresis schedule/setting or lomitapide therapy after week 24 of the study. This means that patients transitioning into this study from a previous evinacumab study will receive evinacumab for at least 48 weeks on a stable background LMT regimen, which enables an evaluation of the durability of evinacumab's LDL-C lowering effect.	Synopsis – Treatment(s) Section 6.2 Study Population Section 7.2 Background Treatment(s) Section 7.7.1 Permitted Medications and Procedures Section 7.7.2 Prohibited Medications and Procedures
The statement was added that adolescent patients will be enrolled only in participating countries where regulatory approval has been obtained to include adolescents, and that only patients ≥18 years of age will be enrolled in countries that have not received regulatory approval to enroll adolescent patients.	Synopsis – Population Section 6.2 Study Population Section 6.2.1 Inclusion Criteria (#1) Section 6.2.3 Exclusion Criteria for Patients from a Previous Evinacumab Study (#6 and #8)
Added exclusion criteria for patients <12 years old and Tanner stage <2.	Section 6.2.2 Exclusion Criteria for Evinacumab-Naïve Patients (#20 and #21) Section 6.2.3 Exclusion Criteria for Patients from a Previous Evinacumab Study (#9 and #10) Section 4.1 Demographic and Baseline Characteristics

Change	Section Changed
Added sampling for PK (evinacumab and ANGPTL3) at weeks 4, 8, 12, 16, 20 and visits A, B, C, D, E only for patients undergoing lipoprotein apheresis in order to assess potential effects of apheresis on evinacumab PK and ANGPTL3 levels	Table 3 Schedule of Events – Open-Label Treatment Period and Follow-Up Section 8.1.3 Footnotes for Schedule of Events Table 3 (now #16)
Removed anti-drug antibody (ADA) sampling at week 4.	Table 3 Schedule of Events – Open-Label Treatment Period and Follow-up
Added blood chemistry assessment at the 12 weeks post last dose visit, and the 20 weeks post last dose visit	Table 3 Schedule of Events – Open-Label Treatment Period and Follow-up
Added hemoglobin A1c (HbA1c) assessment at the 12 weeks post last dose visit	Table 3 Schedule of Events – Open-Label Treatment Period and Follow-up
Replaced the serum pregnancy test at baseline (day 1) with a urine pregnancy test as the serum pregnancy test is now performed at screening and added a urine pregnancy test at run-in..	Table 1 Schedule of Events – Run-In and Screening Table 3 Schedule of Events – Open-Label Treatment Period and Follow-Up Section 8.2.2.6 Pregnancy Testing
Added a footnote that for an adolescent patient not of childbearing potential at Screening, the site confirms whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and pregnancy testing will be administered every 4 weeks.	Section 8.1.1 Footnotes for Schedule of Events Table 1 (#7) Section 8.1.2 Footnotes for Schedule of Events Table 2 (#7) Section 8.1.3 Footnotes for Schedule of Events Table 3 (#9) Section 6.3 Premature Withdrawal from the Study
Added a clause to discourage alcohol consumption 48 hours and smoking and intense physical exercise 24 hours prior to blood sampling for all patients as these may alter laboratory results.	Section 8.2.3 Efficacy Procedures

Change	Section Changed
Updated the anti-drug antibody (ADA) language to state that positive ADA response with a titer >240 in the last sample analyzed will be followed for 3 to 6 months if needed, to determine or follow-up on the off-treatment persistence of ADA.	Section 8.2.5 Anti-Drug Antibody Measurements and Samples
Wording updated to more accurately reflect planned ADA analysis	Section 10.4.6 Analysis of Anti-Drug Antibody Data
Added pharmacokinetic (PK) sampling at week4	Table 3 Open-Label Treatment Period and Follow-Up
Minor editorial revisions.	Title page Section 1 Introduction Section 4.1 Demographic and Baseline Characteristics Section 4.4 Anti-Drug Antibody Variables Section 7.1 Investigational and Reference Treatments Section 7.5 Method of Treatment Assignment Section 8.2.3.1 Lipid Panel Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor Section 10.4.1 Patient Disposition Section 14.1 Good Clinical Practice Statement Section 17.1 Certification of Accuracy of Data

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia
Site Locations	Multi-center
Principal Investigator	Multi-national
Objectives	The primary objectives of the study are: • To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg intravenous (IV) administered every 4 weeks (Q4W) in patients with homozygous familial hypercholesterolemia (HoFH). • To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg IV administered Q4W in adolescent patients with HoFH. The secondary objectives of the study are: • To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, low-density lipoprotein cholesterol [LDL-C], apolipoprotein B [Apo B], non-high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], and triglycerides [TG]) in patients with HoFH • To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, LDL-C, Apo B, non-HDL-C, TC, and TG) in adolescent patients with HoFH • To evaluate the potential development of anti-evinacumab antibodies
Study Design	This is an open-label study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. Eligible patients for this study are male and female patients with HoFH, receiving stable lipid modifying therapy (LMT), as applicable. Lipid modifying therapy may include a maximally tolerated statin, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor antibody and lipoprotein apheresis. Patients with HoFH who have participated in a previous evinacumab study (eg, R1500-CL-1331 and R1500-CL-1629) and evinacumab-naïve patients with HoFH are eligible. This study consists of 4 periods: a run-in period, a screening period, an open-label treatment period, and a follow-up period. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a compassionate use program [CUP], early access program [EAP], or investigator sponsored study [ISS/IST]) and thereby may forgo the 24-week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's end-of-treatment visit (EOT) will be their last study visit. ***Run-in Period***

Patients whose HoFH diagnosis cannot be confirmed by the clinical criteria listed or from previous genotyping results, may enter the run-in period to determine their mutation status.

Patients whose background lipid modifying therapy (LMT) (as applicable) has not been stable prior to baseline (day 1) for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) or whose apheresis settings and/or schedule (as applicable) have not been stable for at least 8 weeks prior to baseline (day1) will enter an up to 10-week run-in period.

Screening Period:

All evinacumab-naïve patients who are on a stable background LMT will enter a 2-week screening period.

Patients who participated previously in an evinacumab study and do not enter this study within 7 days of completing the end of study (EOS) visit of the previous study, must undergo screening.

Open-Label Treatment Period:

Patients who completed the EOS visit in the previous evinacumab study within 7 days of the baseline/day 1 visit for this open-label study do not have to undergo the screening visit and may enroll directly into this study if they fulfill all of the inclusion criteria and none of the exclusion criteria. The EOS visit from the previous study can serve as the baseline/day 1 visit for this open-label study and overlapping assessments do not need to be repeated in this study. Baseline assessments and procedures that do not overlap with assessments at the EOS visit of the previous study should be performed after all EOS assessments and procedures have been completed in the previous evinacumab study.

Starting on day 1 (baseline), all patients will receive evinacumab 15 mg/kg IV administered Q4W (±5 days) at the study site. Patients will remain in the clinic for monitoring for 60 minutes after the end of each IV infusion. For patients unable to go to the site, evinacumab may be administered at an alternative location, which could include the patient's home by a trained nurse or other health professional, as allowed by local laws.

All patients who were supplied with alirocumab 150 mg subcutaneous (SC) by the sponsor in a previous study may continue to be provided with alirocumab 150 mg SC every 2 weeks (Q2W) in this study. Those entering this study after completing a study evaluating the safety and efficacy of alirocumab in patients with HoFH, but did not participate in a prior evinacumab study, may or may not remain on alirocumab as part of their background LMT. Based on the patient's preference and the judgment of the investigator and the patient's health care provider, each patient may:

- continue treatment with alirocumab supplied by sponsor as part of their background LMT
- discontinue alirocumab prior to enrolling into this study
- change to a commercially available PCSK9 inhibitor antibody prior to enrolling into this study

Clinical laboratory samples must be collected and study assessments must be performed before study drug is administered. Patients who are undergoing lipoprotein apheresis or plasma exchange must have their clinical laboratory samples drawn and study assessments performed before undergoing the procedure. Every effort should be made for the patient to receive study drug immediately after completion of the apheresis procedure, but patients can receive study drug 1 day before the apheresis procedure. Patients on plasma exchange should receive the study drug immediately after completing the procedure.

Patients receiving background LMT, which has been proven to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) (eg, statins, ezetimibe, PCSK9 inhibitor antibodies), should make their best effort to maintain a stable regimen for at least 24 weeks and for the duration of the study.

Patients receiving other LMT (eg, apheresis, lomitapide) may have that LMT adjusted after week 24, based on their LDL-C, cardiovascular (CV) risk factors, and judgment of the investigator.

Patients should be on a stable heart healthy diet and exercise regimen throughout the duration of the study, starting at the baseline visit and continuing through the end of the open-label treatment period.

Evinacumab treatment will continue until one of the following occurs:

- Clinical development of evinacumab for the indication described in this study protocol is discontinued
- Clinical development of evinacumab is terminated
- Risk/benefit of evinacumab in this patient population is deemed unfavorable
- Evinacumab is approved by the regulatory authority governing the location of the study site*
- For local discontinuation of study: a decision has been made not to seek approval of an indication for treatment of patients with HoFH in the regulatory region in which the study is being conducted (or, to discontinue efforts to obtain such an approval)

*Note, if in a region evinacumab is not commercially available or available through an early access or compassionate use program, treatment may continue in that region.

Patients who prematurely discontinue from study drug should return to the clinic (within 5 days if possible), for end of treatment visit assessments. A final end of study (EOS) visit should take place with assessments as specified in the EOS visit at 24 weeks after the last dose of study drug.

Follow-up Period:

Patients will be followed for 24 weeks after receiving the last dose of study drug. During this time, pregnancy status of all women of childbearing potential, including those who discontinue prematurely from the study, will be monitored every 4 weeks for 24 weeks post the last dose of study drug either during clinic visits or by phone visit. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a CUP, EAP, or ISS/IST) and thereby may forgo the 24-

	week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's EOT will be their last study visit.
Study Duration	Study duration will vary for each patient in this open-label study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. It will range from months up to approximately 4 years.
End of Study Definition	The end of study is defined as the last visit of the last patient.

Population

Sample Size:	Approximately 120 patients will be enrolled.
Target Population:	The study population will consist of male and female patients ≥12 years of age with HoFH, receiving stable LMT, as applicable. Lipid modifying therapies may include a maximally tolerated statin, ezetimibe, PCSK9 inhibitor and lipoprotein apheresis. Adolescent patients will be enrolled only in participating countries where regulatory approval has been obtained to include adolescents. Countries that have not received regulatory approval to enroll adolescent patients will enroll only patients ≥18 years of age.

Treatment(s)

Study Drug Dose/Route/Schedule:	Starting on day 1 (baseline), patients will receive evinacumab 15 mg/kg IV administered Q4W.
Background Treatment Dose/Route/Schedule:	All patients who were supplied with alirocumab 150 mg SC by the sponsor in a previous study may continue to be provided with alirocumab 150 mg SC Q2W in this study. Those entering this study after completing a study evaluating the safety and efficacy of alirocumab in patients with HoFH, but did not participate in a prior evinacumab study, may or may not remain on alirocumab as part of their background LMT. Based on the patient's preference and the judgment of the investigator and the patient's health care provider, each patient may: • continue treatment with alirocumab supplied by the sponsor as part of their background LMT • discontinue alirocumab prior to enrolling into this study • change to a commercially available PCSK9 inhibitor antibody prior to enrolling into this study Patients receiving background LMT that has been proven to reduce the risk of ASCVD (eg, statins, ezetimibe, PCSK9 inhibitor antibodies) should make their best effort to maintain a stable regimen after week 24 and for the duration of the study. Patients receiving other LMT (eg, apheresis, lomitapide), may have that LMT adjusted after week 24, based on their LDL-C, CV risk factors, and judgment of the investigator.

