Title: A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab

Amgen Protocol Number: 20140128
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Date: 23 June 2014

Amendment 1 date **22 December 2014**

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NCT Number: 02304484
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Investigator's Agreement

I have read the attached protocol entitled "A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab", dated **22 December** 2014, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines. I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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 Principal Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab

Study Phase: *3*

Indication: Hypercholesterolemia

Primary Objective: To characterize the safety and tolerability of long-term administration of evolocumab in subjects with known coronary artery disease and hypercholesterolemia

Secondary Objectives:

To characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C in subjects with known coronary artery disease and hypercholesterolemia

Hypotheses: The primary clinical hypothesis is that long-term exposure of evolocumab will be safe and well tolerated in subjects with known coronary artery disease and hypercholesterolemia. There will be no formal statistical testing done to evaluate the primary endpoint, rather all statistics will be descriptive in nature.

Primary Endpoint:

Subject incidence of adverse events

Secondary Endpoint:

LDL-C at week 52

Study Design: This is a multicenter, open-label extension study designed to assess the long-term safety and efficacy of evolocumab. Subjects who completed study 20120153 and completed **Investigational Product (**IP**)** in 20120153 will be eligible to enroll in this study. To prevent unblinding the parent study, lipid results will remain masked to investigators, site staff, subjects, and the study team for the first 12 weeks of the study; subjects must remain on the same type and dose of background lipid lowering therapy from the parent study (20120153). Atorvastatin will be provided for the first 12 weeks to all subjects that previously elected to receive sponsor-provided atorvastatin in the parent trial. All subjects not on sponsor provided atorvastatin must continue to receive the same statin at the same dose for the first 12 weeks. After week 12, lipid results will be unmasked and investigators may alter background lipid-regulating therapy per local standards of care. All subjects will receive open-label evolocumab for approximately 2 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason or until an administrative decision is made to close the study).

Sample Size: The number of subjects entering this study will depend on the number of subjects completing the parent study (20120153) and subsequent willingness to enroll**.** Approximately 642 subjects are expected to participate in this study.

Estimated Study Duration: Approximately 2 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

Summary of Subject Eligibility Criteria: Subjects who completed study 20120153 and completed IP in 20120153 will be eligible for this study. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration: Subjects will administer evolocumab 420 mg SC QM injections using 3 spring-based prefilled 1.0 mL autoinjector/pens (prefilled AI/Pen) or with a 3.5 mL Automated Mini-Doser (AMD)/Personal Injector. Nonetheless, until laboratory results are unmasked at week 12, subjects must remain on the same background lipid lowering therapy from the parent study, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After 12 weeks, lipid results will be unmasked and investigators may alter background lipid-regulating therapy per local standards of care.

Non Amgen Investigational Product Dosage and Administration: None

Control Group: No control group will be used in this open-label study.

Procedures: Prior to enrolling in this study, subjects will need to completed study 20120153 and completed IP in 20120153. In addition, subjects will need to meet inclusion/exclusion criteria requirements. Subjects will need to sign a new study informed consent form. Subject identification numbers will be the same as those in their parent protocol.

Subjects will visit the site on Day 1 and week 4. Thereafter, subjects will visit the site quarterly for the first year and two additional times during year 2. During these visits vital signs will be **obtained and** adverse events (AEs), serious adverse events (SAEs), concomitant medications will be recorded, and central laboratory tests will be performed for all subjects. **In addition to the protocol-specified study procedures and assessments, investigators should continue to routinely monitor subjects according to local disease management guidelines and perform assessments (eg. ECG, hemoglobin A1c, eGFR, and hematology), as applicable, in routine care.** For a full list of study procedures, including the timing of each procedure, please refer to Section 7.2.

Statistical Considerations

General Considerations

Statistical analyses in this open-label extension study will be descriptive in nature.

There will be a 1-year interim analysis to summarize the data collected in the study period (up to week 52) after all subjects complete the week 52 visits. Additional analyses may be conducted after study 20120153 is closed and individual subjects are unmasked to their lipid values and/or unblinded to treatment assignment.

For all endpoints, results will be summarized by the treatment group to which subjects are randomized in Study 20120153. Unless otherwise specified, the baseline value is defined as the subject's baseline value from the parent study.

The full analysis set (FAS) will include all subjects enrolled in this study. All analyses will be performed using the FAS, unless otherwise specified. There will be no imputation for missing data.

Deaths and major cardiovascular events will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of adjudicated events will be summarized for each treatment group.

Analyses of Primary Endpoint

AEs will be coded using the latest version of MedDRA. Subject incidence of adverse events, serious adverse events, and adverse events leading to withdrawal of the investigational product will be tabulated by system organ class and preferred term.

Analyses of Secondary Endpoints

Secondary endpoints will be summarized at week 52. Descriptive statistics will be presented and differences in group means for the secondary endpoints will be estimated at each scheduled visit.

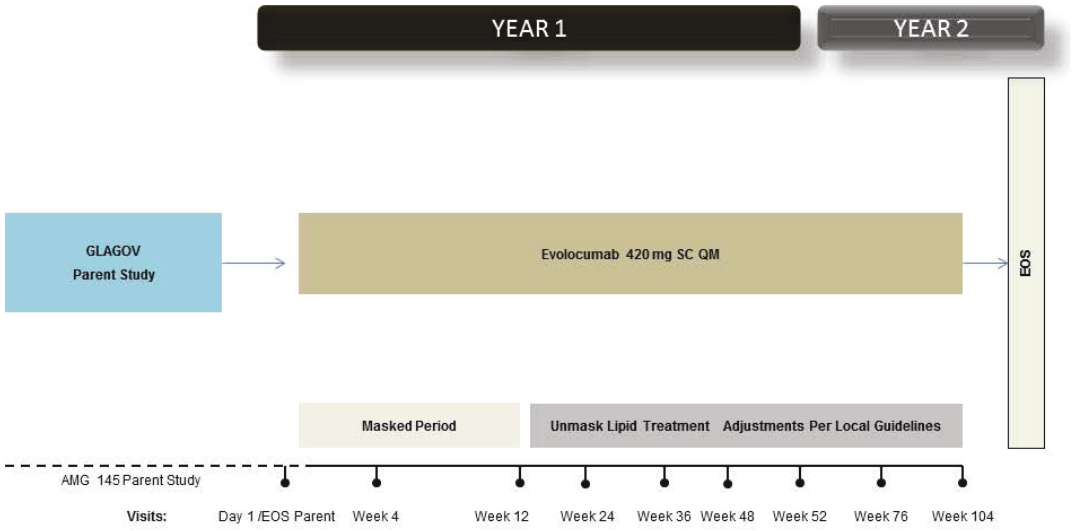
Other Safety Analyses

Measurements of laboratory parameters and vital signs will be summarized at each scheduled visit. Lab shift tables will be provided.

