Title Page

Protocol Title:		A Multicenter, Open-label, Single-arm, Study to Evaluate Safety and Tolerability of Repatha in Patients with Homozygous Familial Hypercholesterolemia (HoFH) in India
Short Protocol Title:		An Open-label Study to Characterize Safety and Tolerability of Repatha in Homozygous Familial Hypercholesterolemia in India
Protocol Number:		20170199
Investigational Product:		Evolocumab
Trade Name:		Repatha
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Investigator's Agreement:

I have read the attached protocol entitled A Multicenter, Open-label, Single-arm, Study to Evaluate Safety and Tolerability of Repatha in Patients with Homozygous Familial Hypercholesterolemia (HoFH) in India, dated **16 August 2017**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Multicenter, Open-label, Single-arm, Study to Evaluate Safety and Tolerability of Repatha in Patients with Homozygous Familial Hypercholesterolemia (HoFH) in India

Short Protocol Title: An Open-label Study to Characterize Safety and Tolerability of Repatha in Homozygous Familial Hypercholesterolemia in India

Study Phase: 4

Indication: Homozygous Familial Hypercholesterolemia (HoFH)

Rationale

In March 2017, Repatha® (evolocumab) was approved in India as prescription medication in combination with other lipid-lowering therapies for adults and adolescents aged 12 years and over with HoFH. This non-comparative, interventional phase 4 study is designed to fulfil the postmarketing requirement to assess safety and tolerability of Repatha in Indian HoFH subjects when administered under the locally approved label.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability in homozygous familial hypercholesterolemia HoFH patients in India exposed to 12 weeks of Repatha	• The subject incidence of treatment-emergent adverse events
Secondary	
• To characterize the efficacy of 12 weeks of Repatha on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB) and lipoprotein(a) [Lp(a)] in HoFH patients in India	• Percent change from baseline in LDL-C at week 12 • Percent change from baseline in ApoB at week 12 • Percent change from baseline in Lp(a) at week 12

Hypotheses

This phase 4 study is descriptive in nature, describing safety and tolerability of Repatha in subjects with HoFH in India.

Overall Design

This open-label, multicenter, non-comparative phase 4 study of Repatha is part of Amgen's postmarketing requirement to the Indian Regulatory Authority. The study population consists of approximately 30 Indian subjects with HoFH and for whom Repatha is indicated in accordance with the approved prescribing information in India.

The assignment of subjects to protocol treatment will be decided by the investigator according to inclusion/exclusion criteria and laboratory assessments at screening (including fasting lipids). Subjects who are enrolled will be instructed to continue to

follow a diet limiting saturated fat to less than 7% of total daily calories and will be required to maintain their current lipid-lowering drug therapy throughout the duration of the trial.

Number of Subjects

Approximately 30 subjects with HoFH will be enrolled in the study.

Summary of Subject Eligibility Criteria

Key inclusion criteria include subjects 12 to 80 years of age with a clinical diagnosis of HoFH who are on a stable, low-fat diet, and taking pre-existing lipid-lowering therapies. Key exclusion criteria include use of mipomersen or lomitapide within 6 months of screening and has previously received evolocumab or any other proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibiting therapy.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

Subjects will receive Repatha 420 mg once monthly (QM) subcutaneous (SC) and study visits will occur approximately every 4 weeks (the week 4 study visit is optional: subjects can either self-administer at home or visit study site and study staff will administer Repatha). For subjects on apheresis, they may receive Repatha 420 mg SC every 2 weeks to correspond with their apheresis schedule (the week 2 and week 6 study visits are optional: subjects can either self-administer at home or visit study site and study staff will administer Repatha). Final administration of Repatha will occur at week 8. The end of study (EOS) visit and the last estimation of lipids will occur at week 12 for all subjects. Subjects will be encouraged to complete all planned visits, study procedures, and measurements until the end of the study regardless of their adherence to Repatha administration.

Procedures

Informed consent must be obtained before starting any screening procedure. The following procedures will occur per the Schedule of Activities: physical examination, physical measurements, demographics, medical history, vital signs, dietary advice, adverse event assessment, concomitant therapies review, laboratory assessments, Tanner staging (for subjects < 18 years old only), and Repatha administration.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1 .

Statistical Considerations

Approximately 30 subjects with HoFH will be enrolled in this study. The primary analysis set is the full analysis set (FAS), which includes all enrolled subjects who have received at least 1 dose of Repatha. Unless specified otherwise, the FAS will be the default analysis set in this study.

The final analysis will be performed at the end of the study (defined as when the last subject enrolled has completed the safety follow-up/EOS visit).