Endpoint(s)

Primary:	The primary endpoint is the incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables during the open-label treatment period in patients treated with evinacumab 15 mg/kg IV Q4W.
Secondary:	The secondary efficacy endpoints are: • The percent and absolute change in LDL-C over time • The percent and absolute change in Apo B over time

	• The percent and absolute change in non-HDL-C over time • The percent and absolute change in TC over time • The percent and absolute change in TGs over time
Procedures and Assessments	Overall safety will be assessed by monitoring/evaluation of TEAEs, physical examinations, electrocardiograms, and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated. Efficacy will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study.
Statistical Plan	No formal statistical testing will be performed for this open-label study. The safety analysis set (SAF) includes all patients who received at least 1 dose or part of a dose of open-label study treatment in this study. The SAF will be the main analysis set for exposure/compliance, clinical safety and efficacy. All safety analyses summaries will be descriptive in nature and no formal inferential testing will be performed. The percent and absolute change in lipid data (eg, LDL-C, Apo B, TG) will be descriptively summarized by visit. Missing data will not be imputed. For both safety and efficacy analyses, the baseline for each patient is defined as follows: • For patients who participated in a previous evinacumab study, R1500-CL-1629, baseline is defined as the last obtained value before the first dose of double-blind study drug in R1500-CL-1629 • For patients who participated in the previous evinacumab study R1500-CL-1331 or did not participate in any previous evinacumab study, baseline is defined as the last obtained value before the first dose of study drug in R1500-CL-1719. (Note: Baseline for patients who participated in R1500-CL-1331 is defined as the baseline from the R1500-CL-1719 study due to the long time between the last study treatment in R1500-CL-1331 and the first study treatment in R1500-CL-1719.)

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 A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B (protein encoded in humans by the APOB gene)
Apo CIII	Apolipoprotein CIII
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CEC	Clinical Events Committee
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CUP	Compassionate Use Program
CV	Cardiovascular
CVD	Cardiovascular disease
NOD	New onset diabetes
EAP	Early access program
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
Hs-CRP	high sensitivity C-reactive protein
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
HoFH	Homozygous familial hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation

IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ISS	Investigator-Sponsored Study
IST	Investigator-Sponsored Trial
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
MedDRA	Medical Dictionary for Regulatory Activities
Non-HDL-C	Non-high-density lipoprotein cholesterol
OLTP	Open-label treatment period
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
POC	Proof-of-concept
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TC	Total cholesterol
TG	Triglycerides
TSH	Thyroid-stimulating hormone

ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

TABLE OF CONTENTS

AMENDMENT HISTORY 3
CLINICAL STUDY PROTOCOL SYNOPSIS....15
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS....21
1. INTRODUCTION 30
2. STUDY OBJECTIVES 33
2.1. Primary Objectives 33
2.2. Secondary Objectives 33
2.3. Exploratory Objective....33
3. HYPOTHESIS AND RATIONALE 33
3.1. Hypothesis 33
3.2. Rationale 33
3.2.1. Rationale for Study Design....33
3.2.2. Rationale for Dose Selection 35
3.2.3. Risk/Benefit Assessment 35
4. STUDY VARIABLES....38
4.1. Demographic and Baseline Characteristics 38
4.2. Primary and Secondary Endpoints....38
4.3. Pharmacokinetic Variables 38
4.4. Anti-Drug Antibody Variables 38
4.5. Ultrasound Imaging 39
5. STUDY DESIGN 40
5.1. Study Description and Duration 40
5.1.1. End of Study Definition....44
5.2. Planned Interim Analysis....44
5.3. Study Committees....44
5.3.1. Independent Data Monitoring Committee 44
5.3.2. Clinical Events Committee 45
6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS....45
6.1. Number of Patients Planned 45
6.2. Study Population....45
6.2.1. Inclusion Criteria 46

6.2.2. Exclusion Criteria for Evinacumab-Naïve Patients 46
6.2.3. Exclusion Criteria for Patients from a Previous Evinacumab Study 49
6.3. Premature Withdrawal from the Study 50
6.4. Replacement of Patients 51
6.5. Re-screening of Patients 51
7. STUDY TREATMENTS 51
7.1. Investigational and Reference Treatments 51
7.2. Background Treatment(s) 51
7.3. Dose Modification and Study Treatment Discontinuation Rules 52
7.3.1. Dose Modification 52
7.3.2. Study Drug Discontinuation 52
7.3.2.1. Reasons for Permanent Discontinuation of Study Drug 52
7.3.2.2. Reasons for Temporary Discontinuation of Study Drug 52
7.4. Management of Acute Reactions 53
7.4.1. Acute Intravenous Infusion Reactions 53
7.4.1.1. Interruption of the Intravenous Infusion 53
7.4.1.2. Termination of the Intravenous Infusion 53
7.4.2. Acute Injection Reactions 54
7.4.2.1. Systemic Injection Reactions 54
7.4.2.2. Local Injection Site Reactions 54
7.5. Method of Treatment Assignment 54
7.5.1. Blinding 54
7.6. Treatment Logistics and Accountability 54
7.6.1. Packaging, Labeling, and Storage 54
7.6.2. Supply and Disposition of Treatments 54
7.6.3. Treatment Accountability 55
7.6.4. Treatment Compliance 55
7.7. Concomitant Medications and Procedures 55
7.7.1. Permitted Medications and Procedures 55
7.7.2. Prohibited Medications and Procedures 56
8. STUDY SCHEDULE OF EVENTS AND PROCEDURES 56
8.1. Study assessments and procedures are presented by study period and visit in Table 1, Table 2 and Table 3. 57

8.1.1. Footnotes for Schedule of Events Table 1 64
8.1.2. Footnotes for the Schedule of Events Table 2 64
8.1.3. Footnotes for Schedule of Events Table 3 65
8.1.4. Early Termination Visit 67
8.1.5. Unscheduled Visits 67
8.2. Study Procedures 67
8.2.1. Procedures Performed Only at the Screening/Baseline Visit 67
8.2.2. Safety Procedures 68
8.2.2.1. Vital Signs 68
8.2.2.2. Physical Examination 68
8.2.2.3. Electrocardiogram 68
8.2.2.4. Tanner Stages 68
8.2.2.5. Laboratory Testing 68
8.2.2.6. Pregnancy Testing 70
8.2.3. Efficacy Procedures 70
8.2.3.1. Lipid Panel 71
8.2.3.2. Specialty Lipid Panel 71
8.2.4. Drug Concentration and Measurements 71
8.2.5. Anti-Drug Antibody Measurements and Samples 71
8.2.6. Ultrasound Imaging 71
8.2.7. Pharmacodynamic Procedures 71
8.2.8. Future Biomedical Research 72
8.2.9. Other Assessments 72
8.2.9.1. Review of Diet 72
8.2.9.2. DNA Sample for HoFH Genotyping 72
8.2.9.3. Genomics Sub-Study (Optional) 72
9. SAFETY DEFINITIONS, REPORTING, AND MONITORING 73
9.1. Obligations of Investigator 73
9.2. Obligations of Sponsor 73
9.3. Definitions 73
9.3.1. Adverse Event 73
9.3.2. Serious Adverse Event 73
9.3.3. Adverse Events of Special Interest 74

9.3.4. Infusion Reactions 74
9.4. Recording and Reporting Adverse Events 74
9.4.1. Adverse Events 74
9.4.2. Serious Adverse Events 75
9.4.3. Other Events that Require Accelerated Reporting to Sponsor 75
9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study 77
9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results 77
9.4.6. Follow-up 77
9.5. Evaluation of Severity and Causality 77
9.5.1. Evaluation of Severity 77
9.5.2. Evaluation of Causality 78
9.6. Safety Monitoring 81
9.7. Investigator Alert Notification 81
10. STATISTICAL PLAN 82
10.1. Statistical Hypothesis 82
10.2. Justification of Sample Size 82
10.3. Analysis Sets 82
10.3.1. Safety Analysis Set 82
10.3.2. Efficacy Analysis Sets 82
10.3.3. Pharmacokinetic Analysis Sets 82
10.3.4. Anti-Drug Antibody Analysis Sets 82
10.4. Statistical Methods 83
10.4.1. Patient Disposition 83
10.4.2. Demography and Baseline Characteristics 84
10.4.3. Efficacy Analyses 84
10.4.4. Safety Analyses 84
10.4.4.1. Adverse Events 84
10.4.4.2. Other Safety 85
10.4.4.3. Treatment Exposure 86
10.4.4.4. Treatment Compliance 86
10.4.5. Pharmacokinetics 86
10.4.5.1. Analysis of Drug Concentration Data 86
10.4.6. Analysis of Anti-Drug Antibody Data 86

10.5. Additional Statistical Data Handling Conventions 87
10.6. Statistical Considerations Surrounding the Premature Termination of a Study 87
11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS 87
11.1. Data Management 87
11.2. Electronic Systems 87
12. STUDY MONITORING 87
12.1. Monitoring of Study Sites 87
12.2. Source Document Requirements 88
12.3. Case Report Form Requirements 88
13. AUDITS AND INSPECTIONS 88
14. ETHICAL AND REGULATORY CONSIDERATIONS 89
14.1. Good Clinical Practice Statement 89
14.2. Patient Confidentiality and Data Protection 90
14.3. Institutional Review Board/Ethics Committee 91
15. PROTOCOL AMENDMENTS 91
16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE 91
16.1. Premature Termination of the Study 91
16.2. Close-out of a Site 91
17. STUDY DOCUMENTATION 92
17.1. Certification of Accuracy of Data 92
17.2. Retention of Records 92
18. DATA QUALITY ASSURANCE 92
19. CONFIDENTIALITY 93
20. FINANCING AND INSURANCE 93
21. PUBLICATION POLICY 93
22. REFERENCES 94
23. INVESTIGATOR'S AGREEMENT 97
SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS 99

LIST OF TABLES

Table 1: Schedule of Events – Run-In and Screening 57
Table 2: Schedule of Events – Screening for Patients with No Run-In 58

Table 3: Schedule of Events – Open-Label Treatment Period and Follow-Up 60

LIST OF FIGURES

Figure 1: Study Flow Diagram.....44

LIST OF APPENDICES

APPENDIX 1. SUMMARY OF THERAPEUTIC LIFESTYLE CHANGES DIET FOR HIGH CHOLESTEROL 98

1. INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that predisposes a person to premature severe cardiovascular disease (CVD) (Kolansky 2008). Familial hypercholesterolemia can be either an autosomal dominant or an autosomal recessive disease that results from mutations in the low-density lipoprotein receptor (LDLR), or in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9); apolipoprotein B (APOB); and low-density lipoprotein (LDL) receptor adaptor protein 1 (LDLRAP1) with a similar phenotype and varying severity.

Homozygous familial hypercholesterolemia (HoFH) is a rare, serious condition that is frequently caused by loss-of-function mutations in both alleles of the LDL receptor gene, resulting in the decreased clearance of LDL particles from plasma. Patients with HoFH have severe hypercholesterolemia (500-1000 mg/dL), resulting in lifelong exposure to high levels of plasma LDL and increased risk of developing atherosclerosis. Accelerated atherosclerosis results in premature CVD and an increased risk of a cardiovascular event. Although double-blind cardiovascular outcome data in this rare population do not exist, observational studies suggest that lowering low-density lipoprotein cholesterol (LDL-C) with statin therapy may reduce the risk of coronary heart disease by 50% to 80% in patients with familial hypercholesterolemia (Harada-Shiba 2010) (Huijgen 2010) (Vermissen 2008) (Neil 2008). The goal of drug therapy in adult patients with FH is to achieve LDL-C reduction ≥50% (Goldberg 2011); however, management of elevated LDL-C in patients with HoFH is challenging with the current existing treatment options. Because patients with HoFH have impaired or deficient LDL-receptor function, they tend to be refractory to statins because the mechanism of action generally lowers LDL-C levels through up-regulation of the hepatic LDL receptor.

Statins can reduce LDL-C by more than 50% in other hypercholesterolemic patients, in HoFH patients; however, statins may provide a decrease of <15 to 30% (Crestor 2003) (Lipitor 1996) (Zocor 1991). When ezetimibe is added to a statin, LDL-C may be reduced by 21 to 27% (Zetia 2002), but many patients with HoFH treated with a high dose statin and ezetimibe remain far from their target LDL-C. Despite the near total loss of functional LDL receptors in HoFH patients, statins are still used as first line therapy in order to maximize residual receptor activity (Raal 2000) (Marais 2008) (Raal 1997).