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

Sponsor: Amgen

Study Design and Treatment Schema



QM Administration of AMG Evolocumab

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	Adverse device effect
AE	Adverse event
AHA	American Heart Association
AI/Pen	1.0 mL Prefilled Autoinjector/Pen
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AMD	3.5 mL Automated Mini Doser / 3.5 mL Personal Injector
AMG 145	Evolocumab
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AUC	Area under the curve
BP	Blood pressure
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Events Committee
CK	Creatine kinase
CHD	Coronary heart disease
C_{max}	Mean maximum measured concentration
CRP	C-reactive protein
CVD	Cardiovascular disease
CTCAE	NCI Common Terminology Criteria for AEs
Day 1	Defined as the first day that protocol-specified investigational product is administered to the subject.
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	**estimated Glomerular Filtration Rate**
End of treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	End-of-study for individual subject
EU	European Union
FAS	Full analysis set
FH	Familial hypercholesterolemia

Abbreviation or Term	Definition/Explanation
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HbA1c	**Hemoglobin A1c**
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IP	Investigational product (evolocumab/AMG 145)
IPIM	Investigational Product Instruction Manual
IV	Intravenous
IVUS	Intravascular Ultrasound
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LH	Luteinizing hormone
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOF	Loss of function
Lp(a)	Lipoprotein(a)
LSP	Lactation Surveillance Program
MedDRA	Medical dictionary for regulatory activities
NASH	Nonalcoholic steatohepatitis
NCEP	National Cholesterol Education Program
NCEP ATP II	NCEP Adult Treatment Panel II (see References)
OLE	Open-Label Extension
PCSK9	Proprotein convertase subtilisin/kexin type 9
PKPD	Pharmacokinetic / pharmacodynamic
Q4W	Every 4 weeks, (Evolocumab/AMG 145 Background Section)
QM	Monthly (QM) is defined as every 4 weeks with a window of ± 7 days for each visit
SAE	Serious adverse event
SC	Subcutaneous
SOC	Standard of care

Abbreviation or Term	Definition/Explanation
TBL	Total bilirubin
T_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

TABLE OF CONTENTS

Page

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

To characterize the safety and tolerability of long-term administration of evolocumab in subjects with known coronary artery disease and hypercholesterolemia

1.2 Secondary

- To characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C in subjects with known coronary artery disease and hypercholesterolemia

1.3 Exploratory

- To evaluate cardiovascular event rates in subjects treated with evolocumab.

2. BACKGROUND

Cardiovascular disease (CVD) remains the most important healthcare issue in the developed world and is rapidly becoming so in large parts of the developing world. Despite the availability of several classes of very effective drugs, dyslipidemia and risk factor control are poorly served and there remains a large unmet medical need for new, effective and well tolerated therapies.

AMG 145 (evolocumab) is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), nonclinical toxicology , and data from five P2 and six P3 clinical trials are contained in the Investigator's Brochure, 2013.

Over the course of the last three decades, considerable technological advances in arterial imaging have permitted visualization of the full extent of atherosclerotic plaque. Intravascular ultrasound (IVUS) used in the parent trial (study 20120153) involves the placement of high frequency ultrasound transducers within the coronary artery lumen, generating high resolution imaging of the full thickness of the artery wall. In general IVUS clinical trials have demonstrated disease progression, in direct association with LDL-C levels. Study 20140128 is a global phase 3 study that will provide long-term safety and efficacy data for evolocumab in a high risk subject population with known coronary artery disease receiving evolocumab in combination with statin and other background lipid lowering therapy. Patients that successfully complete parent study 20120153 will be eligible to participate in this 2 year trial.

2.1 Rationale

This study is being conducted in order to provide high risk subjects that successfully completed study 20120153 (GLAGOV – an 18 month placebo controlled trial) an opportunity to receive evolocumab for 2 years. Participation in this open-label extension will provide close medical supervision via healthcare professionals while on current standard of care therapies and an opportunity to receive an additional therapeutic option for LDL-C lowering.

2.2 Clinical Hypotheses

The primary clinical hypothesis is that long-term exposure of evolocumab will be safe and well tolerated in subjects with known coronary artery disease and hypercholesterolemia. There will be no formal statistical testing done to evaluate the primary endpoint, rather all statistics will be descriptive in nature.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, open-label extension study to assess the long-term safety and efficacy of evolocumab.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

It is anticipated that approximately 230 sites in the US, Canada, Latin America, Asia, Australia, South Africa, and Europe will participate in the study. The number of sites may vary depending on the number of subjects from the parent study (20120153).

3.3 Number of Subjects

The number of subjects entering this study will depend on the number of subjects completing the parent study and their willingness to enroll. The number of subjects expected to participate in this study is approximately 642.

3.3.1 Study Duration for Participants

Subjects that successfully complete Week 80 in the parent study (20120153) without discontinuing evolocumab will be eligible to enroll in this study. Subjects will visit the site on Day 1 and week 4. Thereafter, subjects will visit the site quarterly for the first year and two additional times during year 2. All subjects will receive open-label evolocumab for approximately 2 years (or until the investigator's recommendation of discontinuation,

Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason or until an administrative decision is made to end the study).

3.3.2 End of Study

The study will continue for approximately 2 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is made to end the study).

4. SUBJECT ELIGIBILITY

The study population will consist of male and female subjects who successfully completed study 20120153 and completed IP (evolocumab) in 20120153.

4.1 Inclusion Criteria

Subjects will be eligible for the study if they:

1. Completed study 20120153.

4.2 Exclusion Criteria

Subjects will be **ineligible** for the study if they fulfill any of the following criteria:

1. Female subject of reproductive potential not willing to inform her sexual partner of her participation in the clinical study and to use an acceptable method(s) of **effective** birth control during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab. Female subjects who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal are not required to use contraception.
    - Postmenopausal is defined as: Age $\geq$ 55 years with cessation of menses for 12 months or more; Age < 55 by no spontaneous menses for at least 2 years; Age < 55 years and no spontaneous menses within the past 1 year, but currently amenorrheic AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
    - Acceptable methods of **effective birth control include: sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception]),** surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR Cervical cap with spermicide, OR Contraceptive sponge with spermicide.

- *Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.*

2. Subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during treatment with evolocumab and within 15 weeks after the end of treatment with evolocumab
3. Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (eg, inability or unwillingness to adhere to the protocol)
4. Did not complete IP in the parent study 20120153
5. Disorder that would interfere with understanding and giving informed consent or compliance with protocol requirements
6. Have an unstable medical condition, in the judgment of the investigator
7. Subject's medical condition requires lipid measurement and/or adjustment of background lipid-regulating therapy during the first 12 weeks of study participation
8. Known sensitivity to any of the products to be administered during dosing
9. Currently enrolled in another investigational device or drug study (excluding evolocumab parent study), or less than 30 days since ending another investigational device or drug study(s),or receiving other investigational agent(s)

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee and/or institutional review board (IEC/IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form before commencement of study specific procedures. A subject is considered enrolled once they have completed their end of study visit in the parent protocol and signed the informed consent form.

All subjects who enter the study will keep the same subject identification number from the parent study.

6. TREATMENT PROCEDURES

Evolocumab (AMG 145) will be the investigational product (IP) in this study.

An Investigational Product Instruction Manual (IPIM) containing detailed information regarding the storage, preparation, and administration of the investigational product will be provided separately.

6.1 Evolocumab (AMG 145)

AMG 145 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. AMG 145 will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) 1.0 mL prefilled autoinjector/pen (AI/Pen) or 3.5 mL AMD/Personal Injector for fixed dose, subcutaneous injection. The prefilled AI/Pen contains a 1.0 mL deliverable volume of CCI mg/mL AMG 145 in CCI mM proline, CC mM acetate, CCI (w/v) polysorbate 80, pH CC. The AMD with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith (CZ) cartridge assembly containing 3.5 mL deliverable volume of CCI mg/mL AMG 145 in CCI mM proline, C CI mM acetate, CCI (w/v) polysorbate 80, pH CC. The 3.5 mL AMD/Personal Injector will only be made available for use in this study once it has been determined that the intended user population for AMG 145 can safely and effectively use the device in clinical trials under the guidance of the study investigators.

AMG 145 should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required). AMG 145 should be handled per the instructions provided in the IPIM and the Instructions for Use (IFU) for the prefilled AI/Pen or AMD.