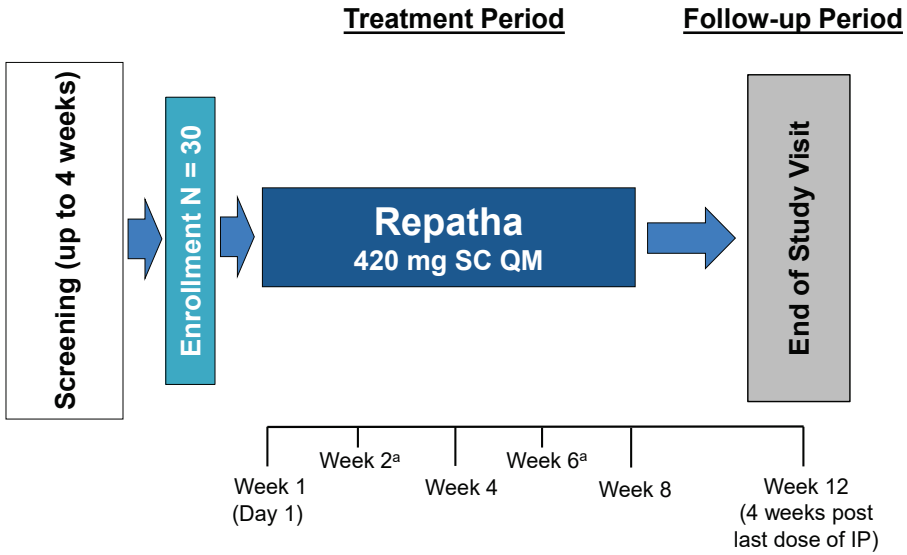
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



IP = investigational product; QM = once monthly; SC = subcutaneous
[a] For subjects on apheresis only.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Procedure	Screening (up to 4 weeks before day 1)	Treatment Period					Follow-up	Notes
		W1 (day 1)	W2[a]	W4[b]	W6[a]	W8	W12[c]	
General and Safety Assessments								
Informed consent	X							
Inclusion and exclusion criteria	X							Includes specific eCRFs for lactation status and HoFH clinical criteria
Demographics	X							
Physical examination	X	X					X	
Physical measurements: weight	X							
Medical history	X							
Vital signs (BP, HR)	X	X				**X**	X	
Dietary advice	X							
AE/SAE/ADE/DRE	X	X	X[d]	X[d]	X[d]	X	X	
Concomitant therapies review	X	X	X[d]	X[d]	X[d]	X	X	
Tanner staging[e]	X						X	
Laboratory Assessments[f]								
Urine and/or serum pregnancy test (females of childbearing potential only)	X						X	Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

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Abbreviations and footnotes defined on last page of table.

Table 2-1. Schedule of Activities

Procedure	Screening (up to 4 weeks before day 1)	Treatment Period					Follow-up	Notes
		W1 (day 1)	W2[a]	W4[b]	W6[a]	W8	W12[c]	
Laboratory Assessments[f] (continued)								
Hematology	X							
Chemistry	X							
Fasting lipids, ApoA1, ApoB	X	X				**X**	X	
Lp(a)	X	X				**X**	X	
Urinalysis	X							
Pharmacogenetics samples (optional)		X						
Study Treatment								
Amgen investigational product		X	X[a]	X	X[a]	X		Administration at weeks 2 and 6 are for subjects on apheresis only.

ADE = adverse device effect; AE = adverse event; Apo = apolipoprotein; BP = blood pressure; DRE = disease-related events; eCRF = electronic case report form; EOS = end of study; FCBP = female of childbearing potential; HoFH = homozygous familial hypercholesterolemia; HR = heart rate; Lp(a) = lipoprotein (a); SAE = serious adverse event; W = Week

[a] Subjects on apheresis only: may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. On weeks 2 and 6, subjects can self-administer Repatha at home, no site visit required. However, if the subject prefers, they can visit study site and study staff will administer Repatha.

[b] For all subjects: on week 4, subjects can self-administer Repatha at home, no site visit required. However, if the subject prefers, they can visit study site and study staff will administer Repatha.

[c] The EOS visit will occur at week 12 (4 weeks after last dose of Repatha).

[d] Will call if subject chooses to administer Repatha at home.

[e] In pediatric subjects 12 to 17 years of age (includes the year after the subject completes the 17th year after birth but not the day of completing the 18th year after birth).

[f] Subjects will fast for 9 hours and abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests.

3. Introduction

3.1 Study Rationale

In March 2017, Repatha® (evolocumab) was approved in India as prescription medication in combination with other lipid-lowering therapies for adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH). This non-comparative, interventional phase 4 study is designed to fulfil the postmarketing requirement to assess safety and tolerability of Repatha in Indian HoFH subjects when administered under the locally approved label.