Mipomersen and lomitapide have been approved in some countries for use in patients with HoFH, and provide an additional ~25% and 40% reduction in LDL-C, respectively, when used along with other lipid-modifying therapies (LMT). However, these new therapies are not commercially available in all countries, and are associated with increases in hepatic fat content and liver function tests, and frequent injection site reactions (mipomersen) or gastrointestinal side effects (lomitapide) that can impact tolerability (Raal 2010, Cuchel 2013).

While PCSK9 inhibitor antibody therapy may provide modest efficacy in the treatment of many patients with HoFH patients with hypercholesterolemia, it appears to be minimally effective in patients with impaired LDL-receptor activity, particularly those patients with null mutations in both LDLR alleles (Raal 2014).

In the recent TESLA study comparing evolocumab on top of statins (with or without ezetimibe) in patients with HoFH, the mean percent reduction in LDL-C at week 12 was 23.1% (Raal 2014).

Evolocumab therapy did not reduce LDL-C in patients with LDL receptor-negative mutations in both alleles (Raal 2014) (Repatha 2015).

High-dose statins, ezetimibe, PCSK9 inhibitor antibodies, mipomersen, and lomitapide may be effective in some patients with HoFH, but many patients still require lipid apheresis. Lipid apheresis can be effective, but entails weekly or bi-weekly treatments, lasting several hours, is both costly and associated with a risk of infections (Vella 2001) (Kajinami 1999), and is not routinely available (Thompson 2010). Despite treatment with lipid-modifying therapies such as pharmacological agents, as well as mechanical removal by lipid apheresis, many patients with HoFH remain far from their LDL-C treatment goal. Therefore, the need for more intensive treatment in HoFH, especially those patients with double null mutations, remains.

Angiopoietin-like 3 (ANGPTL3) has recently emerged as a potential target for the treatment of elevated levels of triglycerides (TG), and for the treatment of elevated levels of LDL-C, both factors in the development of CVD. Angiopoietin-like 3 (ANGPTL3) acts as a natural inhibitor of lipoprotein lipase (LPL), an endothelial-bound enzyme involved in the hydrolysis of the TG content of very-low-density lipoproteins (VLDL) and chylomicron lipoproteins. Patients who are homozygous for loss-of-function (LOF) mutations in ANGPTL3 have lower levels of LDL-C (mean difference of 48% versus control family members). The mechanism by which ANGPTL3 LOF mutations result in lowered LDL-C levels is not fully understood, but appears to be independent of the effects on TGs. It is noteworthy that patients with 1 or 2 ANGPTL3 LOF alleles also have reported reductions in serum high-density lipoprotein cholesterol (HDL-C) levels. The mechanism for this may be linked to the inhibitory effect of ANGPTL3 on endothelial lipase (EL), which is involved in the hydrolysis of HDL phospholipids. Importantly, no health deficits have been reported in the (relatively small number of) patients who are homozygous for ANGPTL3 LOF mutations. These data suggest that inhibiting ANGPTL3 may be a meaningful and well-tolerated strategy for lowering serum LDL C and TGs.

Evinacumab (REGN1500) is a fully human monoclonal antibody (mAb), created with Regeneron's VelocImmune technology platform, which specifically binds to ANGPTL3.

Evinacumab (REGN1500) is a fully human monoclonal antibody, created with Regeneron's VelocImmune® technology platform, which specifically binds to ANGPTL3 and prevents its inhibition of lipoprotein lipase, thereby increasing hydrolysis of TG. Experiments performed in animals demonstrate that the administration of evinacumab results in a reduction of serum LDL C and serum TGs. In an open-label, single-arm, proof-of-concept (POC) study in patients with genetically-defined HoFH (Study R1500-CL-1331), treatment with evinacumab in 9 patients resulted in a mean percent reduction of LDL-C from baseline of 49.2% at week 4 (the primary endpoint). A peak mean reduction of 52.1% was observed at week 6. Three patients enrolled in Study R1500 CL 1331 are homozygous for null mutations in the LDL-R. Evinacumab provided 37.3% (range: 26-44%) reductions in LDL-C at week 4 in these 3 null/null HoFH patients. Evinacumab in this POC study has been well tolerated.

The LDL-C lowering effect observed with evinacumab in R1500-CL-1331 was confirmed in R1500-CL-1629, the pivotal study evaluating evinacumab in patients with HoFH, and the parent study from which most patients continued into this current study, R1500-CL-1719. R1500-CL-1629 was a randomized, double-blind, placebo-controlled study which enrolled adult and adolescent patients with HoFH. The 24-week double-blind treatment period has completed, and the results are briefly described here. 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 placebo (47% reduction for evinacumab compared to a 2% increase for placebo, $p<0.0001$). This reduction corresponds 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 significantly 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 were no AEs leading to death or discontinuation of study treatment. Two patients (4.5%), both in the evinacumab treatment group, experienced 1 serious TEAE (SAE) each (urosepsis and suicide attempt); neither of the events were considered related to therapy or led to discontinuation of study treatment and both were reported to be recovered/resolved. Treatment with evinacumab was not associated with any safety concerns related to hepatic TEAEs or laboratory parameters, muscle events or CK elevations, pancreatitis, neurocognitive events, neurologic events, cataracts, new onset diabetes (NOD), diabetic complications, or immune complex diseases. A review of safety labs, vital signs, and ECG did not reveal any significant differences between evinacumab treatment and placebo.

This study was designed to evaluate the long-term safety and tolerability of evinacumab in participants with HoFH who are either evinacumab naïve, or have participated in other evinacumab studies (ie, R1500-CL-1331, R1500-CL-1629). All participants received evinacumab at a dose of 15 mg/kg IV every 4 weeks (Q4W).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg intravenously (IV) administered every 4 weeks (Q4W) in patients with HoFH.
- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg IV administered Q4W in adolescent patients with HoFH

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, LDL-C, Apo B, non-HDL-C, total cholesterol [TC], and TG) in patients with HoFH
- To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, LDL-C, Apo B, non-HDL-C, TC, and TG) in adolescent patients with HoFH
- To evaluate the potential development of anti-evinacumab antibodies

2.3. Exploratory Objective

An exploratory objective of this study is to explore vascular changes using imaging techniques.

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Blockade of ANGPTL3 with evinacumab will reduce or maintain consistent long-term reduction in LDL-C and demonstrate an acceptable safety profile in patients with HoFH.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is being conducted in patients with HoFH, which may include patients who have participated in a previous evinacumab study (eg, R1500-CL-1331, R1500-CL-1629) and also evinacumab-naïve patients with HoFH. The study is intended to provide long-term safety, efficacy and pharmacokinetics (PK) information on evinacumab treatment of adult and adolescent patients with HoFH. The study population will include individuals ≥12 years of age. Because this disease is characterized by severe hypercholesterolemia from birth and, subsequently, the onset of premature CVD during childhood, the HoFH population includes children and adolescents. Allowing individuals ≥12 years of age to enroll in this study will ensure the study population is reflective of the patient population manifesting disease in adolescence and adulthood.

Considering the severity of this disease, evinacumab will be added on top of the patient's background LMT, including statins, ezetimibe, and PCSK9 inhibitors. Patients receiving background LMT that has been proven to reduce the risk of ASCVD (eg, statins, ezetimibe, PCSK9 inhibitor antibodies) should make their best effort to maintain a stable regimen for the entire duration of the study. This guidance is provided so that patients will be able to receive maximal benefit from the treatment. Patients receiving other LMT (eg, apheresis, lomitapide) may have that LMT adjusted after week 24, based on their LDL-C, CV risk factors, and the judgment of the investigator.

This study employs a single-arm, open-label design, which is appropriate since the primary objective of this study is long-term safety and tolerability. A run-in period is included to ensure all patients entering this study are on a stable background LMT regimen. This is important because a stable background LMT regimen will ensure a stable LDL-C at the onset of the study, which is necessary to adequately assess the secondary objective of efficacy, particularly for the evinacumab-naïve patients entering this study.

The study population will include patients with HoFH, diagnosed by either clinical criteria or genotyping. Patients entering this study from another evinacumab trial will not have to fulfill an LDL-C entry criterion. No criterion is applied to this population because most of the patients had to fulfill an LDL-C entry criterion of ≥70 mg/dL prior to entering the previous evinacumab study in which they participated. These patients are transitioning into this study with the goal of maintaining their LMT regimen (including evinacumab) and thus maintaining their LDL-C. This stability allows for the evaluation of the long-term safety and efficacy of evinacumab in patients with HoFH.

Patients who are evinacumab-naïve will have to fulfill an LDL-C criterion of ≥70 mg/dL at screening. This threshold is the target LDL-C recommended in the different treatment guidelines for patients at very high risk for ASCVD, which includes patients with HoFH (Grundy, 2018) (Catapano, 2016).

Another consideration for the LDL-C entry criterion in this study is that for this severe patient population that falls at the very extreme end of the spectrum of patients with hypercholesterolemia, LDL-C levels should be managed so that they are as low as possible. As mentioned above, patients with HoFH have severe hypercholesterolemia (≥500 mg/dL). Plasma levels of LDL-C are elevated from birth, with reports of elevations greater than 4-fold in infants with HoFH. The resulting lifelong exposure to high levels of plasma LDL-C leads to a significantly increased risk of developing atherosclerosis. This accelerated atherosclerosis results in premature CVD and an increased risk for cardiovascular events. To manage these long-term sequelae of extremely elevated levels of LDL-C, patients with HoFH need to achieve the lowest possible LDL-C for as long as possible (Gidding 2015).

Although double-blind cardiovascular outcome data in this rare population do not exist, observational studies suggest that lowering LDL-C with statin therapy may reduce the risk of coronary heart disease by 50% to 80% in patients with FH (Harada-Shiba 2010) (Huijgen 2010) (Vermissen 2008) (Neil 2008). Additionally, recent outcomes data with ezetimibe, evolocumab, and alirocumab for the primary or secondary prevention of CVD in high risk patients with hypercholesterolemia have further demonstrated that, similar to statins, other lipid lowering agents can also significantly reduce the risk of CHD. The LDL-C levels achieved in these recent outcomes studies ranged from a median of 30 mg/dL in the evolocumab outcomes study

(FOURIER) (Sabatine 2017) to approximately 50 mg/dL in the studies with ezetimibe (IMPROVE-IT) (Cannon 2015) and alirocumab (ODYSSEY OUTCOMES) (Steg 2018). Importantly, these LDL-C levels were associated with a 7 to 15% reduction in cardiovascular events (Cannon 2015, Sabatine 2017, Steg 2018). When these data are positioned within the context of this study, it provides additional evidence for the LDL-C entry criteria outlined.

3.2.2. Rationale for Dose Selection

The evinacumab 15 mg/kg IV Q4W dose regimen to be studied in this study is the dose regimen evaluated in the pivotal phase 3, double-blind, placebo-controlled study in patients with HoFH (R1500-CL-1629). It was selected based on safety in the phase 1 and phase 2 studies and the substantial LDL-C reduction observed with that dose in HoFH patients in study R1500-CL-1331. The 15 mg/kg IV Q4W dose regimen will continue to be evaluated in this study to obtain long-term safety, additional efficacy, and PK information, with the intended dose for registration in patients with HoFH.

The higher dose regimen of 20 mg/kg IV Q4W demonstrated favorable tolerability when given as an 8-week treatment in otherwise healthy subjects (R1500-CL-1321). Long-term administration of evinacumab at the 15 mg/kg IV Q4W regimen is expected to also demonstrate favorable tolerability because the evinacumab exposure within each dosing interval is expected to be lower than 20 mg/kg IV and the accumulation of serum concentration with a monthly dosing frequency is predicted to be minimal. From an efficacy perspective, the 15 mg/kg IV dose resulted in evinacumab concentrations above 100 mg/L for approximately 4 weeks, an exposure threshold associated with target saturation and maximal effect on TG reduction (R1500-CL-1321 and R1500-HV-1214). Based on these PK/pharmacodynamics (PD) data, combined with the efficacy data from the POC study in HoFH (R1500-CL-1331), 15 mg/kg IV is expected to maintain target saturation and thereby, provide maximal benefit during the monthly dosing interval.