The prefilled AI/Pen or AMD should be inspected for IP quality, expiry, and damage before using. Damaged, expired, or degraded product should not be used and any issues with the prefilled AI/Pen or AMD should be reported to Amgen. Further details are provided in the IPIM and IFU.

6.1.1 Dosage, Administration, and Schedule

IP will be administered at the investigator site during scheduled visits via self-administration or by a qualified staff member. Between scheduled visits to the site, IP will be administered at home or other locations by subjects (or designee, which may include a qualified health care professional) in accordance with instructions in the IPIM. Subjects who prefer not to self-administer IP may return to the study site for administration by qualified site personnel.

IP administration at each on-site visit must be done after vital signs, ECG, and blood draw procedures, if applicable. The date, time, and volume of evolocumab administered will be collected and recorded on the individual subject's electronic Case Report Form (eCRF) for doses administered at the study site. During the first two IP administrations

(day 1 and week 4), subjects will be kept for observation for at least 30 minutes before being discharged.

Self-administration, defined as SC administration of IP by the subject or designee, will occur on a monthly basis between visits to the investigator site (eg, at home). The patient (or designee) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first two self-administered doses must be administered in a clinic by the patient or designee under the supervision of a healthcare provider.

IP will be administered with a total volume of 3.0 mL QM, via 3 separate autoinjections or with a total volume of 3.5 mL QM via 1 administration by a AMD. Injection sites should be rotated throughout the study. The autoinjector SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

Details of preparing and administering all study products are included in the IPIM provided by Amgen prior to the start of the study.

6.1.2 Dosage Adjustments

Dose adjustments during the study (including discontinuation of IP) are discouraged, but will be permitted for subjects that experience intolerable adverse events. If an investigator wants to make a dose adjustment they must contact the medical monitor prior to doing so. All dose adjustments must be clearly documented and recorded on the appropriate eCRF page and in the source documents.

Subjects who are Late for a Scheduled Dose of Investigational Product (evolocumab)
Administration of IP should occur within the visit window for each scheduled dose. IP must never be administered within less than 7 days of a previous dose.

Subjects who Miss a Scheduled Dose of Investigational Product Completely
Subjects that completely miss a scheduled IP administration will continue in the study and receive scheduled IP at the next scheduled administration. However, this must be clearly documented both in the source documents and the case report forms.

6.1.3 Background Lipid-Lowering Therapy

Considering the patient population enrolled in GLAGOV (Study 20120153), subjects should receive optimized lipid-lowering therapy during the OLE. Lipid therapy should remain unchanged for the duration of Study 20120153 participation (up to 18 months) and for an additional 12 weeks in the OLE; local guidelines should be taken into consideration when determining optimal levels of treatment.

6.1.4 Criteria for Withholding of Investigational Product

Reports from the central laboratory after each clinic visit must be reviewed as soon as possible after receipt and before the next administration of IP (evolocumab). If any of the criteria below are met for withholding IP, statin, or other applicable background lipid therapy, the subject must be instructed to stop the applicable treatment and an additional visit must be scheduled for the required laboratory evaluations. If a subject is experiencing elevations of laboratory values and is receiving other lipid therapies that may result in such elevations, eg, ezetimibe or niacin, the additional therapies should also be evaluated for a potential role in these elevations and considered for discontinuation. Ezetimibe or niacin can result in elevation of CK or liver function tests.

6.1.4.1 Elevation of Creatine Kinase (CK)

If CK is > 5x ULN, CK must be retested before IP is administered. In addition, investigators will ask study subjects to promptly report muscle pain, soreness, cramps, or weakness especially if accompanied by malaise or fever. If such symptoms occur and no scheduled study laboratory assessments are performed, the subject's CK levels should be measured by unscheduled assessment. If CK is > 5x ULN, the subject must be instructed as soon as possible to discontinue statin, other applicable lipid background therapy, and/or Amgen IP (evolocumab). CK must be retested before statin, other lipid background therapy, and/or IP (evolocumab) administration can be continued. A sample for urinalysis must be collected and sent to the central laboratory if CK is elevated > 10x ULN on retest as per table below.

The following rules apply for scheduled laboratory assessments and for unscheduled CK measurements:

CK at scheduled or unscheduled visit	CK on retest	Investigational Product and/or Statin and/or other lipid lowering therapies Administration
> 5x ULN	> 10x ULN	Discontinue both statin, other lipid lowering therapies, and IP[a]. Collect urine sample for urinalysis. Contact Amgen Medical Monitor.
	> 5x to ≤ 10x ULN	Discontinue statin, other lipid lowering therapies, and retest CK before administration. Consider continuing IP if alternative explanation.
	≤ 5x ULN	Consider continuing statin, other lipid lowering therapies and IP

[a] CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation of statin, other lipid lowering therapy or IP

6.1.4.2 Elevation of Liver Function Tests

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL], or international normalized ratio [INR] or signs/symptoms of hepatitis may meet the criteria for withholding of IP, statin, and other applicable lipid background therapy. If the subject experiences an ALT or AST > 3X ULN, then they must be followed as detailed under section on close observation in Appendix A.

IP, statin and other applicable lipid background therapy must be discontinued and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x upper limit of normal (ULN) or INR > 1.5

AND

- AST or ALT > 3x ULN

AND

- no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic steatohepatitis (NASH) or other fatty liver disease

IP, statin and other applicable lipid background therapy should also be withheld and the subject should be evaluated for DILI if ANY of the following criteria are met:

- AST or ALT > 8x ULN at any time
- AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks
- TBL > 3x ULN at any time

- ALP > 8x ULN at any time
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3x ULN, IP should be withheld.

If IP, statin and other applicable lipid background therapy is withheld due to any of the conditions above, the subject should be followed according to recommendations in Appendix A for possible DILI.

6.1.4.3 Criteria for Rechallenge After Withholding or Discontinuation of IP (Evolocumab), Statin and Other Applicable Lipid Background Therapy

The decision to re-challenge the subject after therapy changes due to CK elevation or elevation of liver function tests should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen.

If signs or symptoms recur with rechallenge of IP, then IP should be permanently discontinued. If signs or symptoms recur with rechallenge of statin background therapy, the statin may be substituted by another statin in consultation with the Amgen medical monitor, if possible, or the statin therapy may be discontinued. If signs or symptoms recur with rechallenge of other applicable lipid background therapy, this therapy may be discontinued.

6.2 Background Atorvastatin Lipid-Lowering Therapy

Atorvastatin will be provided for the first 12 weeks of this study for subjects who were taking Amgen-supplied atorvastatin in the parent study GLAGOV and continue into this extension study.

All other lipid-regulating drugs that are allowed per protocol and prescribed for the subject, must be commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs.

6.3 Medical Devices

IP will be administered per via three prefilled AI/Pens or one 3.5 AMD, provided by Amgen (Section 6.1). Additional details regarding the use of the AI/Pens and the 3.5 mL AMD are provided in the IPIM and in the Instructions for Use (IFU) brochure.

Medical supplies (eg, alcohol prep pads), 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 these necessary medical supplies.

6.4 Product Complaints, Including Device Complaints

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

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

Concerns or irregularities about the packaging, appearance or usage of the prefilled AI/Pen or AMD or other Amgen provided, protocol-required product in this study are to be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity. Should any such concerns or irregularities occur please do not use the IP until Amgen confirms that it is permissible to use.