3.2 Background

3.2.1 Disease

Homozygous familial (most commonly referred to as HoFH) is a rare genetic disorder occurring in approximately 1:1 000 000 individuals. Many of these represent compound heterozygotes possessing different mutations on each of the low-density lipoprotein receptor (LDLR) alleles (Goldstein et al, 2001). The geographical prevalence and characterization of the specific LDLR mutations among homozygous patients though often well known in western population; is not so well characterized in India. The incidence of major cardiovascular illness among homozygous individuals is higher than that of affected familial hypercholesterolemia heterozygotes, with events such as myocardial infarction happening by the second decade of life (Goldstein et al, 2001). Due to the rapid and aggressive nature of atherosclerosis in HoFH, it is commonly studied and treated as a disease beginning in childhood and manifesting with untoward morbidity and mortality in affected adults. This also applies to other, even more rare genetic causes of dyslipidemia that fall under the umbrella diagnosis of familial hypercholesterolemia. These conditions include mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9; dominant-gain of function), apolipoprotein B (ApoB; dominant-loss of function) and autonomic recessive hypercholesterolemia (ARF; recessive-loss of function). High-dose statin therapy has reduced both low-density lipoprotein cholesterol (LDL-C) (in the range of 10% to 25%) as well as cardiovascular event rates among patients with HoFH (Neil et al, 2008; Raal et al, 1997). However, the response to therapy has been limited in part by the biology underlying this disease, and possibly by the concomitant elevation of PCSK9 levels that result from statin treatment (Lakoski et al, 2009). In addition to maximal medical therapy, some patients have been placed on a biweekly to weekly schedule of lipid apheresis, a process similar to hemodialysis where LDL-C is physically removed from their circulation. Though a

helpful tool in the treatment of HoFH, this invasive procedure is cumbersome, expensive, and not readily available in India.

HoFH LDL receptor mutation results in impaired LDL receptor function and impaired LDL-C clearance. The response variability is based on LDL receptor functionality according to the genetic defect associated with the LDL receptor activities even between subjects confirmed as HoFH. Therapies supporting LDL-C clearance through LDL-C receptor function, like Repatha, can be expected to further reduce LDL-C with existing pharmacologic therapies. Repatha in addition to lipid-lowering therapies in HoFH subjects, shown to have a safety profile response and being effective and well-tolerated (Raal et al, 2014).

3.2.2 Amgen Investigational Product Background: Repatha

Repatha (evolocumab) is a full human monoclonal IgG2 directed against human PCSK9. Repatha binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR, preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, Repatha increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels. Following single subcutaneous (SC) administration of 140 mg or 420 mg of Repatha, maximum suppression of circulating unbound PCSK9 occurred by 4 hours. Unbound PCSK9 concentrations returned toward baseline when Repatha concentrations decreased below the limit of quantitation. Repatha has been found to be effective in reducing LDL-C levels in patients with HoFH in the TESLA study. This study was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients with HoFH. In this trial, 33 patients received SC injections of 420 mg of Repatha once monthly (QM) and 16 patients received placebo as an adjunct to other lipid-lowering therapies (eg, statins, ezetimibe). The mean age at baseline was 31 years, 49% were women, 90% White, 4% were Asian, and 6% other. The trial included 10 adolescents (ages 13 to 17 years), 7 of whom received Repatha. The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe. In these patients with HoFH, the difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 12 was -31% (95% CI: -44%, -18%; $p < 0.0001$) (Raal et al, 2014).

A detailed description of the chemistry, pharmacology, efficacy, and safety of Repatha is provided in the Investigator's Brochure.

4. Objectives, Endpoints, and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability in homozygous familial hypercholesterolemia HoFH patients in India exposed to 12 weeks of Repatha.	• The subject incidence of treatment-emergent adverse events
Secondary	
• To characterize the efficacy of 12 weeks of Repatha on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB) and lipoprotein(a) [Lp(a)] in HoFH patients in India	• Percent change from baseline in LDL-C at week 12 • Percent change from baseline in ApoB at week 12 • Percent change from baseline in Lp(a) at week 12

4.2 Hypotheses

This phase 4 study is descriptive in nature, describing safety and tolerability of Repatha in subjects with HoFH in India.

5. Study Design

5.1 Overall Design

This open-label, multicenter, non-comparative phase 4 study of Repatha is part of Amgen's post-marketing requirement to the Indian Regulatory Authority. The study population consists of approximately 30 Indian subjects with HoFH and for whom Repatha is indicated in accordance with the approved prescribing information in India.