Pharmacokinetics information is not available from patients aged 12 to 17 years. Evinacumab systemic elimination features a combination of linear clearance and non-linear, target-driven clearance. The linear clearance for monoclonal antibodies is often similar between adults and adolescents after adjusting for body-weight. The comparison of nonlinear clearance between adolescents and adults is not known. However, at 15 mg/kg IV, the contribution of target-mediated clearance is likely to be low since target saturation appeared to be present. Therefore, evinacumab clearance in adolescents is likely to be similar to adults and the same dose as the adult dose is expected to yield evinacumab exposure in the range associated with observed efficacy and tolerability in adults. In the event that PK information from adolescent patients becomes available while this study is ongoing, and data suggest meaningful differences in PK/PD between adolescents and adults, an amendment to the protocol will be considered to modify the dose of study drug for adolescent patients.

3.2.3. Risk/Benefit Assessment

As mentioned above, patients with HoFH have a lifetime burden of extremely high LDL-C levels. These life-long exposures to profound hypercholesterolemia is directly responsible for vascular endothelial damage and accelerated atherosclerosis, greatly increasing the risk for premature coronary artery disease (CAD), peripheral artery disease, and valvular disease,

especially aortic stenosis. The deposition of cholesterol in vascular and extravascular compartments, such as tendons and skin, results in xanthomas and the deposition of lipid in the cornea of the eyes causes corneal arcus and an increase in intraocular pressure. If left untreated, most patients with HoFH develop atherosclerosis before the age of 20 years, and generally do not survive past the third decade of life (Ito 2015, Cuchel 2014).

The goal of therapy in these patients is to slow the progression of atherosclerosis with the aim of reducing CV events and mortality. Patients with HoFH should be provided aggressive interventions to achieve these goals. Despite the approval of newer treatments, including evolocumab, lomitapide, and mipomersen, the need for more intensive therapies remains. Evinacumab could be a new addition to the armamentarium of LMT that could contribute to lowering the LDL-C in patients with HoFH.

The ACC/AHA and the EAS guidelines for FH both recommend an initial goal of at least a 50% reduction in LDL-C in patients with FH to reduce the risk of CVD (Gidding 2015, Cuchel 2014). The EAS Consensus Panel recommends that lipid-lowering therapies should be started as early as possible in patients with HoFH. This is based on evidence that initiation of treatment early can delay the onset of clinically evident ASCVD. If the 50% reduction in LDL-C is achieved, the ACC/AHA and EAS additionally recommends further LDL-C lowering to achieve LDL-C levels of <100 mg/dL (<2.5 mmol/L) in the absence of CAD or other major risk factors or <70 mg/dL (<1.8 mmol/L) in the presence of ASCVD or other major risk factor (Gidding 2015, Cuchel 2014). A limitation to both sets of recommendations is that they are based on clinical trials of patients without FH because of the lack of true long-term outcome studies in patients with FH. Indeed, due to the long-term sequelae of extremely elevated levels of LDL-C described above, at a minimum patients with HoFH need to achieve the goals described in the guidelines, but would benefit from more aggressive treatments to achieve the lowest LDL-C possible for as long as possible (Gidding 2015).

Historically, these LDL-C targets have been challenging to achieve with the available treatment options, in part because the mutations observed in this patient population renders major classes of lipid lowering treatments as either ineffective or less efficacious. However, with additional, newer classes of pharmacotherapy, achieving these goals and even lowering LDL-C beyond these goals is slowly becoming a reality. Moreover, results of several recent outcomes trials suggest that achieving lower LDL-C levels than the current recommended target levels may provide additional CV benefit. The LDL-C levels achieved in the outcomes studies with ezetimibe, evolocumab, and alirocumab ranged from a median of 30 mg/dL in the evolocumab outcomes study (FOURIER) (Sabatine 2017) to approximately 50 mg/dL in the studies with ezetimibe (IMPROVE-IT) (Cannon 2015) and alirocumab (ODYSSEY OUTCOMES) (Steg 2018). These LDL-C levels were associated with a 7-15% reduction in cardiovascular events (Cannon 2015, Sabatine 2017, Steg 2018). Additionally, the LDL-C levels in all 3 studies were also associated with an acceptable safety profile.

Considering the growing evidence for aggressively treating LDL-C, even in the setting of what some might consider patients with HoFH that might be at their “goal” LDL-C (ie, 70 mg/dL), the benefits of adding evinacumab and potentially lowering the LDL-C even further become apparent. For patients entering this study from another evinacumab trial there is no LDL-C entry criterion as these patients would have been treated with evinacumab for at least 24 weeks prior to entering this study and would have achieved their maximal lipid lowering effect.

Preliminary data from the proof-of-concept study in patients with HoFH demonstrate the efficacy of evinacumab in this patient population, even in the most difficult-to-treat patients with null/null mutations in the LDLR gene. Recent data from study R1500-CL-1629 in adult and adolescent patients with HoFH demonstrated that adding evinacumab to other lipid-lowering therapies decreased LDL-C by a mean of 49% from baseline to week 24. This efficacy data was accompanied by an acceptable safety profile. 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). The accumulated safety information from the completed and ongoing clinical studies had identified the risk of systemic hypersensitivity reactions (including anaphylaxis and infusion reactions). The important potential risks (based on preclinical evaluation or risks associated with monoclonal antibodies in general) include embryofetal toxicity and immunogenicity. These risks will be managed through careful patient selection, routine monitoring, and complete disclosure of safety information.

Patients entering this study should be on a stable background LMT, which may or may not include a statin, ezetimibe, and a PCSK9 inhibitor. There are 2 PCSK9 inhibitors that are commercially available in many countries; evolocumab is approved for use in patients with HoFH in most countries, and alirocumab is currently being evaluated in a phase 3 double-blind placebo-controlled study in patients with HoFH (study R727-CL-1628, ODYSSEY HoFH). Patients entering this study may be taking either evolocumab or alirocumab. Patients who complete study R727-CL-1628 (ODYSSEY HoFH) with alirocumab are permitted to participate in this study and may continue to receive alirocumab as part of their background LMT.

Evinacumab and PCSK9 inhibitors, including alirocumab have different mechanisms of action and concomitant administration of both agents is not expected to perturb the action of the other. Rather, their distinct mechanisms of action are anticipated to complement each other to lower LDL-C since they work at different sites of action. Additionally, the safety profile of each agent is considered acceptable and the concurrent use of the 2 agents together is not expected to augment or exacerbate potential AEs. From the perspective of PK drug-drug interactions, co-administration of evinacumab with a PCSK9 inhibitor and the other possible background LMT (statin, ezetimibe, etc) is not expected to result in drug-drug interactions with each other or other drugs. Therefore, the concurrent use of evinacumab with PCSK9 inhibitors, including alirocumab is considered to have an acceptable benefit/risk profile.

The safety of the use of evinacumab alone or concomitantly with alirocumab will be carefully monitored in this study. Safety monitoring will include ongoing reviews by an Independent Data Monitoring Committee (IDMC) and by the sponsor's safety monitoring team and clinical study team. If significant safety trends or findings are identified by either the IDMC or the sponsor, they will be escalated and appropriately evaluated to understand the best course of action.

Taken together, the benefit/risk profile for the treatment with evinacumab in patients with HoFH is considered to be favorable and additional reduction in LDL-C may translate into significant clinical benefit.

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then,

the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical and surgical history, medication history, and apheresis schedule (if applicable), alcohol and smoking habits for each patient. In addition, baseline characteristics will include Tanner staging for adolescent patients.

4.2. Primary and Secondary Endpoints

The primary endpoint is the incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables during the open-label treatment period in patients treated with evinacumab 15 mg/kg IV Q4W.

The definition of the baseline value for computation of the change from baseline can be found in Section 10.4.3.

The secondary efficacy endpoints are:

- The percent and absolute change in LDL-C over time
- The percent and absolute change in Apo B over time
- The percent and absolute change in non-HDL-C over time
- The percent and absolute change in TC over time
- The percent and absolute change in TGs over time

4.3. Pharmacokinetic Variables

The PK variable is C_{trough} collected at specified time points.

4.4. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include status (positive or negative) and titer as follows:

- Treatment emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative or missing.
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold or greater over baseline titer levels when baseline is positive in the ADA assay

The definition of persistent and transient ADA will be defined a priori in the SAP.

- Titer values
- Titer category, by patient's maximal titer value
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- Neutralizing ADA for samples that are positive in the ADA assay

4.5. Ultrasound Imaging

Carotid intima-media thickness (cIMT in mm) for adolescent patients will be determined at sites with this capability. An assessment should be made at run-in/screening or as soon as possible thereafter, then at week 24 and 1 year followed at yearly intervals.

5. STUDY DESIGN

5.1. Study Description and Duration

This is an open-label study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH.

Eligible patients for this study are male and female patients with HoFH, receiving LMT, as applicable. Lipid modifying therapies may include maximally tolerated statin, ezetimibe, PCSK9 inhibitor antibody, or other lipid lowering therapies, including lipoprotein apheresis. Patients may include those who have participated in a previous evinacumab study (eg, R1500-CL-1331 and R1500-CL-1629) and evinacumab-naïve patients with HoFH.

This study consists of a run-in period (for patients who may require HoFH genotyping, patients whose background medical LMT has not been stable prior to screening, or those whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a screening period, an open-label treatment period and a follow-up period. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a compassionate use program [CUP], early access program [EAP], or investigator sponsored study [ISS/IST]) and thereby may forgo the 24-week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's end-of-treatment visit (EOT) will be their last study visit.

Run-in Period:

Apheresis therapy - Patients who are undergoing apheresis therapy must have initiated lipoprotein apheresis at least 3 months prior to screening and must receive stable weekly apheresis (every 7 ±1 days), or other stable regimen (±2 days) and/or stable settings for at least 8 weeks prior to screening. Patients whose schedule and/or apheresis settings have not been stable for at least 8 weeks before the baseline (day 1) visit, will enter an up to 10-week run-in period before screening. After the run-in period, patients whose lipoprotein apheresis schedule remains stable will be eligible to enter the 2-week screening period.

Lipid modifying therapy - Patients who are on background LMT that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibody, 12 weeks on maximum tolerated dose of lomitapide) before the baseline (day 1) visit will enter a run-in period 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 may enter the run-in period to determine their mutation status.

Screening Period:

Patients who are required to enter a 2-week screening period:

- Evinacumab treatment-naïve patients.
- Patients from a previous evinacumab study who do not enter this study within 7 days of completing the end of study (EOS) visit of the previous study.

Open-Label Treatment Period:

Patients who completed the EOS visit in the previous evinacumab study within 7 days of the baseline/day 1 visit for this open label study do not have to undergo the screening visit and may enroll directly into this study if they fulfill all of the inclusion criteria and none of the exclusion criteria.

The EOS visit from the previous study can serve as the baseline/day 1 visit for this open-label study and overlapping assessments do not need to be repeated in this study. Baseline assessments and procedures that do not overlap with assessments at the EOS visit of the previous study should be performed after all EOS assessments and procedures have been completed in the previous evinacumab study.

Starting on day 1 (baseline), patients will receive evinacumab 15 mg/kg IV administered Q4W (±7 days) at the study site. Patients will remain in the clinic for monitoring for 60 minutes after the end of each IV infusion. For patients unable to go to the site, evinacumab may be administered at an alternative location, which could include the patient's home by a trained nurse or other health professional, as allowed by local laws.

All patients who were supplied with alirocumab 150 mg subcutaneous (SC) by the sponsor in a previous study may continue to be provided with alirocumab 150 mg SC every 2 weeks (Q2W) in this study. Those entering this study, after completing a study evaluating the safety and efficacy of alirocumab in patients with HoFH, but did not participate in a prior evinacumab study, may or may not remain on alirocumab as part of their background LMT.

Based on the patient's preference and the judgment of the investigator and the patient's health care provider, each patient may:

- continue treatment with alirocumab supplied by the sponsor as part of their background LMT
- discontinue alirocumab prior to enrolling
- change to a commercially available PCSK9 inhibitor antibody prior to enrolling into this study

Clinical laboratory samples must be collected and study assessments must be performed before study drug is administered.