Examples of potential product complaints that need to be reported to Amgen include, but are not limited to:

- broken container or cracked container
- usage of the AI/pen due to misunderstanding of the IFU or error on the part of the user, or other inability to appropriately use the product
- devices: issues with delivery of IP by device or malfunction of the AI/pen or 3.5 mL AMD (eg, bent or broken needle, cracked or broken barrel, etc.)
- missing labels, illegible labels, incorrect labels, and/or suspect labels
- change in IP appearance, for example color change or visible presence of foreign material
- unexpected quantity or volume, for example number of tablets or amount of fluid in the prefilled AI/Pen or 3.5 mL AMD cartridge
- evidence of tampering or stolen material

If possible, please have the AI/Pen or 3.5 mL AMD cartridge or other Amgen provided protocol-required suspect product available for examination when making a product complaint. Maintain AI/Pen or 3.5 mL AMD cartridge or other Amgen provided protocol-required suspect product at appropriate storage conditions until further instructions are received from Amgen.

The investigator is responsible for ensuring that all product complaints observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of IP or EOS, whichever is later, are reported to Amgen within 24 hours of discovery or notification of the product complaint.

For more details regarding the identification and reporting of product and device complaints, refer to the IPIM and the IFU.

6.5 Concomitant Therapy, Physical Exercise, and Diet

Prior to week 12 lipid-regulating concomitant lipid-regulating medications cannot be altered (since lipid testing is prohibited), unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After the masked period (Week 12 visit), laboratory results (Section 7.2.2.4) will no longer be masked and investigators may alter background lipid-regulating therapy per local standards of care. All subjects should maintain their current regimen of diet and exercise for at least the first 12 weeks of the study, but should also be encouraged to continue to do so through the remainder of the study. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting, long runs or other strenuous activity) 48 hours prior to each visit since such activity could affect creatine kinase levels.

6.6 Excluded Treatments During Study Period

The use of magnesium or aluminum hydroxide-containing antacids is not recommended within the period of two hours before and two hours after dosing with statins given the potential for interference with absorption.

7. STUDY PROCEDURES

Subjects that successfully complete study 20120153 and completed IP (evolocumab) in study 20120153 will be eligible to enroll in this study. In addition, subjects will need to meet eligibility criteria. Subjects will need to sign a new study informed consent form. Subject numbers will be the same as those in their parent study. Subjects will visit the site on Day 1 and week 4. Thereafter, subjects will visit the site quarterly for the first year and two additional times during year 2. During these visits vital signs will be obtained and adverse events (AEs), serious adverse events (SAEs), concomitant medications will be recorded, and central laboratory tests will be performed. All subjects will receive open-label evolocumab for approximately 2 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is

made to close the study).For the purpose of this study, a month is defined as 4 weeks and a quarter is defined as 12 weeks.

Written informed consent must be obtained and will be implemented before protocol specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential subject prior to entering into the study. The procedures to be performed at each clinic visit are described below. IP should not be administered until all study procedures are completed at each visit. Subject visit schedule will be the same for all subjects. **In addition to the protocol-specified study procedures and assessments described below, investigators should continue to routinely monitor subjects according to local disease management guidelines and perform assessments (eg. ECG, hemoglobin A1c, eGFR, and hematology), as applicable, in routine care.**

7.1 Schedule of Assessments

	YEAR 1				YEAR 2	
Study Day / Timepoint	EOS Parent Day 1 OLE [a]	Week 4	Quarterly Visits Weeks: 12, 24, 36, and 48	Week 52	Month 6 (Week 76)	Year 2 (Wk 104) EOS/ET OLE[e]
General Procedures						
Medical History	X					
Informed consent	X					
Vital Signs (HR, BP)	X	X	X	X	X	X
AEs/SAEs/CV Events	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Body Weight	X			X		X
Waist circumference	X			X		X
Physical exam	X			X		X
Central Laboratory						
Fasting Lipids	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X
Serum pregnancy (females of childbearing potential) and FSH	X[b]	X[c]	X[c]	X[c]	X[c]	X
Investigational Product						
IP dispense[d]	X	X	X	X	X	
IP reconcile	X	X	X	X	X	X

[a] D1 = day of first administration of investigational product for the open-label extension (OLE); subjects will sign a new OLE consent.

[b] FSH = in applicable subjects for study entry only – see exclusion criteria

[c] Serum pregnancy testing will occur at week 4,week 24, week 52, and every 6 months thereafter.

[d] Subjects or caregivers will administer evolocumab monthly both at site visits and between site visits. Last IP will be administered at week 100.

[e] The EOS procedures should be used as a guide for the depth of information obtained for any subject that elects to discontinue IP but continue via follow-up (see section 8).

7.2 General Study Procedures

7.2.1 Enrollment (Week 80 Parent/Day 1 OLE + 14 days)

Day 1 for OLE study and the week 80 visit for the parent study should occur on the same day. All efforts should be made to minimize any time gaps between the parent study EOS and Day 1 in the OLE study. The following procedures will be performed:

- Obtain consent
- Medical History
- Vital signs: sitting blood pressure (BP), heart rate (HR)

- AEs/SAEs/CV Events
- Concomitant medications
- Body weight and waist circumference
- Physical exam
- Blood draw for serum pregnancy (females of childbearing potential only) and FSH (for applicable subjects)
- Blood draw for fasting lipids (≥ 9 hour fasting sample) and chemistry
- Dispense and reconcile IP
- Observe IP Administration evolocumab (AMG 145) QM unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures).

Enrollment - subjects will have the risks and benefits of participating in this study explained to them. Subjects that meet inclusion/exclusion criteria will need to sign a new OLE informed consent form, if they already have not done so, before enrolling. Subjects will administered their first injection at the site (must be after completion of vital signs and blood draw procedures). Self-administration, defined as SC administration of IP by the subject or designee, will occur between visits to the investigator site (eg, at home). The patient (or designee) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first two self-administered doses must be administered in a clinic by the patient or designee under the supervision of a healthcare provider. Day 1 is defined as the first day that protocol-specified investigational product is administered.

The following visits are for Year 1 only:

7.2.1.1 Week 4 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/SAEs/CV Events
- Concomitant medications
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample) and chemistry
- Dispense and reconcile IP
- Observe IP Administration (evolocumab/AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures)

7.2.1.2 Weeks 12, 24, 36, and 48 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/SAEs/CV Events
- Concomitant medications

- Blood draw for serum pregnancy (performed at week 24 for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample) and chemistry
- Dispense and reconcile IP
- Observe IP Administration (evolocumab/AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures)

7.2.1.3 Week 52 - End of Year 1 Visit (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/SAEs/CV Events
- Concomitant medications
- Body Weight and waist circumference
- Physical exam
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample) and chemistry
- Dispense and reconcile IP
- Observe IP Administration (evolocumab/AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures)

The following visits are for Years 2:

7.2.1.4 Week 76 Month 6/Year 2 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/SAEs/CV Events
- Concomitant medications
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample) and chemistry
- Dispense and reconcile IP
- Observe IP Administration (evolocumab/AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures).

7.2.1.5 Week 104 (± 7 days)/End of Study/Early Term OLE Visit

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/SAEs/CV Events
- Concomitant medications
- Body weight and waist circumference
- Physical exam
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample) and chemistry
- Reconcile IP

Completion of the study is defined as the last day that protocol-specified procedures are conducted for an individual subject. At the end of the study, vital status must be obtained for all subjects within the limits of local law. It is preferable that all end of study procedures are carried out. Subjects who are not deceased, have not withdrawn consent, or are not lost to follow-up, should have at minimum an End of Study assessment for Vital Status (alive or deceased), Adverse Events, Serious Adverse Events, and Potential Endpoints. Sites should interrogate public databases, if necessary to obtain this information. If deceased, the date and reported cause of death should be obtained.