The assignment of subjects to protocol treatment will be decided by the investigator according to inclusion/exclusion criteria and laboratory assessments at screening (including fasting lipids). Subjects who are enrolled will be instructed to continue to follow a diet limiting saturated fat to less than 7% of total daily calories (Iyengar et al, 2016) and will be required to maintain their current lipid-lowering drug therapy throughout the duration of the trial. Subjects will receive Repatha 420 mg QM SC and study visits will occur approximately every 4 weeks (the week 4 study visit is optional: subjects can either self-administer at home or visit study site and study staff will administer Repatha). For subjects on apheresis, they may receive Repatha 420 mg SC every 2 weeks to correspond with their apheresis schedule (the week 2 and week 6

study visits are optional: subjects can either self-administer at home or visit study site and study staff will administer Repatha). If the subject chooses to self-administer Repatha at home during the optional site visits, the staff will call the subject to collect any adverse events or changes in concomitant medication. Final administration of Repatha (for all subjects) will occur at week 8. The end of study (EOS) visit and the last estimation of lipids will occur at week 12 for all subjects. The following procedures will occur per the Schedule of Activities: physical examination, physical measurements, demographics, medical history, vital signs, dietary advice, adverse event assessment, concomitant therapies review, laboratory assessments, Tanner staging (for subjects < 18 years old only), and Repatha administration (see Table 2-1). Subjects will be encouraged to complete all planned visits, study procedures, and measurements until the end of the study regardless of their adherence to Repatha administration.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 30 subjects with HoFH will be enrolled in the study.

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 15 investigative sites in India will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for week 12.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date

when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The EOS date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable.

5.3.2 Study Duration for Subjects

After signing the informed consent, the subject should be enrolled within 4 weeks. Including the screening period, the investigational product administration dates (weeks 1, 4, and 8 [and weeks 2 and 6 for subjects on apheresis]), and an EOS visit that occurs at week 12 (4 weeks after last dose of investigational product), the total duration of study participation for a subject will be up to approximately 16 weeks.

5.4 Justification for Investigational Product Dose

The Repatha dose being used in this study is in accordance with the terms of its marketing authorization in India. The dose for this study is 420 mg given QM SC for 8 weeks. For subjects on apheresis, they may initiate treatment with 420 mg SC every 2 weeks to correspond with their apheresis schedule.

Repatha will be administered at 140 mg in 1.0 mL (3 administrations by prefilled autoinjector/pen [AI/pen]) for a total of 3.0 mL (420 mg evolocumab) administered. The SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

5.5 Patient Input on Study Design

Not applicable.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice/Web Response System (IxRS).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 If the subject is ≥ 18 years of age, the subject has provided informed consent prior to initiation of any study specific activities/procedures. If the subject is < 18 years of age, the subject's legally acceptable representative has provided informed consent

102 Male or female ≥ 12 to ≤ 80 years of age at the time of signing the informed consent

103 Clinical diagnosis of HoFH based on a history of an untreated LDL-C concentration greater than 500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of familial hypercholesterolemia in both parents

104 On a stable, low-fat diet and taking pre-existing lipid-lowering therapies (such as statins, cholesterol-absorption inhibitors, bile-acid sequestrants or nicotinic acid, or combinations thereof) with no plan to change medication or dosage within 4 weeks of screening and during the time frame of the trial, with fasting central laboratory LDL-C concentration > 130 mg/dL (3.4 mmol/L) at screening

105 Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) by central laboratory at screening

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

201 Use of mipomersen or lomitapide within 6 months of screening.

202 Known active infection or major hematologic, renal, metabolic, gastrointestinal, hepatic, or endocrine dysfunction.

203 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

204 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 15 weeks after the last dose of Repatha. (Females of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test).

205 Female subjects of childbearing potential unwilling to use **an** acceptable method of effective contraception during treatment and for an additional 15 weeks after the last dose of Repatha. Refer to Appendix 5 for additional contraceptive information.

206 Subject has known sensitivity to any of the products to be administered during dosing.

207 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

208 Subject has previously received evolocumab or any other PCSK9-inhibiting therapy.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study (up to 4 weeks before enrollment) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned IxRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

6.4 Screen Failures

Subjects ≥ 18 years of age who are considered for entry into the study and have the risks and benefits of participating in the study explained will enter screening by signing and dating the informed consent form for this study. If the subject is < 18 years of age, the subject's legally acceptable representative has to provide informed consent. Screening should be completed and the subject randomized or screen failed within 4 weeks of signing the informed consent.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

7. Treatments

Study treatment is defined as any investigational product(s) or medical device(s) intended to be administered to a study subject according to the study protocol.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] Repatha
Dosage Formulation	Repatha will be presented as a sterile, preservative-free solution in a single-use, disposable, handheld mechanical (spring-based) prefilled AI/pen for fixed dose, SC injection. The prefilled AI/pen contains a 1-mL deliverable volume of 140 mg/mL evolocumab.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	140 mg/mL 420 mg QM (subjects on apheresis: 420 mg Q2W)
Route of Administration	SC
Accountability	The amount dispensed, amount returned, date dispensed, date returned, package lot number of Repatha is to be recorded on each subject's eCRF(s).
Dosing Instructions	Subjects have the option of self-administration, defined as SC administration of IP by the subject, designee, or a qualified health care professional in a non-investigator site setting (eg, at home). If IP is administered on site, it must be performed after all scheduled assessments. After IP administration at the first dosing visit, subjects will remain at site for observation for at least 30 minutes before being discharged.
Device	AI/pen

AI/Pen = autoinjector/pen; eCRF = electronic case report form; IP = investigational product; QM = once monthly; Q2W = every 2 weeks; SC = subcutaneous
[a] Repatha will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

There are no non-Amgen non-investigational products used in this study.