Patients who are undergoing apheresis or plasma exchange must have their clinical laboratory samples drawn and study assessments performed before undergoing the procedure. Every effort should be made for the patient to receive study drug immediately after completion of the apheresis procedure, but patients can receive study drug 1 day before the apheresis procedure. Patients undergoing plasma exchange should receive the study drug immediately after completing the procedure.-Given the impact of lipoprotein apheresis, PCSK9 inhibitors, and mipomersen on lipid parameters, it is important to match the time of the baseline activities with the timing of the week 24 activities. This would mean that the timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen should match the timing of the week 24 sample collection relative to the most recently completed apheresis procedure, administration of a PCSK9 inhibitor or mipomersen.

Patients receiving background LMT that has been proven to reduce the risk of ASCVD (eg, statins, ezetimibe, PCSK9 inhibitor antibodies) should make their best effort to maintain a stable regimen after week 24 and for the duration of the study.

Patients receiving other LMT (eg, apheresis, lomitapide) may have that LMT adjusted after week 24, based on their LDL-C levels, CV risk factors, and judgment of the investigator.

Patients should be on a stable heart healthy diet and exercise regimen throughout the duration of the study, starting at the baseline visit and continuing through the end of the open-label treatment period.

Treatment will continue until 1 of the following occurs:

- Clinical development of evinacumab for the indication described in this study protocol is discontinued
- Clinical development of evinacumab is terminated
- Risk/benefit of evinacumab in this patient population is deemed unfavorable
- Evinacumab is approved by the regulatory authority governing the location of the study site*
- For local discontinuation of study: a decision has been made not to seek approval of an indication for treatment of patients with HoFH in the regulatory region in which the study is being conducted (or, to discontinue efforts to obtain such an approval)

*Note, if in a region evinacumab is not commercially available or available through an early access or compassionate use program, treatment may continue in that region.

Overall safety will be assessed by monitoring/evaluation of treatment emergent adverse events (TEAEs), physical examinations, electrocardiograms (ECG), 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 study end date should be followed until resolution, stabilization, or collection of outcome and related data.

Efficacy will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study.

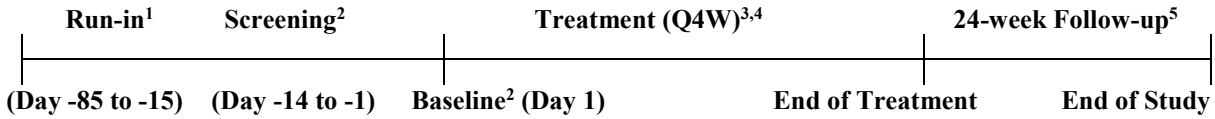
Patients who prematurely discontinue from study drug should return to the clinic (within 5 days if possible), for end of treatment visit assessments. A final EOS visit should take place with assessments as specified in the EOS visit at 24 weeks after the last dose of study drug.

Follow-up Period:

Patients will be followed for 24 weeks after receiving the last dose of study drug. During this time, pregnancy status of all women of childbearing potential (WOCBP), including those who discontinue prematurely from the study will be monitored every 4 weeks for 24 weeks post the last dose of study drug either during clinic visits or by phone visit. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a CUP, EAP, or ISS/IST) and thereby may forgo the 24-week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's EOT will be their last study visit.

A study flow diagram is in Figure 1

Figure 1: Study Flow Diagram



1. Patients who may require HoFH genotyping and patients whose background LMT/apheresis settings and/or schedule has not been stable prior to baseline (day 1) will enter an up to 10-week run-in period.
2. All patients who are on a stable background LMT will enter a 2-week screening period except for those from a previous evinacumab study who completed an end of study visit within 7 days prior to the baseline/day 1 visit for this open-label study.
3. Patients who completed an end of study visit in a previous evinacumab study within 7 days of the baseline/day 1 visit for this open-label study do not have to undergo the screening visit and may enroll directly into this study. The EOS visit from the previous study can serve as the baseline/day 1 visit for this open-label study and overlapping assessments do not need to be repeated in this study. Only those assessments and procedures not done in the previous study must be conducted at the baseline visit. These specific assessments to be administered to all patients are identified in the Schedule of Events, Table 3.
4. Starting on day 1 (baseline), patients will receive evinacumab 15 mg/kg IV administered Q4W.
5. Patients will be followed for 24 weeks after receiving the last dose of study drug. Patients who enter a CUP, EAP, or ISS/IST may forgo the 24-week follow-up period after the last dose. For these patients, the EOT visit will be their last visit.

5.1.1. End of Study Definition

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

5.2. Planned Interim Analysis

In order to provide information from this study, data may be analyzed on an ongoing basis. The results will not be used to change the conduct of the ongoing study in any aspect.

Additionally, an interim analysis is planned for the subpopulation of adolescent patients. This planned interim analysis will be conducted as soon as all adolescent patients have been enrolled and all their data through week 24 have been collected and validated. For adolescent patients, the analysis will consist of the final analysis of the primary (safety) and secondary (lipids) endpoints collected during the initial 24 weeks of study treatment exposure. The safety and lipids analyses will be performed on all data collected and validated at the time of this adolescent subpopulation interim analysis.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An 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.

5.3.2. Clinical Events Committee

The Clinical Events Committee (CEC) is composed of experts in the field of CVD, independent of the sponsor and the investigators. This committee will be responsible for defining, validating, and classifying (in a blinded fashion) pre-specified cardiovascular (CV) events and all deaths.

Patients with suspected or confirmed CV events that occur from study entry until the end of the study will have a corresponding adjudication package prepared and submitted to the CEC. The events should also be reported as SAEs, as appropriate. Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories include:

- Coronary heart disease death
- Nonfatal myocardial infarction
- Fatal and nonfatal ischemic stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization

In addition, other deaths (besides coronary heart disease deaths) will be classified by the CEC. All coronary revascularizations (percutaneous coronary intervention, coronary artery bypass graft surgery) will be submitted to the CEC and analyzed.

A charter and an adjudication operational manual will specify additional details regarding the procedures, criteria, and classification used for adjudication of these events.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

This is an open-label study that will enroll patients with HoFH, including both those who may have participated in a previous evinacumab study (R1500-CL-1331 or R1500-CL-1629) and also evinacumab-naïve patients with HoFH. Approximately 120 patients will be enrolled.

6.2. Study Population

The study population will consist of male and female patients ≥12 years of age with HoFH receiving stable LMT, as applicable. Lipid modifying therapies may include maximally tolerated daily statin, ezetimibe, PCSK9 inhibitor antibody or other lipid lowering therapies, including lipoprotein apheresis. This includes patients with HoFH who participated in other evinacumab studies (eg, R1500-CL-1331, R1500-CL-1629) or evinacumab-naïve patients. Adolescent patients will be enrolled only in participating countries where regulatory approval has been obtained to include adolescents. Countries that have not received regulatory approval to enroll adolescent patients will enroll only patients ≥18 years of age.

HoFH is defined by having at least one of the following (either genetic or clinical criteria):

Genetic Criteria:

1. 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

OR

2. Documented homozygous or compound heterozygous mutations in Apo B or PCSK9
   - Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible

Clinical Criteria:

Untreated TC >500 mg/dL (12.93 mmol/L) and TGs <300 mg/dL (3.39 mmol/L)

AND

both parents with documented TC >250 mg/dL (6.47 mmol/L) OR cutaneous or tendinous xanthoma before the age of 10 years

6.2.1. Inclusion Criteria

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

1. Male and female patients ≥12 years of age with HoFH. Patients aged ≥12 years old will be enrolled only in countries where permitted by the Regulatory Agency and Institutional Review Board (IRB) or Ethics Committee (EC).
2. Diagnosis of functional HoFH by at least 1 of the following genetic or clinical 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. Presence of homozygous or compound heterozygous mutations in Apo B or PCSK9

      Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible

   c. Untreated TC >500 mg/dL (12.93 mmol/L) and TG <300 mg/dL (3.39 mmol/L)

      AND

      both parents with documented TC >250 mg/dL (6.47 mmol)

      OR cutaneous or tendinous xanthoma before the age of 10 years
3. For patients who have participated in a previous evinacumab or alirocumab study: completion of the study in which they participated.
4. Willing and able to comply with clinic visits and study-related procedures.
5. Provide signed informed consent.

6.2.2. Exclusion Criteria for Evinacumab-Naïve Patients

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

1. Concomitant medications and procedures that have not been stable prior to the baseline visit (see Section 7.7.2 for medications and procedures and their associated required duration of therapy).
2. Any new condition or worsening of an existing condition, which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
3. History of a MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the baseline visit.
4. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins.

   Note: patients on thyroid replacement therapy can be included if the dosage of replacement therapy has been stable for at least 12 weeks prior to screening and the thyroid stimulating hormone (TSH) level is within the normal range of the central laboratory at the screening visit.
5. Newly diagnosed (within 3 months prior to screening visit diabetes mellitus or poorly controlled (HbA1c >9%) diabetes.
6. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to screening visit.

   Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as ‘systemic’ and are allowed.
7. Use of estrogen or testosterone therapy unless the regimen has been stable 6 weeks prior to the screening visit and no plans to change the regimen during the study.
8. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit.
9. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.
10. History of New York Heart Association (NYHA) Class IV heart failure within 12 months before screening.
11. Laboratory findings during the screening period (applies to patients undergoing Screening):
    - 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)
    - Positive serum beta-human chorionic gonadotropin or urine pregnancy test in WOCBP

- TSH >1.5 x ULN of the central laboratory (1 repeat lab is allowed) for patients not on thyroid replacement therapy
- Positive test for hepatitis B surface antigen and/or hepatitis C antibody (associated with a positive HCV RNA polymerase chain reaction)
- eGFR <30 mL/min/1.73 m2 (calculated by central lab)
- Postmenopausal status will be confirmed by measurement of follicle-stimulating hormone (FSH)

12. Member of the clinical site study team and/or his/her immediate family.
13. Pregnant or breastfeeding women.
14. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 24 weeks after the last dose of study drug. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner
    e. and/or sexual abstinence†, ‡

*Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy, and/or oophorectomy.

Oocyte donation is prohibited during the study and for 24 weeks after the last administration of study drug.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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 amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

15. Men who are sexually active with WOCBP and are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last injection of study drug: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for up to 24 weeks after the last injection of study drug.
16. LDL-C level <70 mg/dL at the screening visit.
17. Use of any active investigational drugs (except alirocumab) within 1 month or 5 half-lives prior to the screening visit, whichever is longer.

18. Age <12 years at the screening visit.
19. Tanner stage <2 at the screening visit.

6.2.3. Exclusion Criteria for Patients from a Previous Evinacumab Study

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

1. Significant protocol deviation in the previous study based on the investigator's judgment, such as non-compliance by the patient.
2. Concomitant medications and procedures that have not been stable prior to the baseline visit (see Section 7.7.2 for medications and procedures and their associated required duration of therapy).
3. Adverse event leading to permanent discontinuation from previous study.
4. Any new condition or worsening of an existing condition, which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
5. Member of the clinical site study team and/or his/her immediate family.
6. Pregnant or breastfeeding women.
7. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 24 weeks after the last dose of study drug. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner
    e. and/or sexual abstinence†, ‡

*Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy, and/or oophorectomy.

Oocyte donation is prohibited during the study and for 24 weeks after the last administration of study drug.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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 amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

8. Men who are sexually active with WOCBP and are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last injection of study drug: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for up to 24 weeks after the last injection of study drug.
9. Age <12 years at the screening visit.
10. Tanner stage <2 at the screening visit.

6.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.4.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

Early Termination from the Study

Patients who prematurely discontinue from study drug or the study should return to the clinic (within 5 days if possible), for end of treatment visit assessments. The assessments completed should include pregnancy testing for WOCBP. They should then return for all regularly scheduled study visits and complete all assessments except dosing of study drug.