Subjects will also be monitored for very low LDL-C (< 25 mg/dL [0.6 mmol/L]).

7.2.2 Standardization of Study Procedures

7.2.2.1 Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) should be measured at each visit. BP should continue to be measured in the same arm as in the parent study unless a concomitant condition favors the use of a different arm. The appropriate size cuff should be used. The diastolic blood pressure (DBP) will be recorded as the pressure noted when sound disappears (Korotkoff Phase V). Blood pressure and heart rate measurements should be determined after the subject has been seated for at least 5 minutes. The subject's pulse should be measured for 30 seconds and the number should be multiplied by 2 to obtain heart rate.

7.2.2.2 Waist Circumference

Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or ½ inch and entered in the source document.

7.2.2.3 Blood Sample Use

Any blood sample collected according to the Schedule of Assessments (Section 7.1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

Amgen may do additional testing on the remaining samples (ie, residual and back-up) to investigate and better understand hypercholesterolemia metabolic disorders, the dose response and/or prediction of response to evolocumab, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

7.2.2.4 Lipid Measurements

Central laboratory lipid results will be masked to investigators, subjects, and the study team until the week 12 visit is completed. Investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels between week 80 of the parent study and week 12 of the extension study. Consequently, lipid lowering concomitant medications may not be adjusted based upon such results, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After the week 12 visit occurs, central laboratory results will be available to sites and investigators may alter background lipid-regulating therapy per local standards of care. If a lipid panel is drawn prior to week 12, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

Subjects will also be monitored for very low LDL-C (< 25 mg/dL [0.6 mmol/L]).

7.2.2.5 Laboratory Assessments

All on-study laboratory samples will be processed and sent to the central laboratory.

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all blood samples. The date and time of sample collection will be recorded in the source documents at the site.

Table 1 below outlines the specific analytes for serum chemistry, hematology, and other testing to be conducted.

Table 1. Analyte Listing

Chemistry	Other Labs
Sodium	Fasting lipids • Total cholesterol • HDL-C • LDL-C • Triglycerides • VLDL-C • non-HDL-C
Potassium	FSH
Chloride	Pregnancy test
Bicarbonate	Anti-evolocumab antibodies (drawn per investigator's discretion for safety assessments)
Total protein	
Albumin	
Calcium	
Magnesium	
Phosphorus	
Glucose	
BUN or Urea	
Creatinine	
Uric acid	
Total bilirubin	
Direct bilirubin	
CK	
ALP	
LDH	
AST (SGOT)	
ALT (SGPT)	

Investigators may not adjust lipid lowering background therapy until the week 12 (Quarter 1) visit is conducted (Section 6.5). Furthermore, central laboratory lipid results will not be reported to the investigator prior to week 12 since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study. Investigators should not perform local testing of these analytes.

7.2.3 Sample Storage and Destruction

All samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to hypercholesterolemia, metabolic disorders, and/or evolocumab. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor will be 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 principal investigator or 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). Following the request from the subject, the principal investigator will provide the sponsor

with the required study and subject numbers so that any remaining plasma and blood samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw from the treatment, procedures, or study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of full 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 including any follow-up in person, by phone, through 3rd parties including relatives or friends, via discussion with other treating physicians, and by use of medical records; subject data up to withdrawal of full consent will be included in the analysis of the study. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study. The investigator should ask the subject's consent to perform the procedures listed under the final study visit.

Subjects may decline to continue receiving IP or other protocol-required procedures at any time during the study. If this occurs, the investigator will discuss with the subject appropriate procedures for discontinuation from IP or other protocol-required procedures and should encourage the subject to continue with collection of data, including endpoints and adverse events. These subjects, as well as those who have stopped receiving IP or other protocol-required procedures for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations. If the subject is unable or unwilling to continue the schedule of observation, the investigators should clarify what type of follow-up the subject is agreeable to: in person, by phone/mail, through family/friends, in correspondence/communication with other physicians, and/or from review of the medical records. For these subjects, the EOS procedures should be used as a guide for the depth of information obtained for any subject that elects to continue via follow-up.

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Reasons for removal from protocol-required investigational product include**, but are not limited to**:

- withdrawal of full consent
- subject request to end investigational product administration
- administrative decision by Amgen (other than subject request or safety concern)
- decision by the primary investigator / physician
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix C)
- safety concern (eg, adverse event)
- death

8.2 Replacement of Subjects

There will be no replacement of subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

An adverse device effect (ADE) is any adverse event related to the use of a 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.

9.1.2 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

All adverse events (see Section 9.2 – serious adverse events) are reported after signing of the informed consent. 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 are reported using the applicable eCRF (eg, Adverse Event Summary eCRF), including events that are also reported to the CEC for adjudication.

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 [and/or toxicity per protocol],
- Assessment of relatedness to Amgen investigational product (evolocumab), or other protocol-required therapies
- Assessment of relatedness to the Amgen device (prefilled AI/Pen or 3.5 mL AMD/Personal Injector), and
- Action taken.

The adverse event toxicity grading scale used will be the NCI Common Terminology Criteria for AEs (CTCAE) grading score. The toxicity grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to Amgen IP: evolocumab and/or other protocol-required therapies. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by Amgen IP: evolocumab and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to the Amgen device: Prefilled AI/Pen or 3.5 mL AMD/ Personal Injector used to administer (evolocumab) IP. The relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the Amgen device?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity/procedure”?

The investigator is responsible for reviewing laboratory test results and determining 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) should not 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) should be recorded as the adverse event.

The investigator's clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject, or subject's parent/legal guardian, may also voluntarily withdraw from treatment/protocol required therapies due to an adverse event, refer to section 8.1 for additional instructions on the procedures recommended for safe withdrawal from treatment/protocol required therapies or the study. If the subject withdraws full consent, the subject should be encouraged to undergo, at a minimum, an end-of-study assessment.

The investigator is expected to follow any reported adverse events until resolved, improved to baseline, or stabilized.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury

(see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 “life threatening” CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator’s judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the subject’s medical record.

9.2.2 Reporting Procedures for 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 30 days after the last dose of IP or EOS, whichever is later, are recorded in the subject’s medical records and are submitted to Amgen, including events that are also reported to the CEC for adjudication. All serious adverse events must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the applicable eCRF (eg Serious Adverse Event Report Form).

The serious adverse event must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the applicable Serious Adverse Event Report Form. See Appendix B for a sample of the Serious Adverse Event Report Form.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event 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 for the purposes of expedited reporting.

The investigator must assess whether the serious adverse event is possibly related to Amgen IP: evolocumab or other protocol-required therapies. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by Amgen IP (evolocumab) or other protocol-required therapies?

The investigator must assess whether the serious adverse event is possibly related to the Amgen device: Prefilled AI/Pen or 3.5 mL AMD/Personal Injector used to administer IP (evolocumab). The relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the Amgen device?

The investigator must assess whether the serious adverse event is possibly related to any other study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until resolved, improved to baseline, or stabilized.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

If a subject is permanently withdrawn from the protocol required therapies because of a serious adverse event, this information must be submitted to Amgen within 24 hours.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

The investigator is to notify the appropriate IRB/EC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through an additional 15 weeks after the end of treatment with IP (evolocumab).