7.1.3 Medical Devices

The investigational medical device(s) provided by Amgen for use in this study are prefilled AI/pens (Table 7-1).

The Repatha AI/pen is a single-use, disposable, handheld mechanical “spring-based” device for fixed dose SC injection of 140 mg/mL of Repatha with a 1-mL deliverable volume.

Additional details are in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

All lipid-lowering drugs (statins, fibrates and ezetimibe, bile-acid sequestering resin, omega 3 fatty acids or niacin) that are allowed per protocol and that the subject may be taking, must be commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). All such therapy needs to be unchanged during the entire time of screening and study participation unless a change is clinically necessary.

7.1.5 Other Treatment Procedures

There are no other treatment procedures required by this study.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- Repatha
- AI/pen

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments are not permitted during the study, including screening:

- treatments for inhibition of PCSK9 or any investigational therapies other than study provided investigational product
- mipomersen or lomitapide
- other drugs (besides those mentioned above) that significantly affect lipid metabolism (eg, systemic cyclosporine, systemic steroids [intravenous, intramuscular, or oral; *Note: hormone replacement therapy is permitted*], vitamin A
- all lipid therapies not taken at the time of screening and enrollment.

The following treatments are not recommended because of their potential impact on metabolism of certain statins: medications or foods that are known potent inhibitors of cytochrome P450 3A (CYP3A) (eg, itraconazole, ketoconazole, and other antifungal azoles), macrolide antibiotics (erythromycin, clarithromycin) and the ketolide antibiotic (telithromycin), human immunodeficiency virus (HIV) or hepatitis C virus (HCV) protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 L]) should not be used during the study.

7.2 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with investigational product.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

There will be no dose adjustments in this study. If, in the opinion of the investigator, a subject is unable to tolerate the dose, that subject will discontinue Repatha but will continue to return for all other study procedures and measurements until the end of the study.

7.4.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.1.1 Amgen Investigational Product: Repatha

The decision to rechallenge the subject after therapy changes should be discussed and agreed unanimously by the subject, investigator, and Amgen. If signs or symptoms recur with rechallenge of Repatha, then Repatha should be permanently discontinued.

The reason for dose stopping and rechallenge of Repatha is to be recorded on each subject's eCRF.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and/or device during the study are provided in the IPIM.

7.6 Treatment Compliance

Administration of Repatha will occur at the study site at week 1 (day 1), week 4 (option to self-administer at home or at site), and week 8. For subjects on apheresis, they may also receive Repatha on week 2 and week 6 to correspond with their apheresis schedule (option to administer at home or at site). Non-compliance is to be documented in the medical file and will be reflected in the eCRF. Non-compliant subjects are to be re-educated on the importance of adhering to the study drug administration schedule and reminded that repeated cycles of non-compliance could be a reason for discontinuation of study treatment.

7.7 Treatment of Overdose

The effects of overdose of this product are not known.

7.8 Prior and Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from informed consent through the EOS study visit.

For concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

All details for lipid regulating treatment will be collected on the appropriate eCRF.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- decision by sponsor
- lost to follow-up
- death
- ineligibility determined
- protocol deviation
- non-compliance
- adverse event
- subject request
- pregnancy

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before starting any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject or legal representative has signed the informed consent form, the site will register the subject in the IxRS and screen the subject in order to assess eligibility for participation. The screening window is up to 4 weeks.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 7 days. The date of the first dose of investigational product is defined as day 1 (week 1). All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered last during each visit that it is required.

9.1.3 End of Study

Upon permanent discontinuation from the study for any reason, the EOS visit will be performed 4 weeks (± 2 days) after the last dose of investigational product.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex and age will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started prior to enrollment through signing of the informed consent form. Medical history will include information on the subject's concurrent medical conditions, including cardiac risk factors and congestive heart failure details. The current severity will be collected for

each condition that has not resolved. Record all findings on the appropriate medical history eCRF.

In addition to the medical history above, HoFH by clinical diagnosis must date back to the original diagnosis.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate eCRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Weight (in kilograms) should be measured without shoes.