If a patient is discontinuing the study and will not be able to return for all regularly scheduled study visits, at a minimum, they should return for end of study assessments at least 24 weeks after their last dose of study drug. All sexually active males and WOCBP should be reminded to continue to maintain highly effective contraceptive measures for 24 weeks after the last dose of study drug. At the end of treatment/early termination visit, all WOCBP will be provided with urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. Patients will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

The investigator should make the best effort to contact any patient (eg, contacting the patient's family or private physician, review available registries or health care database) who fails to return to the site, and to determine health status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). The site will be provided a retention manual outlining the best practices for patient retention.

6.4. Replacement of Patients

Patients prematurely discontinued from the study drug will not be replaced.

6.5. Re-screening of Patients

Patients who do not meet eligibility criteria during the initial screening may re-screen only once. Patients who are re-screened 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 once for the assessments that did not meet eligibility criteria.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Eligible patients will receive open-label evinacumab at a dose of 15 mg/kg IV Q4W starting on day 1. Patients will be monitored for at least 60 minutes after the end of each IV infusion, and vital signs will be obtained pre-dose and 30 minutes and 60 minutes after the end of the IV infusion.

The IV dose should be prepared using the patient's most recent weight. Further instructions on dose preparation are provided in the pharmacy manual.

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

Instructions on management of infusion reactions and injection site reactions are provided in Section 7.4.

7.2. Background Treatment(s)

Patients who are undergoing apheresis therapy must have initiated LDL apheresis at least 3 months prior to screening and must receive stable weekly apheresis (every 7 ±1 days), or other stable regimen (±2 days) and/or stable settings for at least 8 weeks prior to screening. Patients whose schedule and/or apheresis settings have not been stable for at least 8 weeks before the screening visit will enter an up to 10-week run-in period.

Patients who are on background LMT that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies) before the screening visit will enter a run-in period to stabilize their LMT before entering the screening period.

Patients receiving background LMT that has been proven to reduce the risk of ASCVD (eg, statins, ezetimibe, PCSK9 inhibitor antibodies), should make their best effort to maintain a stable regimen after week 24 and for the duration of the study.

Patients receiving other LMT (eg, apheresis, lomitapide) may have that LMT adjusted after week 24, based on their LDL-C, CV risk factors, and judgment of the investigator.

All patients who were supplied with alirocumab 150 mg SC by the sponsor in a previous study may continue to be provided with alirocumab 150 mg SC Q2W in this study. Those entering this

study after completing a study evaluating the safety and efficacy of alirocumab in patients with HoFH, but did not participate in a prior evinacumab study, may or may not remain on alirocumab as part of their background LMT. Based on the patient's preference and the judgment of the investigator and the patient's health care provider, each patient may:

- continue treatment with alirocumab supplied by the sponsor as part of their background LMT
- discontinue alirocumab prior to enrolling into this study
- change to a commercially available PCSK9 inhibitor antibody prior to enrolling into this study

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.3.2. Study Drug Discontinuation

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

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.4.

7.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- Acute systemic infusion reactions with AEs including, but not limited to, anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, or severe hypotension
- Serious or severe allergic reactions considered related to study drug
- Patient withdraws consent

The investigator may permanently discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of permanent study drug discontinuation.

7.3.2.2. Reasons for Temporary Discontinuation of Study Drug

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

Resumption of study drug requires consultation and agreement between the investigator and the medical monitor.

7.4. Management of Acute Reactions

7.4.1. 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 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

7.4.1.1. 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.

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.

7.4.1.2. Termination of the Intravenous Infusion

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

- anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

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

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

7.4.2. Acute Injection Reactions

7.4.2.1. Systemic Injection Reactions

Acute systemic reactions following administration of study drug should be treated using clinical judgment, based on standard clinical practice, in order to determine the appropriate response.

7.4.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to the Food and Drug Administration (FDA) September 2007 Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.5. Method of Treatment Assignment

This is an open-label study. Starting on day 1, all patients will receive open-label evinacumab 15 mg/kg IV Q4W.

7.5.1. Blinding

Study treatment will not be blinded in this open-label study.

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

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

7.6.2. Supply and Disposition of Treatments

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

and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee.

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

7.6.4. Treatment Compliance

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

7.7. Concomitant Medications and Procedures

Any treatment administered, including apheresis and plasma exchange, from the time of informed consent to the 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.

7.7.1. Permitted Medications and Procedures

The use of all medications and nutritional supplements known to alter serum lipids, including (but not limited to) statins, ezetimibe, fibrates, niacin, bile acid resins, red yeast rice, lomitapide, mipomersen, and PCSK9 inhibitor antibodies is permitted as long as that therapy has been initiated prior to the baseline visit (day 1) and has been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibody therapy, 12 weeks for lomitapide, 6 months for mipomersen).

Patients from previous evinacumab studies who are receiving background LMT or who are undergoing apheresis should continue the same stable LMT and a stable apheresis schedule (as applicable) as at the time of the EOS visit of the previous study without any adjustments.

The use of lomitapide is permitted as long as the therapy has been stable on the maximum tolerated dose for 12 weeks prior to the baseline visit (day 1). If lomitapide therapy was discontinued prior to baseline (day 1), there should be at least an 8-week washout period prior to the baseline visit.

Lipoprotein apheresis is permitted as long as the patient's schedule and setting have been stable for at least 8 weeks prior to the baseline visit. All patients on lipoprotein apheresis should make every effort to adhere to their stable weekly regimen (every 7 ±1 days), or other stable regimen

(±2 days) and/or stable settings. If lipoprotein apheresis was discontinued prior to baseline (day 1), there should be at least a 6-week washout period prior to the baseline visit.

Plasma exchange is also allowed. The patient should be on a stable schedule, and study drug administration should occur after the procedure.

Patients' apheresis schedule and lomitapide therapy (if applicable) may be adjusted after week 24, based on their LDL-C, CV risk factors, and judgment of the investigator.

Patients receiving background LMT that has been proven to reduce the risk of ASCVD (eg, statins, ezetimibe, PCSK9s inhibitor antibodies) should make their best effort to maintain a stable regimen after study week 24 and for the duration of the study.

7.7.2. Prohibited Medications and Procedures

The following concomitant medications and procedures are prohibited for the duration of the study (unless already stable on the medication or procedure prior to the baseline visit):

- Background mipomersen treatment that has not been stable for 24 weeks (6 months) before baseline (day 1)
- Nutraceuticals and all medications known to alter serum lipids, at a dose/amount that has not been stable for at least 4 weeks prior to baseline (day 1)
- Thyroid replacement therapy, unless the dosage of replacement therapy has been stable for at least 12 weeks prior to baseline (day 1)
- Background maximally tolerated dose of lomitapide that has not been stable for 12 weeks before baseline (day 1); washout period less than 8 weeks prior to baseline (day 1) in cases when lomitapide therapy was discontinued prior to enrollment; any changes in lomitapide therapy during participation in this study prior to week 24.
- Background PCSK9 inhibitor antibody therapy that has not been stable for at least 8 weeks prior to baseline (day 1)
- Lipoprotein apheresis that has not been stable for at least 8 weeks prior to the baseline visit; apheresis schedule that is not an every 7 day (±1 day), or other stable schedule (±2 days); any changes to apheresis schedule or settings prior to week 24; washout period less than 6 weeks prior to baseline (day 1) in cases when apheresis was discontinued prior to enrollment.
- Any changes to the background LMT during participation in this study prior to at least week 24

Note: Patients from previous evinacumab studies who are receiving background LMT or who are undergoing apheresis should continue the same stable LMT and a stable apheresis schedule (as applicable) as at the time of EOS visit of the previous study without any adjustments.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

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.

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

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

Study Procedure	Run-in[9]	Screening[1]
Visit	**-1**	**1A**
Day	**-85 to -15**	**-14 to -1**
Visit Window (Day)		
Week	**-12 to -2**	**-2 to -1**
Screening:		
Informed Consent	X	
Inclusion/Exclusion		X
Medical/Surgical History	X	X
Alcohol/Smoking Habits		X
Medication History	X	X
Demographics		X
Treatment:		
Concomitant Medications and Procedures (including LMT and apheresis)[2]	X	X
Efficacy:		
Lipid Panel[3]		X
Specialty Lipid Panel[3]		X
Safety:		
Adverse Events	X	X
Physical Examination		X
Measured Height		X
Body Weight		X
Vital Signs	X	X
Electrocardiogram[4]		X
Tanner Stage[5]		X
Contraception Use Reminder		X
Laboratory Testing:		
Hematology		X
Blood Chemistry		X
Sex Hormones[5,6]		X
Serum Pregnancy Test[7]		X
Urine Pregnancy Test[7]	X	

Study Procedure	Run-in[9]	Screening[1]
Visit	**-1**	**1A**
Day	**-85 to -15**	**-14 to -1**
Visit Window (Day)		
Week	**-12 to -2**	**-2 to -1**
Urinalysis		X
hs-CRP		X
FSH[7]	X	
TSH[8]		X
Hepatitis B Surface Antigen[8]		X
Hepatitis C Antibody[8]		X
Research Samples		X
DNA Sample for HoFH Genotyping[10]	X	
Other:		
Review of Diet	X	X
Reminder of LMT Compliance	X	X
Carotid Ultrasound Imaging[11]	X	

Table 2: Schedule of Events – Screening for Patients with No Run-In

Study Procedure	Screening[1]
Visit	**1A**
Day	**-14 to -1**
Visit Window (Day)	
Week	**-2 to -1**
Screening:	
Informed Consent	X
Inclusion/Exclusion	X
Medical/Surgical History	X
Alcohol/Smoking Habits	X
Medication History	X
Demographics	X
Treatment:	
Concomitant Medications and Procedures (including LMT and apheresis)[2]	X

Study Procedure	**Screening[1]**
Visit	**1A**
Day	**-14 to -1**
Visit Window (Day)	
Week	**-2 to -1**
Efficacy:	
Lipid Panel[3]	X
Specialty Lipid Panel[3]	X
Safety:	
Adverse Events	X
Physical Examination	X
Measured Height	X
Body Weight	X
Vital Signs	X
Electrocardiogram[4]	X
Tanner Stage[5]	X
Contraception Use Reminder	X
Laboratory Testing:	
Hematology	X
Blood Chemistry	X
Sex Hormones[5,6]	X
Serum Pregnancy Test[7]	X
Urine Pregnancy Test[7]	
Urinalysis	X
hs-CRP	X
FSH[7]	X
TSH[8]	X
Hepatitis B Surface Antigen[8]	X
Hepatitis C Antibody[8]	X
Research Samples	X
DNA sample for HoFH Genotyping[9]	X
Other:	
Review of Diet	X
Reminder of LMT Compliance	X
Carotid Ultrasound Imaging[10]	X

Table 3: Schedule of Events – Open-Label Treatment Period and Follow-Up

Study Procedure	**Baseline[1]**	**Open-Label Treatment Period**						**Q4-Week Visit Sequence[13]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**
Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**±7 days**	**±7 days**
Visit Window (Day)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Baseline:									
Informed Consent	X								
Treatment:									
Administer IV Open-Label Study Drug[3,4]	X	X	X	X	X	X	X	X	X
Concomitant Medications and Procedures (including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X
Efficacy:									
Lipid Panel[3,5]	X		X	X	X		X		X
Specialty Lipid Panel[3,5]	X		X		X		X		X
Safety:									
Adverse Events	X	X	X	X	X	X	X	X	X
Physical Examination	X								
Measured Height[6]	X						X		
Body Weight	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X
Electrocardiogram[7]	X						X		
Tanner Stage[6]							X		
Contraception Use Reminder	X	X	X	X	X	X	X	X	X

Study Procedure	**Baseline[1]**	**Open-Label Treatment Period**						**Q4-Week Visit Sequence[13]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**
Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**±7 days**	**±7 days**
Visit Window (Day)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Laboratory Testing[2]:									
Hematology	X		X		X		X		X
Blood Chemistry	X		X		X		X		X
Sex Hormones[6,8]							X		
Serum Pregnancy Test[9]									
Urine Pregnancy Test[9]	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X
hs-CRP	X		X		X		X		X
HbA1C	X			X			X		
Research Samples	X		X				X		X
ADA Samples[10]	X		-				X		
Pharmacokinetics (PK) of Evinacumab [11]	X[12]	X[17]	X[17]	X[12]	X[17]	X[17]	X[12]	X[17]	
Optional DNA sample[16]									
Other:									
Review of Diet	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X
Carotid Ultrasound Imaging[18]							X		