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through an additional 15 weeks after the end of treatment with IP (evolocumab).
Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of the event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Primary Endpoint

Subject incidence of adverse events

10.1.2 Secondary Endpoint

- LDL-C at week 52

10.1.3 Exploratory Endpoints

- Subject incidence of adjudicated events
  - Subject incidence of adjudicated events
  - death by any cause
  - cardiovascular death
  - myocardial infarction
  - hospitalization for unstable angina
  - coronary revascularization
  - stroke
  - transient ischemic attack (TIA)

  - hospitalization for heart failure
- Subject incidence of non-coronary revascularization
- Change and percent change from baseline at each scheduled visit in each of the following parameters:
  - LDL-C
  - Total cholesterol
  - Non-HDL-C
  - Total cholesterol/HDL-C ratio
  - VLDL-C
  - HDL-C
  - Triglycerides

10.1.4 Safety Endpoints

- Changes from baseline in safety laboratory values (including clinical chemistry) and vital signs at each scheduled visit

10.1.5 Analysis Set

The full analysis set (FAS) includes all subjects enrolled in this study. This analysis set will be used for all analyses**.**

10.1.6 Baseline Covariates

Baseline covariates include, but are not limited to:

- Age
- Gender
- Ethnicity or race
- LDL-C
- Lipid modifying background therapy (eg statin, ezetimibe)

10.2 Sample Size Considerations

The number of subjects entering this study will depend on the number of subjects completing the study 20120153 and willingness to enroll. The enrollment rate of subjects entering other AMG 145 open label extension studies in the past was about 90%. Assuming 75% of the subjects will complete study 20120153 and be eligible to enroll in this extension study, the sample size will be 950 x 0.75 x 0.9 = 642 subjects.

10.3 Interim Analysis and Early Stopping Guidelines

There will be a 1-year interim analysis to summarize the data collected in the study period (up to week 52) after all subjects complete the week 52 visits. There are no plans to modify or discontinue this study based on the results of the interim analysis. If

required to satisfy evolocumab development program needs, additional analyses may be performed periodically throughout the study after the parent study is closed and individual subjects are unblinded to their lipid values as required by overall evolocumab development program.

10.4 Planned Methods of Analysis

10.4.1 General Approach/Considerations

Statistical analyses in this open-label extension study will be 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.

One year interim and final analyses will be based on data collected from this study. Descriptions of any integrated analyses with the parent study are out of scope for this study.

For all endpoints, results will be summarized by the treatment group to which subjects are randomized in Study 20120153, unless otherwise specified.

Unless specified otherwise, the baseline value is defined as the subject's baseline value from the parent study.

There will be no imputation for missing data.

Death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated analyses across the program.

10.4.2 Analysis of Key Study Endpoints

10.4.2.1 Primary Endpoint Analyses

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Subject incidences of treatment-emergent adverse events, serious adverse events, and adverse events leading to withdrawal of investigational product will be tabulated.

Subgroup analyses on the primary endpoint will be conducted by category of each baseline covariate specified in Section 10.1.6.

10.4.2.2 Secondary Endpoint Analyses

The secondary endpoints will be summarized at week 52. Descriptive statistics will be provided.

10.4.2.3 Exploratory Endpoint Analyses

Subject incidence of adjudicated adverse events will be summarized. The percent change and change from baseline in laboratory-based exploratory endpoints at each scheduled visit will be summarized.

10.4.2.4 Safety Endpoint Analyses

Safety Laboratory Parameters

Laboratory parameters will be summarized using descriptive statistics at each scheduled visit. Laboratory shift tables for certain analytes will be provided using the CTCAE v.4 toxicity criteria. The results will be based on the maximum (ie, worst) shift from baseline to the end of study.

Vital Signs

Vital signs will be summarized using descriptive statistics at each scheduled visit.

Concomitant Medications

Concomitant medications of interest will be summarized.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent template form is provided for the investigator to use to customize accordingly to his or her site's requirements. Updates to the template will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject.

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.

11.2 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. 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.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRFs or other documents submitted to Amgen, subjects should be identified by a unique subject identification number only, with a complete and accurate date of birth on the demographics CRF.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their initials (for faxed reports, in accordance with local laws and regulations), date of birth (in accordance with local laws and regulations), and a unique subject identification number.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB 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 named representatives to have access to his/her study-related records, including personal information, without violating the confidentiality of the subject.

11.4 Investigator Signatory Obligations

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

The coordinating investigator, identified by Amgen, will either be:

- 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IEC/IRB must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IEC/IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator should notify the IEC/IRB 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 (IP) 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 (IP), and by what mechanism, after termination of the trial and before it is available commercially.

12.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's CRF 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.

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 should include:

- Subject files containing completed study-related worksheets, 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 IEC/IRB and Amgen
- If kept, proof of receipt/delivery sheet, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

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

12.3 Study Monitoring and Data Collection

The Amgen representative 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, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

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

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, drug 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.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs (eCRF) will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the EDC system database for site resolution and closed by Amgen reviewer.
- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit—week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The Investigator is responsible to comply with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the

Schedule of Assessments (Section 7.1), 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.

12.5 Language

eCRFs **must** be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal 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 should 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), which states:

- Authorship credit should 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;(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 should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should 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 should qualify for authorship, and all those who qualify should be listed.
- Each author should 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 corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 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. Depending on the type of study, and if permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

13. REFERENCES

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA*. 1993 ;269:3015-3023.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0 for AE grading and information. The CTCAE is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

When an AE cannot be graded by CTCAE v4.0 the following severity grade may be used:

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING: Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
5	FATAL

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation according to the criteria specified in Section 6.1.4.2 (3x ULN for AST/ALT and 2x ULN for TBL) require the following:

- The event should 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 eCRF (eg, adverse event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities should be completed.

Other events of hepatotoxicity and potential DILI should be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1.

Additional Clinical Assessments and Observation

All subjects in whom IP is withheld due to potential DILI or who experience AST/ALT elevations >3x ULN should undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that should be performed during this period include:

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL >2x ULN or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours
  - Subjects should be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the IP has been discontinued AND the subject is asymptomatic
- Obtain PT/INR, fractionated bilirubin and any other potentially relevant laboratory evaluations of liver function or disease
- Obtain complete blood count (CBC) with differential to assess for eosinophilia
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain 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 medications (including non-prescription medicines & herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A,B,C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of DILI including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation as specified in Section 6.1.4.2.
- Follow the subject until all laboratory abnormalities return to baseline or normal. The "close observation period" should continue for a minimum of 4 weeks after drug discontinuation.

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

Appendix B. Sample Serious Adverse Event Report Form

AMGEN evolocumab (AMG 145) 20140128	Clinical Trial Serious Adverse Event Report (3–IMP) *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

US: +1 888 814 8053

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth (Day Month Year)	Sex	Race
		☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *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)	Potential Endpoint? (No / Yes)	Check only if event co-current before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship: In there a reasonable possibility that the event may have been caused by If yes see section 10 — evolocumab (AMG 145) (No / Yes)	Pre-filled autoinjector /pen (AI/pen) (No / Yes)	3.5 mL personal injector/ automated mini-doser (AMD) (No / Yes)	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted (Day Month Year)	Date Discharged (Day Month Year)
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date (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
evolocumab (AMG 145) ☑ Open Label						
Pre-filled autoinjector/pen (AI/pen) ☑ Open Label						
3.5 mL personal injector/automated mini-doser (AMD) ☑ Open Label						

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

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

FORM-065033 Clinical Trial SAE Report (3–IMP) V5.0 Effective date: 20-August-2014 (This is a variant of parent FORM-015482)
SAER Created: 21-AUG-2014 Page 1 of 2

AMGEN evolocumab (AMG 145) 20140128	Clinical Trial Serious Adverse Event Report (3–IMP) *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

	Site Number	Subject ID Number	

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										

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

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

Signature of Investigator or Designee	Title	Date

FORM-065033 Clinical Trial SAE Report (3–IMP) V5.0 Effective date: 20-August-2014 (This is a variant of parent FORM-015482)
SAER Created: 21-AUG-2014 Page 2 of 2

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: 20140128

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
				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: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

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# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20140128

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
				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 withdrew 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: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Amendment 1

Protocol Title: A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab

Amgen Protocol Number 20140128

Amendment Date: 22 December 2014

Rationale:

This document provides the rationale and detailed list of changes for Protocol Amendment 1, dated 22 December 2014, from the original study protocol, dated 23 June 2014.