9.2.1.6 Dietary Advice

Subjects who are enrolled will be instructed to continue to follow a diet limiting saturated fat to less than 7% of total daily calories (Iyengar et al, 2016).

9.2.1.7 Tanner Staging (Sexual Maturity Ratings)

Tanner staging is widely used to assess adolescents' physical development during puberty in 5 stages (up to 18 years of age). Also known as Sexual Maturity Ratings, Tanner stages are a way of assessing the degree of maturation of secondary sexual characteristics (see Appendix 8 for guidance). The developmental stages of the adolescent's sexual characteristics will be rated and recorded separately on appropriate eCRF (ie, one stage for pubic hair and one for breasts in females, one stage for pubic hair and one for genitals in males), because these characteristics may differ in their degree of maturity.

9.2.2 Efficacy Assessments

Efficacy will be determined as percent change from baseline in LDL-C, ApoB, and Lp(a) at week 12 (collected as indicated in Table 12-1).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after signing of the informed consent through the EOS visit are reported using the Event eCRF.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product and determined to be serious, must be reported on the Event eCRF as serious adverse events.

Disease-related events pre-defined for this study include: manifestations and complications of atherosclerotic vascular disease such as coronary artery disease, angina, myocardial infarction, ischemic stroke, transient ischemic attack, carotid artery disease, peripheral vascular disease (including complications such as claudication), and testing suggesting progression of atherosclerotic vascular disease.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the EOS visit are reported using the Event eCRF.

9.2.3.1.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through EOS visit are reported using the Event eCRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of

after EOS. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 4 weeks after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.1.6 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

Product complaints are described in Section 7.1.6.

Further details regarding adverse device effects can be found in Appendix 4.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, and heart rate. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

9.2.3.3 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event eCRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

9.2.4.1 Pregnancy Testing

A high sensitive (urine or serum) pregnancy test should be completed at screening for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

A pregnancy test should be performed at week 12/EOS after discontinuing protocol-required therapies.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.5 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations (such as those of the PCSK9 gene or the LDLR gene) to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cardiovascular disease and/or to identify subjects who may have positive or negative response to Repatha. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

The final disposition of samples will be described in Appendix 6.

10. Statistical Considerations

10.1 Sample Size Determination

Approximately 30 subjects with HoFH will be enrolled in this study.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

The primary analysis set is the full analysis set (FAS), which includes all enrolled subjects who have received at least 1 dose of Repatha. Unless specified otherwise, the FAS will be the default analysis set in this study.

10.2.2 Covariates

No covariates will be used in this study.

10.2.3 Subgroups

No subgroups will be used in this study.

10.2.4 Handling of Missing and Incomplete Data

Incomplete adverse event start dates and concomitant medications start or stop dates will be imputed and the detailed rules will be specified in statistical analysis plan.

No imputation will be done for the secondary endpoints.

10.3 Adaptive Design

Not applicable.

10.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the EOS, as defined in Section 5.3.1.

10.4.1 Planned Analyses

The final analysis will be performed at the end of the study (defined as when the last subject enrolled has completed the safety follow-up/EOS visit).

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

Statistical analyses are descriptive in nature. No statistical inference is planned.

Subject disposition, demographics, and baseline characteristics will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum and maximum. For categorical variables, the frequency and percentage will be given.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	Descriptive statistics will be summarized for each secondary endpoint.
Exploratory	Not applicable.

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Subject incidence of treatment-emergent adverse events will be summarized.

10.4.2.3.2 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, drug related adverse events, adverse events leading to withdrawal from investigational product, and treatment-emergent adverse events will also be provided. Subject incidence of disease-related events, fatal disease-related events, and device-related events, if applicable, will be tabulated by system organ class and preferred term.

10.4.2.3.3 Exposure to Investigational Product

The number of days on investigational product and the total dose of investigational product will be summarized using descriptive statistics.

10.4.2.3.4 Exposure to Concomitant Medication

Number and proportion of subjects receiving concomitant medications will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoB	apolipoprotein B
ARF	autonomic recessive hypercholesterolemia
BIL	bilirubin
CBC	complete blood count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CPK	creatine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450 3A
DILI	drug-induced liver injury
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EOS	end of study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HoFH	homozygous familial hypercholesterolemia
HRT	hormonal replacement therapy
ICF	informed consent form

Abbreviation or Term	Definition/Explanation
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
IxRS	interactive voice/web response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
Lp(a)	lipoprotein(a)
PCSK9	proprotein convertase subtilisin/kexin type 9
POR	Proof of Receipts
QM	once monthly
SC	subcutaneous
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
ULN	upper limit of normal
WHODRUG	World Health Organization Drug

Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory. Subjects will fast for 9 hours and abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Central Laboratory: Other Labs
Sodium	Specific gravity	RBC	Serum pregnancy
Potassium	pH	Hemoglobin	Fasting lipid panel:
Chloride	Blood	Hematocrit	• Total cholesterol
Bicarbonate	Protein Glucose	Platelets	• LDL-C
Total protein	Bilirubin	WBC	• HDL-C
Albumin	WBC	Differential:	• VLDL-C
Calcium	RBC	• Neutrophils	• non-HDL-C
Adjusted calcium	Epithelial cells	• Eosinophils	ApoA1
Magnesium	Bacteria	• Basophils	ApoB
Phosphorus	Casts	• Lymphocytes	Lp(a)
Glucose	Crystals	• Monocytes	
BUN or Urea			
Creatinine			
Uric acid			
Total bilirubin			Local labs
ALP			Urine pregnancy
LDH			
AST (SGOT)			
ALT (SGPT)			

ALP = alkaline phosphatase; ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL-C = high-density lipoprotein cholesterol; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); non-HDL-C = non-high-density lipoprotein cholesterol; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VLDL-C = very low-density lipoprotein cholesterol; WBC = white blood cell count.

Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample

informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from

study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9).

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic case report form (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An investigator who provided significant contributions to either the design or interpretation of the study
- An investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Amgen (or designee) will perform Self-Evident Corrections to obvious data errors in the clinical trial database. Self-Evident Corrections will be documented in the eCRF Standard Instructions and the eCRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 12 and end of study]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System/Interactive Web Response System (IxRS) (if used, such as subject ID and randomization number) and eCRF entries if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the eCRF or entered in the electronic eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed eCRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen

- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition
• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events. • Disease-related events that would qualify as an adverse event or serious adverse event: – An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event. • Disease-related events that do not qualify as adverse events or serious adverse events: – An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an

adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, 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.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 7.1.3 for the list of Amgen medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording
• When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event electronic case report form (eCRF). – Additionally, the investigator is required to report a fatal disease-related event on the Event eCRF. • The investigator must assign the following adverse event attributes: – Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – Dates of onset and resolution (if resolved); – Severity (or toxicity defined below); – Assessment of relatedness to investigational product, other protocol-required therapies, or devices; and – Action taken. • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event eCRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event eCRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product and device and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event eCRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an Electronic Serious Adverse Event (eSAE) Contingency Form (paper form; see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on an eSAE Contingency Form (paper form; see Figure 12-1).

Adverse Device Effects: Recording, Evaluating, and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event eCRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN Study # 20170199 Evolocumab (Repatha)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: + 91 22 6786 9146 / 6786 9138

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <IPdevice> No✓	<IPdevice> Yes✓	<IPdevice> No✓	<IPdevice> Yes✓	<IPdevice> No✓	<IPdevice> Yes✓	<IPdevice> No✓	<IPdevice> Yes✓	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study # 20170199 Evolocumab (Repatha)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170199 Evolocumab (Repatha)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for adult female subjects of childbearing potential or for pediatric subjects who have reached puberty are outlined in Section 6.2.

Adult female subjects of childbearing potential or for pediatric studies who have reached puberty must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 15 weeks after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- premenopausal female with 1 of the following:
  - documented hysterectomy;
  - documented bilateral salpingectomy; or
  - documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable:
  1) review of subject's medical records; 2) subject's medical examination; or
  3) subject's medical history interview.
- premenarchal female
- postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)

- intrauterine device (IUD)
- intrauterine hormonal-releasing system (IUS)
- bilateral tubal ligation/occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide
- double-barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Contraception Methods for Male Subjects

Male participants are not required to use birth control during treatment with evolocumab.

However, they should let their female partner know that they are in this study.

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- periodic abstinence (calendar, symptothermal, postovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 15 weeks.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 15 weeks of the study drug. This information will be forwarded to Amgen Global Patient

Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 15 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 15 weeks.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 204.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 15 weeks after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

FAX# +91 22 6786 9146 / 6786 9138

1. Case Administrative Information

Protocol/Study Number: 20170199

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm___/ dd___/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Repatha (evolocumab)				mm___/dd___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm___/ dd___/ yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# +91 22 6786 9146 / 6786 9138

1. Case Administrative Information

Protocol/Study Number: 20170199

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax (____)** _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
Repatha (evolocumab)				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix 6. Sample Storage and Destruction

Any blood samples collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cardiovascular disease, the dose response and/or prediction of response to Repatha, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining [sample types (eg, blood, tumor)] samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Appendix 3 for subject confidentiality.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit BIL glucuronidation (eg, indinavir, atazanavir)
- alpha-1 antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic fatty liver disease including steatohepatitis
- non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate electronic case report form (eCRF) (eg, Event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- repeat AST, ALT, ALP, BIL (total and direct), and INR within 24 hours
- in cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- complete blood count (CBC) with differential to assess for eosinophilia
- serum total immunoglobulin IgG, anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody -1 to assess for autoimmune hepatitis
- serum acetaminophen (paracetamol) levels

- a more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents
  - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - prior and/or concurrent use of alcohol, recreational drugs and special diets
  - concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- viral serologies
- creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
- appropriate liver imaging if clinically indicated
- appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, and INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding eCRFs.