Table 3: Schedule of Events – Open-Label Treatment Period and Follow-Up (Contd)

Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit14	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose15	12 weeks post last dose	PV 16 weeks post last dose15	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	±7	±7	±7	±7		F/U ±5	F/U ±5	F/U ±5	F/U ±5	F/U ±5
Treatment:										
Administer IV Open-Label Study Drug[3]	X	X	X	X						
Concomitant Medications and Procedures including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Lipid Panel[3,5]	X	X		X	X		X			X
Specialty Lipid Panel[3,5]		X		X	X		X			X
Safety:										
Adverse Events	X	X	X	X	X	X	X	X	X	X
Physical Examination										X
Measured Height[6]				X	X					X
Body Weight	X	X	X	X	X					X
Vital Signs[4]	X	X	X	X	X		X		X	X
Electrocardiogram[7]				X	X					X
Tanner Stage[6,8]				X	X					X
Contraception Use Reminder	X	X	X	X	X	X	X	X	X	X

Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit14	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose15	12 weeks post last dose	PV 16 weeks post last dose15	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	±7	±7	±7	±7		F/U ±5	F/U ±5	F/U ±5	F/U ±5	F/U ±5
Laboratory Testing[2]:										
Hematology		X		X	X		X		X	X
Blood Chemistry		X		X	X		X		X	X
Sex Hormones[6,8]				X	X					X
Serum Pregnancy Test[9]					X					X
Urine Pregnancy Test[9]	X	X	X	X		X	X	X	X	X
Urinalysis		X		X	X					X
hs-CRP		X		X	X					X
HbA1C	X			X	X		X			X
Research Samples				X	X					X
ADA Samples[10]				X	X					X
Pharmacokinetics (PK) of Evinacumab[11]	X[12]			X[12]	X[12]					X[12]
Optional DNA Sample[16]	X									
Other:										
Review of Diet	X	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X	X
Carotid ultrasound imaging[18]				X						X

8.1.1. Footnotes for Schedule of Events Table 1

1. All evinacumab-naïve patients will enter the screening period. Patients who participated in a previous evinacumab study and who completed an end of study visit in the previous evinacumab study within 7 days prior to the baseline/day 1 visit for this open label study do not have to enter the screening period and may enroll directly in this study. Patients from previous evinacumab studies who do not enter this study within 7 days of completing the EOS visit of the previous study, must undergo screening.
2. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure.
3. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
4. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
5. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
6. Sex hormones include luteinizing hormone, FSH, estradiol, and total testosterone.
7. WOCBP only, confirm required contraception use and reminder of pregnancy reporting. For adolescent patients not of childbearing potential at Screening, confirm whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and administer pregnancy tests administered every 4 weeks.
8. For evinacumab treatment naïve patients only.
9. Only for patients who require HoFH genotyping, stabilization of their lipoprotein apheresis schedule or stabilization on their background medical LMT.
10. DNA sample for HoFH genotyping should be taken only for patients who have not been enrolled in a previous evinacumab or alirocumab clinical study.
11. Carotid ultrasound imaging for adolescent patients 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 or as soon as possible thereafter. The assessments should be separated by at least 1 day.

8.1.2. Footnotes for the Schedule of Events Table 2

1. All evinacumab-naïve patients will enter the screening period. Patients who participated in a previous evinacumab study and who completed an end of study visit in the previous evinacumab study within 7 days prior to the baseline/day 1 visit may enroll directly and do not have to enter a run-in or screening period. Patients from previous evinacumab studies who do not enter this study within 7 days of completing the EOS visit of the previous study, must undergo screening.

2. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure.
3. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
4. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
5. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
6. Sex hormones include luteinizing hormone, FSH, estradiol, and total testosterone
7. WOCBP only, confirm required contraception use and reminder of pregnancy reporting. For adolescent patients not of childbearing potential at Screening, confirm whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and administer pregnancy tests administered every 4 weeks.
8. For evinacumab-naïve patients only.
9. DNA sample for HoFH genotyping should be taken only for patients who have not been enrolled in a previous evinacumab or alirocumab clinical study.
10. Carotid ultrasound imaging for adolescent patients 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 or as soon as possible thereafter. The assessments should be separated by at least 1 day.

8.1.3. Footnotes for Schedule of Events Table 3

1. For patients directly transitioning from a previous evinacumab study: all assessments and procedures should be performed after end of study assessments and procedures have been completed in the previous study, if applicable. Only assessments not performed at the previous end of study visit need to be performed at the baseline visit.
2. All laboratory samples should be collected before administration of study drug.
3. Study assessments should be performed and blood samples should be collected before study drug administration. For patients undergoing apheresis or plasma exchange: Study assessments should be performed and blood samples should be collected before the procedure. Every effort should be made for the patient to receive study drug immediately after completion of the apheresis procedure, but patients can receive study drug 1 day before the apheresis procedure. Patients undergoing plasma exchange should receive study drug after the procedure. The timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen should match the timing of the week 24 sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen. Depending on the duration between the apheresis procedure and sample collection, the visit window may not apply.

4. Vital signs (temperature, sitting blood pressure, pulse, and respiration rate) should be measured before study drug administration on days when study drug is administered. On dosing days, patients should remain in the clinic for 60 minutes after the end of the IV infusion for monitoring. Pulse and blood pressure should be measured 30 and 60 minutes after the end of the IV infusion.
5. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
6. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
7. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
8. Sex hormones include luteinizing hormone, FSH, estradiol, and total testosterone.
9. All patients will be reminded of protocol-specified contraception use and pregnancy reporting. For adolescent patients not of childbearing potential at Screening, confirm whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and administer pregnancy tests administered every 4 weeks.
10. The ADA sample should be drawn before study drug administration or immediately prior to the apheresis procedure, if applicable.
11. Including assay of total ANGPTL3.
12. PK sample collected in all patients. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure. For patients undergoing plasma exchange, a PK sample should be collected immediately before and after the procedure. For patients who are not undergoing apheresis, the PK sample should be drawn before the dose of study drug.
13. After the week 24 visit, visits are in a strict sequence of A through F and should occur every 4 weeks. After visit F, the sequence repeats (visits A through F) until the end of treatment visit.
14. The end of treatment visit should occur 4 weeks post the last dose. Patients who prematurely discontinue from study drug should return to the clinic within 5 days if possible for end of treatment visit assessments. At this visit, WOCBP will be provided with urine pregnancy tests with instructions to test for pregnancy at home every 4 weeks after this visit and Q4W when phone visits are scheduled (weeks 8 and 16 post last dose). Urine pregnancy testing will be done during clinic visits at week 12, week 20, and week 24. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a CUP, EAP, or ISS/IST) and thereby may forgo the 24-week follow-up period of the study. The follow-up period was intended to be an off-drug follow-up. No off-drug follow-up period is required for these patients. In this situation, the patient's EOT will be their last study visit.

15. 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. Women of childbearing potential will report the results of their home pregnancy test. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a CUP, EAP, or ISS/IST) and thereby may forgo the 24-week follow-up period of the study. No off-drug follow-up period is required for these patients. In this situation, the patient's EOT will be their last study visit.
16. Should be collected at the baseline visit or at any study visit for patients who have not previously been enrolled in an evinacumab or alirocumab clinical study.
17. PK sample (including ANGPTL3) only for evinacumab-naïve adolescent patients.
18. Carotid ultrasound imaging for adolescents will be performed only at sites with this capability and will be performed at 24 weeks and 1 year and at yearly intervals thereafter.

8.1.4. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic for 2 visits: an end of treatment/early termination visit and an end of study visit. The end of treatment/early termination visit should take place within 5 days of treatment discontinuation, if possible. A final end of study (EOS) visit should take place with assessments as specified in the EOS visit at 24 weeks after the last dose of study drug described in Table 3.

Sexually active patients who discontinue the study prematurely should be reminded to maintain highly effective contraceptive measures for 24 weeks after the last dose of study drug. At the end of treatment/early termination visit, WOCBP will be provided urine pregnancy tests with instructions to test for pregnancy Q4W until the EOS visit. All patients should also be notified of Q4W follow-up phone calls to confirm contraception use, remind them of pregnancy reporting, and to obtain the results of the urine pregnancy test. Patients who upon their study completion, may continue to receive treatment outside of the clinical trial (such as through a CUP, EAP, or ISS/IST) and thereby may forgo the 24-week follow-up period of the study. No off-drug follow-up period is required for these patients. In this situation, the patient's EOT will be their last study visit.

8.1.5. 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.

8.2. Study Procedures

8.2.1. 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: TSH, FSH, hepatitis B surface antigen, hepatitis C antibody.

8.2.2. Safety Procedures

8.2.2.1. Vital Signs

Vital signs, including temperature, sitting blood pressure and pulse and respiration rate, will be collected predose at time points according to Table 1, Table 2, and Table 3. Post-dose blood pressure and pulse rate will be collected 30 minutes and 60 minutes after the end 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.

8.2.2.2. Physical Examination

A thorough and complete physical examination including height and weight 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.

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

8.2.2.4. Tanner Stages

The Tanner stages will be assessed throughout the study for all patients ≥12 years old and <18 years old at specified time points shown in Table 1, Table 2, and Table 3. If possible, for each adolescent patient, the Tanner stages assessment should be performed by the same investigator/designee trained to assess pubertal development.

8.2.2.5. Laboratory Testing

All laboratory samples will be collected at visits according to Table 1, Table 2, and Table 3, before the dose of study drug is administered and/or before apheresis is performed, if applicable.

Detailed instructions for blood sample collection are in the laboratory manual provided to study sites and specific tests are listed below.

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: high sensitivity C-reactive protein (hs-CRP), TSH, FSH, hemoglobin A1c (HbA1c), sex hormones (luteinizing hormone, FSH, estradiol, and total testosterone), and pregnancy test (serum and urine).

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 9.4.5.

8.2.2.6. Pregnancy Testing

Women of childbearing potential will have urine pregnancy testing approximately every 4 weeks throughout the study from screening through the end of study visit, and a serum pregnancy test at the screening visit, end of treatment/early termination visit, and end of study visit. During some follow-up visits, and in case of early termination, pregnancy testing will occur at home via a urine pregnancy test. Patients will report results of the home urine pregnancy test to clinical site study personnel during follow-up visit or phone visits.

8.2.3. Efficacy Procedures

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

Alcohol consumption within 48 hours and smoking or intense physical exercise within 24 hours, prior to blood sampling are discouraged.

Total cholesterol, calculated LDL-C, TG, and non-HDL-C will be directly measured by the central laboratory. Low-density lipoprotein cholesterol will be calculated using the Friedewald formula. If TG values exceed 400 mg/dL (4.52 mmol/L), LDL-C will be measured via the beta quantification method (rather than via the Friedewald formula). If the LDL-C value is less than

25 mg/dL (0.65 mmol/L), LDL-C will be measured via the beta quantification method (rather than the Friedewald formula). Non-HDL-C will be calculated by subtracting HDL-C from TC. High-density lipoprotein cholesterol (HDL-C) will be measured for assessing non-HDL-C but is not an efficacy variable for this study.

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

8.2.3.1. Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Table 1, Table 2, and Table 3, for assessment of the lipid profile, comprising calculated LDL-C, non-HDL-C, HDL, 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.

8.2.3.2. Specialty Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Table 1, Table 2, and Table 3 for assessment of the specialty lipid profile, comprising Apo B, ratio of Apo B/Apo A-1, and lipoprotein a (Lp[a]) as well as for Apo CIII. Apolipoprotein A-1 will be measured for assessing ratio of Apo B/Apo A-1 but is not an efficacy variable for this study. The specialty lipid panels will be assessed in the same sample that is collected for the lipid panel.

8.2.4. Drug Concentration and Measurements

Samples for drug concentration will be collected at visits listed in Table 3. Any unused samples may be used for exploratory biomarker research or other investigations.

8.2.5. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3. Any unused samples collected for ADA assessments may be used for exploratory biomarker research or other investigations.