The purpose of the amendment is to:

- Update Key Sponsor Contact information
- Minor updates and clarifications

Description of Changes:

Section: Document header

Replace:

23 June 2014

With:

22 December 2014

Section: Title page

Key Sponsor Contact(s)

Replace:

PPD , MD
One Amgen Center Drive, MS 27-2-F
Thousand Oaks, CA 91320-1799, USA
PPD

With:

PPD
One Amgen Center Drive, MS 27-2-F
Thousand Oaks, CA 91320-1799, USA
PPD

Section: Title page

Add:

Amendment 1 Date: **22 December 2014**

Section: Investigator's Agreement

1st paragraph

Replace:

I have read the attached protocol entitled "A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab", dated 23 June 2014, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled "A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab", dated **22 December** 2014, and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis, "Study Design"

Replace:

Subjects who completed study 20120153 and completed IP in 20120153 will be eligible to enroll in this study.

With:

Subjects who completed study 20120153 and completed **Investigational Product (**IP**)** in 20120153 will be eligible to enroll in this study.

Section: Protocol Synopsis, "Procedures"

2nd paragraph

Replace:

Subjects will visit the site on Day 1 and week 4. Thereafter, subjects will visit the site quarterly for the first year and two additional times during year 2. During these visits vital signs will be obtained and adverse events (AEs), serious adverse events (SAEs), concomitant medications will be recorded, and central laboratory tests will be performed for all subjects.

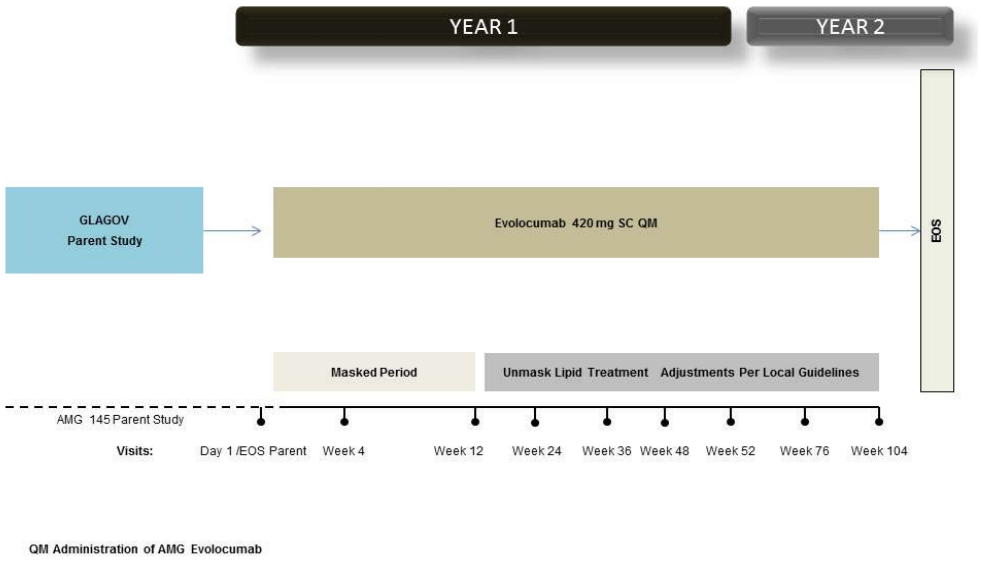
With:

Subjects will visit the site on Day 1 and week 4. Thereafter, subjects will visit the site quarterly for the first year and two additional times during year 2. During these visits vital signs will be **obtained and** adverse events (AEs), serious adverse events (SAEs), concomitant medications will be recorded, and central laboratory tests will be performed for all subjects. **In addition to the protocol-specified study procedures and assessments, investigators should continue to routinely monitor subjects**

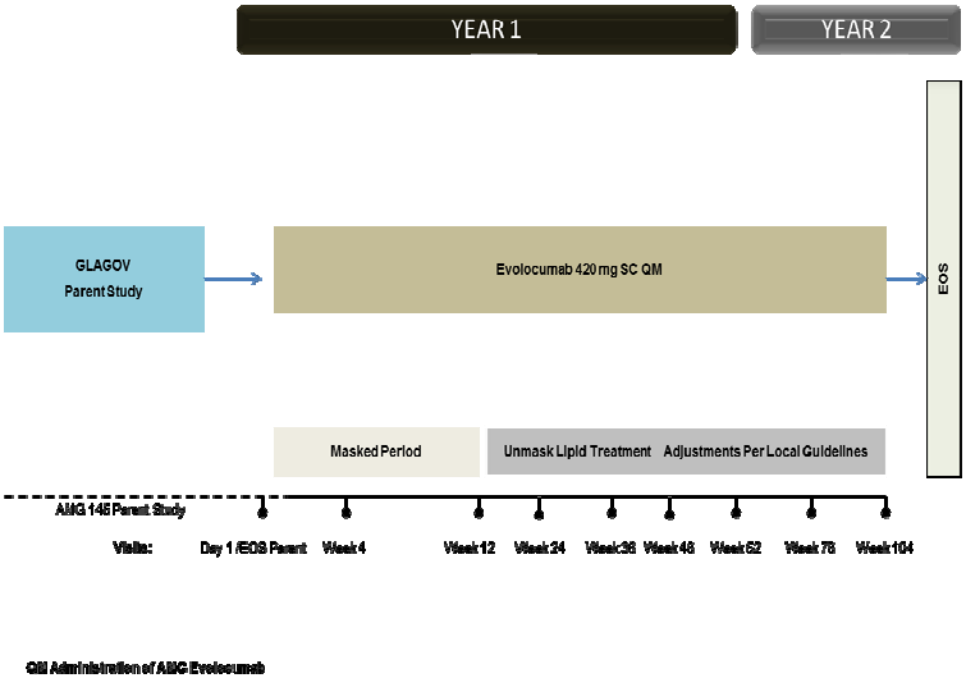
according to local disease management guidelines and perform assessments (eg, ECG, hemoglobin A1c, eGFR, and hematology), as applicable, in routine care.

Section: Study Design and Treatment Schema

Replace:



With:



Section: Study Glossary

Add:

eGFR	**estimated Glomerular Filtration Rate**
HbA1c	**Hemoglobin A1c**

Section: 4.2, Exclusion Criteria

2nd paragraph

Replace:

1. Female subject of reproductive potential not willing to inform her sexual partner of her participation in the clinical study and to use an acceptable method(s) of birth control during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab. Female subjects who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy,bilateral tubal ligatio or who are postmenopausal are not required to use contraception.
    - Postmenopausal is defined as: Age ≥ 55 years with cessation of menses for 12 months or more; Age < 55 by no spontaneous menses for at least 2 years; Age < 55 years and no spontaneous menses within the past 1 year, but currently amenorrheic AND with postmenopausal gonadrotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of “postmenopausal range” for the laboratory involved.
    - Acceptable methods of birth control include: sexual abstinence, surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR Cervical cap with spermicide, OR Contraceptive sponge with spermicide.