Appendix 8. Tanner Stages (Sexual Maturity Ratings)

The table below or equivalent locally used guidance should be used for the assessment of sexual maturity (Tanner Staging) in this study.

The table is adapted from Lifshitz (2007).

FEMALES			
Stage	BREAST	PUBIC HAIR STAGING	CONCOMITANT CHANGES
1	Prepubertal, papilla elevation	No pigmented hair	
2	Budding; larger areole; palpable and visible elevated contour	Pigmented hair, mainly labial	Accelerating growth rate
3	Enlargement of the breast and areola	Coarser, spread of pigmented hair over mons	Peak growth rate, thicker vaginal mucosa, axillary hair
4	Secondary mound of areola and papilla	Adult type but smaller area	Menarche (stage 3 or 4) decelerating growth rate
5	Mature	Adult distribution	

MALES				
Stage	GENITAL SIZE	PUBIC HAIR STAGING	CONCOMITANT CHANGES	PRADER ORCHIDOMETER
1	Prepubertal	No pigmented hair	Long testis axis < 1.5 cm	1 – 3 mL
2	Early testicular, penile and scrotal growth	Minimal pigmented hair at base of penis	Early voice changes; testes length 2.5 – 3.3 cm	3 – 6 mL
3	Increased penile length and width; scrotal and testes growth	Dark, coarse, curly hair extends midline above penis	Light hair on upper lip, acne, maximal growth, testes length 3.3 – 4.0 cm	8 – 12 mL
4	Increased penis size including breadth; pigmented scrotum	Considerable, but less than adult distribution	Early sideburns; testes 4.0 – 4.5 cm	> 12 mL
5	Adult size and shape	Adult distribution, spread to medial thighs or beyond	Beard growth; testes > 4.5 cm	> 15 mL

Superseding Version 1

Protocol Title: A Multicenter, Open-label, Single-arm, Study to Evaluate Safety and Tolerability of Repatha in Patients With Homozygous Familial Hypercholesterolemia (HoFH) in India

Amgen Protocol Number (evolocumab) 20170199

Superseding Version Date: 16 August 2017

Rationale:

A superseding version of this protocol has been drafted to address the following errors identified after publication of the original protocol (dated 04 August 2017):

- In the Schedule of Activities (Table 2-1) additional visits were added to the table to account for subjects on apheresis (weeks 2 and 6). During the update of the table, the scheduled visits for vital signs and 2 laboratory assessments were not moved accordingly to week 8 (they were mistakenly left at the renamed column for week 4).
- Contraception guidance provided in exclusion criteria 205 required alignment with the information provided in Appendix 5.
- In addition, administrative updates were made to account for this superseding version.

Description of Changes

Section: Global

Change: Updated version date from 04 August 2017 to **16 August** 2017.

Section: Title Page

Add:

Protocol Date:	Document Version	Date
	Original	04 August 2017
	Superseding Version 1	**16 August 2017**

Section: 2.2 Schedule of Activities, Table 2-1

Replace:

Procedure	Screening (up to 4 weeks before day 1)	Treatment Period					Follow-up	Notes
		W1 (day 1)	W2[a]	W4[b]	W6[a]	W8	W12[c]	
General and Safety Assessments								
Vital signs (BP, HR)	X	X		X			X	
Laboratory Assessments[f]								
Fasting lipids, ApoA1, ApoB	X	X		X			X	
Lp(a)	X	X		X			X	

With:

Procedure	Screening (up to 4 weeks before day 1)	Treatment Period					Follow-up	Notes
		W1 (day 1)	W2[a]	W4[b]	W6[a]	W8	W12[c]	
General and Safety Assessments								
Vital signs (BP, HR)	X	X				**X**	X	
Laboratory Assessments[f]								
Fasting lipids, ApoA1, ApoB	X	X				**X**	X	
Lp(a)	X	X				**X**	X	

Section: 6.2 Exclusion Criteria

Replace:

205 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception or acceptable method of effective contraception during treatment and for an additional 15 weeks after the last dose of Repatha. Refer to Appendix 5 for additional contraceptive information.

With:

205 Female subjects of childbearing potential unwilling to use **an** acceptable method of effective contraception during treatment and for an additional 15 weeks after the last dose of Repatha. Refer to Appendix 5 for additional contraceptive information.