Patients who exhibit a positive ADA assay response with a titer >240 in their last sample analyzed will not participate in any other studies or under any treatment with evinacumab and will be followed 3 to 6 months after EOS visit until the titers have returned to <240 or to within 2 dilution steps from the pre-treatment baseline titer.

8.2.6. 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).

8.2.7. Pharmacodynamic Procedures

Total ANGPTL3 concentrations in serum will be measured using the PK samples collected at time points listed in Table 3.

8.2.8. Future Biomedical Research

Research samples (serum/plasma) will be collected at time points listed in Table 3. 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 HoFH and other diseases. 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.

8.2.9. Other Assessments

8.2.9.1. Review of Diet

Patients will be asked to follow a heart-healthy diet throughout the duration of the study, starting at the baseline visit and continuing through the end of the open-label treatment period (OLTP), until the last study visit. Patients will be queried on compliance with their diet at time points listed in Table 1, Table 2, and Table 3.

Details are provided in Appendix 1.

8.2.9.2. DNA Sample for HoFH Genotyping

A required blood sample for DNA isolation will be collected to identify or confirm a known mutation in PCSK9, LDLR, APOB, and/or LDLRAP1 gene. Genotyping will be done for patients who have not been enrolled previously in an evinacumab or alirocumab trial.

8.2.9.3. Genomics Sub-Study (Optional)

The genomic sample will be taken for patients who have not been enrolled previously in an evinacumab or alirocumab study. Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) 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 double-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 hypercholesterolemia 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 and related diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole genome sequencing, DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic sub-study will not be reported in the CSR.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

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

9.2. Obligations of Sponsor

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

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

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

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IRBs/ECs as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease, which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.

- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room 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. See Section 9.4 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

9.3.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

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

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

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

- SAE with an onset within 30 days of the end of study or within 168 days (24 weeks) of last study drug administration if the patient early terminated from the study - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE,

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, 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.

Adverse Events of Special Interest: All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2.

Adverse events of special interest for evinacumab include the following:

- Anaphylactic reactions
- 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)
- Allergic events and/or local injection site reactions that require medical treatment or that require consultation with another physician for further evaluation
- Pregnancy
- Symptomatic overdose with investigational medicinal product
- Neurocognitive events
- New onset of diabetes*
- Pancreatitis

Adverse events of special interest for alirocumab include the following:

- Increase in ALT: ALT ≥3 x ULN (if baseline ALT <ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN)
- Allergic events and/or local injection site reactions that require consultation with another physician for further evaluation
- Pregnancy
- Symptomatic overdose with investigational medicinal product
- Neurologic events that require additional examinations/procedures and/or referral to a specialist
- Neurocognitive events
- Cataracts
- New onset of diabetes*

  *New onset of diabetes is defined as any of the following:

  – Type 1 or type 2 diabetes TEAE (grouping of MedDRA terms will be specified in the statistical analysis plan [SAP])

  – 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)

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

Refer to the study reference manual for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

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

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

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

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

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

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

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

Injection Site Reactions

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

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

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

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

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

No:

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

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

Relationship of Adverse Events to Study Conduct:

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

No:

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

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the course of the study
- resolve or improve after discontinuation from study participation
- reappear or worsen when study participation is resumed

Relationship of Adverse Events to Injection Procedure, Study Procedure, or Background Treatment:

The relationship of AEs to injection procedure, study procedure, or background treatment will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the injection procedure, study procedure, or background treatment?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the injection procedure, study procedure, or background treatment.

Related: There is a reasonable possibility that the event may have been caused by the injection procedure, study procedure, or background treatment.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

A list of factors to consider in assessing the relationship of AEs to injection procedure, study procedure, or background treatment is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the injection procedure, study procedure, or background treatment?

No:

- due to the patient's disease state or clinical condition

- do not follow a reasonable temporal sequence following the injection procedure, study procedure, or background treatment
- do not reappear or worsen when the injection procedure, study procedure, or background treatment is resumed
- are not a suspected response to the injection procedure, study procedure, or background treatment based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the injection procedure, study procedure, or background treatment
- resolve or improve after discontinuation of study drug or injection procedure, study procedure, or background treatment
- reappear or worsen when the injection procedure, study procedure, or background treatment is resumed
- are known or suspected to be a response to the injection procedure, study procedure, or background treatment based upon preclinical data or prior clinical data

9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and 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.

9.7. Investigator Alert Notification

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

10. STATISTICAL PLAN

This section provides the basis for the SAP for this study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

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

10.2. Justification of Sample Size

Since this study is an open-label single treatment arm study for patients with HoFH, no calculation for sample size was performed. Approximately 120 patients will be enrolled.

To gain experience with evinacumab in the subpopulation of adolescent patients, this study will plan to enroll approximately 14 patients in the age range of 12 years to <18 years old. Due to the rare patient population planned for evaluation, the sample size of 14 patients was chosen for practical reasons, centered on the feasibility to identify and enroll these patients into the trial and regulatory precedent.

10.3. Analysis Sets

10.3.1. Safety Analysis Set

The safety analysis set (SAF) includes all patients who received at least 1 dose or part of a dose of open-label study treatment in this study. The SAF will be the main analysis set for exposure/compliance, clinical safety and efficacy.

10.3.2. Efficacy Analysis Sets

The SAF will be the main analysis set for efficacy.

10.3.3. Pharmacokinetic Analysis Sets

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

10.3.4. Anti-Drug Antibody Analysis Sets

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

10.4. Statistical Methods

In general, data will be presented in 3 patient groups, depending on the status of previous evinacumab treatment exposure:

- Continue evinacumab: patients who received evinacumab in a previous study (eg, R1500-CL-1331 or R1500-CL-1629);
- New evinacumab: patients without previous exposure to evinacumab (ie, evinacumab-naïve);
- Total: all patients, regardless of previous (or not) evinacumab exposure.

These 3 evinacumab exposure groups will be provided for all patients in the respective patient analysis sets. Assuming there are enough patients in the subpopulation of adolescent patients to perform the evaluation, the 3 evinacumab treatment exposure groups will be provided again for the subpopulation of adolescent patients [yes/no]. Adolescent patients [yes] are defined as ranging in age from 12 years to < 18 years old. Adult patients, defined as ≥ 18 years of age, will also be provided.

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

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

10.4.1. Patient Disposition

The following will be provided by the status of previous evinacumab treatment exposure, and again for the subpopulation of adolescent patients [yes/no]:

- The total number of screened patients: defined as originally having met the inclusion criteria and signed the ICF
- The total number of enrolled patients, defined as all screened patients with a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used.
- The total number of patients in each analysis set (Section 10.3)
- The total number of patients who completed the OLTP (ie, as collected on the end of study CRF)
- The total number of patients who did not complete the OLTP
- The total number of patients who discontinued open-label study treatment by main reason for permanent treatment discontinuation
- The total number of patients who completed the study
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by the status of previous evinacumab treatment exposure for all patients in the SAF, and again for the subpopulation of adolescent patients [yes/no].

10.4.3. Efficacy Analyses

The percent and absolute change in lipid data (eg, LDL-C, Apo B, TG) will be descriptively summarized for each visit by the status of previous evinacumab treatment exposure for all patients in the SAF, and again for the subpopulation of adolescent patients [yes/no] for patients in the SAF. A within-patient t-test (lipids with a normal distribution) or Wilcoxon signed-rank test (non-parametric test for lipids with a non-normal distribution such as TG) will be provided for secondary efficacy endpoints to descriptively compare each patient's week 24 assessment to their baseline assessment. Missing data will not be imputed.

The baseline value used for determining percent and absolute change for each patient is defined as follows:

- For patients who participated in the previous evinacumab study R1500-CL-1629, baseline is defined as the last obtained value before the first dose of double-blind study drug in R1500-CL-1629.
- For patients who participated in the previous evinacumab study R1500-CL-1331 or did not participate in any previous evinacumab study, baseline is defined as the last obtained value before the first dose of study drug in R1500-CL-1719. (Note: Baseline for patients who participated in R1500-CL-1331 is defined as the baseline from the R1500-CL-1719 study due to the long time between the last study treatment in R1500-CL-1331 and the first study treatment in R1500-CL-1719.)

10.4.4. Safety Analyses

The summary of safety results will be presented in the SAF as described in Section 10.4. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the same baseline definitions described above in Section 10.4.3.

10.4.4.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug
- The open-label TEAE period is defined from the day of the first open-label study treatment administration to the day of the last open-label study treatment administration + 168 days
- The post-treatment period is defined as the time from the day after the end of the respective TEAE periods to the last study visit

Open-label TEAEs are defined as those events that developed, worsened, or became serious during the open-label TEAE period.

Analysis

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

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 by the status of previous evinacumab treatment exposure, and again for the subpopulation of adolescent patients [yes/no].

Summaries of all TEAEs will at least include:

- All TEAEs (and patient listing)
- All treatment-emergent SAEs, including patient deaths (and patient listing)
- Treatment-emergent AESIs (eg, hypersensitivity and anaphylaxis, defined by a pre-specified grouping) (Section 9.4.3)
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT, 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)

10.4.4.2. 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. Potentially clinically significant value criteria will be provided in the SAP.
- PCSV criteria will determine which patients had at least 1 PCSV during the respective open-label TEAE period, taking into account all evaluations performed during this period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSV percentage.
- Open-label treatment period (OLTP): The treatment period used for quantitative analysis of laboratory and vital signs data in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open-label study treatment + 28 days.

Analysis

Summary statistics of raw data and change from baseline in all continuous laboratory variables (excluding variables in lipid panel) and all vital signs parameters will be presented for each protocol-scheduled visit assessed during the OLTP period.

For selected parameters, mean changes from baseline with the corresponding standard error may be plotted over time (at same time points).

Number and percentage of patients with a potentially clinically significant value (PCSV) at any time point during the open-label TEAE 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, regardless of baseline level.

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

10.4.4.3. Treatment Exposure

The duration of study drug exposure for the open-label treatment period will be calculated as:

- Patient duration of study drug exposure in weeks: (last study drug administration date + 28 – first study drug administration date +1) / 7, regardless of unplanned intermittent discontinuations
- The total number of study drug infusions by patient

10.4.4.4. Treatment Compliance

Compliance during the OLTP will be assessed by infusion frequency, specifically:

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

10.4.5. Pharmacokinetics

10.4.5.1. Analysis of Drug Concentration Data

Descriptive statistics of evinacumab serum concentration at each sampling time will be provided. No formal statistical analysis will be performed.

10.4.6. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient and time point will be provided. Prevalence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%).

The influence of ADAs on drug concentrations will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

10.5. Additional Statistical Data Handling Conventions

Additional analysis and data conventions will be provided in the SAP, including the definitions for the analysis windows around each planned visit.

10.6. 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 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. 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) tool: Medidata Rave.

11.2. 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
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

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. Source Document Requirements

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

The investigator must keep all source documents on file with the CRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

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

13. 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.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. 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.

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

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

Informed Consent for Adult Patients

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

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

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

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

Informed Consent for Pediatric Patients

To be used as applicable, see Section 6.2.

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, 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).

14.2. Patient 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.

14.3. Institutional Review Board/Ethics Committee

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

- The protocol, ICF, and any other materials to be provided to 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.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment.

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

16.1. 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.

16.2. 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 patient's interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

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

17.2. 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.

18. DATA QUALITY ASSURANCE

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

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, Section 13).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All subject/patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient/subject final CRF (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Evinacumab in 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)

APPENDIX 1. SUMMARY OF THERAPEUTIC LIFESTYLE CHANGES DIET FOR HIGH CHOLESTEROL

Total Fat	25% - 35% total calories*
Saturated fat*	<7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates†	50% - 60% total calories*
Protein	~15% total calories
Cholesterol	<200 mg/dL (5.172 mmol/L)
Plant Sterols	2g
Soluble Fiber such as psyllium	10g - 25g

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat. Trans-fatty acids are another LDL-raising fat that should be kept at a low intake.

† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia

Protocol Number: R1500-CL-1719

Protocol Version: R1500-CL-1719 Amendment 7

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 Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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