- *Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.*

With:

1. Female subject of reproductive potential not willing to inform her sexual partner of her participation in the clinical study and to use an acceptable method(s) of **effective** birth control during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab. Female subjects who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal are not required to use contraception.
    - Postmenopausal is defined as: Age ≥ 55 years with cessation of menses for 12 months or more; Age < 55 by no spontaneous menses for at least 2 years; Age < 55 years and no spontaneous menses within the past 1 year, but currently amenorrheic AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
    - Acceptable methods of **effective birth control include: sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception]),** surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR Cervical cap with spermicide, OR Contraceptive sponge with spermicide.

- *Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.*

Section: 7, Study Procedures

Add:

In addition to the protocol-specified study procedures and assessments described below, investigators should continue to routinely monitor subjects according to local disease management guidelines and perform assessments (eg ECG, hemoglobin A1c, eGFR, and hematology), as applicable, in routine care.

Section: 8.1, Removal of Subjects

Replace:

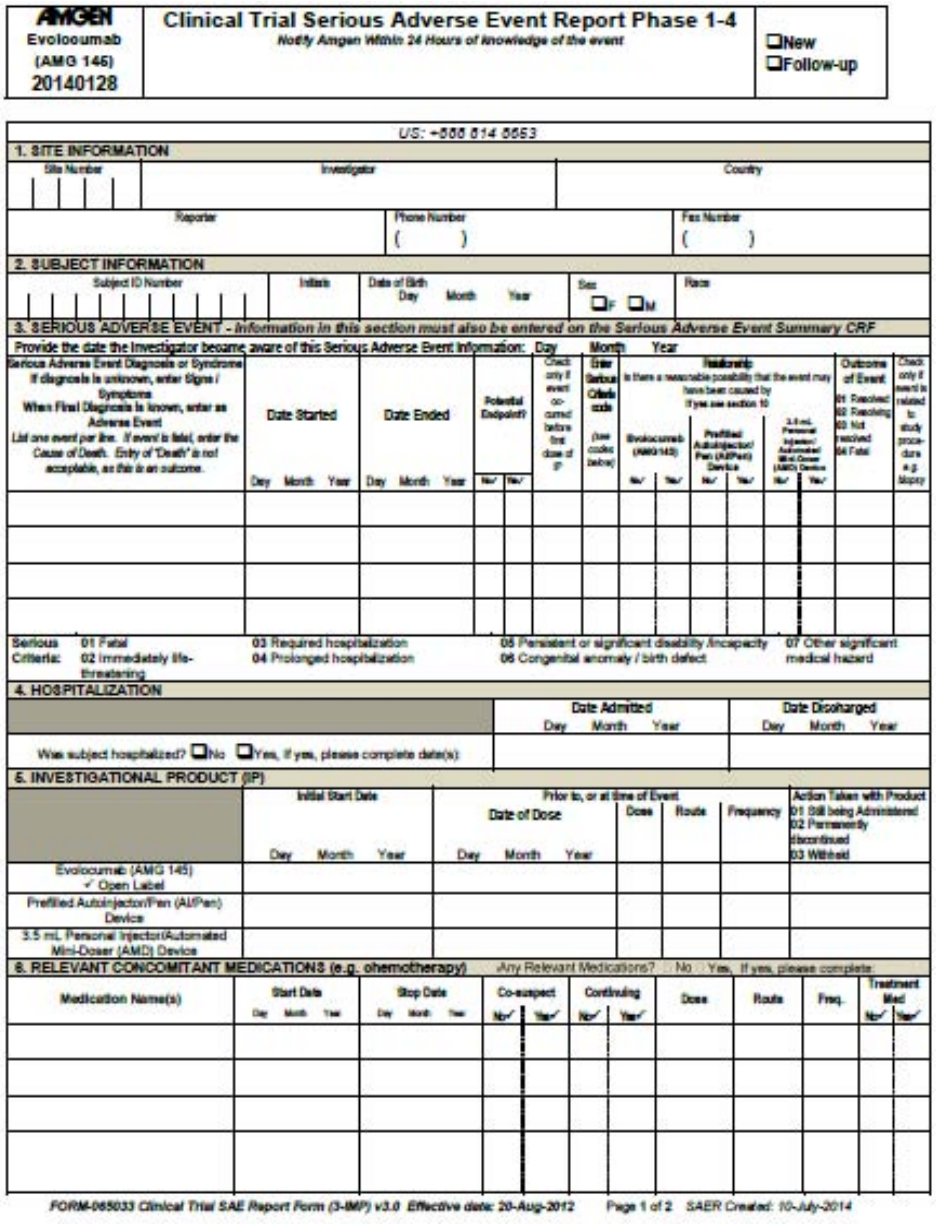
Reasons for removal from protocol-required investigational product might include:

With:

Reasons for removal from protocol-required investigational product include**, but are not limited to**:

Section: Appendix B, Sample Serious Adverse Event Report Form

Replace:



AMGEN
Evolocumab
(AMG 145)
20140128

Clinical Trial Serious Adverse Event Report Phase 1-4
Notify Amgen Within 24 Hours of Knowledge of the event

☐New
☐Follow-up

US: +866 814 5553

1. SITE INFORMATION

Site Number | Investigator | Country

Reporter | Phone Number ( ) | Fax Number ( )

2. SUBJECT INFORMATION

Subject ID Number | Initials | Date of Birth Day Month Year | Sex ☐F ☐M | Race

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event 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	Potential Endpoint? No✓	Yes✓	Check only if event co-current before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by If yes see section 10 Evolocumab (AMG 145) No✓	Yes✓	Prefilled Autoinjector/Pen (AI/Pen) Device No✓	Yes✓	3.5 mL Personal Injector/ Automated Mini-Doser (AMD) Device No✓	Yes✓	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure e.g. biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized? ☐No ☐Yes, if yes, please complete date(s)		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date 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
Evolocumab (AMG 145) ✓ Open Label						
Prefilled Autoinjector/Pen (AI/Pen) Device						
3.5 mL Personal Injector/Automated Mini-Doser (AMD) Device						

6. RELEVANT CONCOMITANT MEDICATIONS (e.g. chemotherapy) Any Relevant Medications? ☐No ☐Yes, If yes, please complete

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

FORM-065033 Clinical Trial SAE Report Form (3-IMP) v3.0 Effective date: 20-Aug-2012 Page 1 of 2 *SAER Created: 10-July-2014*

With:

AMGEN
evolocumab
(AMG 145)
20140128

Clinical Trial Serious Adverse Event Report (3–IMP)
Notify Amgen Within 24 Hours of knowledge of the event

☐New
☐Follow-up

US: +1 888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth (Day Month Year)	Sex	Race
		☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the investigator became aware of this Serious Adverse Event information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *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)	Potential Endpoint?	Check only if event co-current before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the event may have been caused by the IP? If yes see section 10 — evolocumab (AMG 145)	Pre-filled autoinjector /pen (AI/pen)	3.5 mL personal injector/ automated mini-doser (AMD)	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted (Day Month Year)	Date Discharged (Day Month Year)
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date (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
evolocumab (AMG 145) ☑ Open Label						
Pre-filled autoinjector/pen (AI/pen) ☑ Open Label						
3.5 mL personal injector/automated mini-doser (AMD) ☑ Open Label						

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

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

FORM-065033 Clinical Trial SAE Report (3–IMP) V5.0 Effective date: 20-August-2014 (This is a variant of parent FORM-015482)
SAER Created: 21-AUG-2014 Page 1 of 2