Title: A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries

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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Investigator's Agreement

I have read the attached protocol entitled "A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries", dated**19 February 2020**, 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 the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries

Study Phase: 3b

Indication: Dyslipidemia

Primary Objective: To describe the safety and tolerability of long-term administration of evolocumab.

Secondary Objective(s): The secondary objectives are to describe the effects of long-term administration of evolocumab on low-density lipoprotein cholesterol (LDL-C) levels and to describe the effects of long-term administration of evolocumab in subjects achieving an LDL-C level < 40 mg/dL (1.03 mmol/L).

Exploratory objectives are provided in Section 1.3.

Hypothesis: The primary clinical hypothesis is that long-term exposure of evolocumab will be safe and well tolerated in subjects with clinically evident atherosclerotic cardiovascular disease (CVD).

Primary Endpoint: The primary endpoint is the subject incidence of adverse events.

Secondary Endpoints: The secondary endpoints are the percent change of LDL-C from baseline at each scheduled visit and the achievement of an LDL-C < 40 mg/dL (1.03 mmol/L) at each scheduled visit.

Exploratory endpoints are provided in Section 10.1.1.3.

Study Design: This is a multicenter, open-label extension (OLE) study designed to assess the extended long-term safety of evolocumab in subjects who have completed the FOURIER trial (Study 20110118). FOURIER is a randomized placebo-controlled study of evolocumab, in patients with clinically evident atherosclerotic CVD on stable effective statin therapy. Subjects at sites participating in FOURIER OLE (Study 20160250) who are eligible and have signed the FOURIER OLE informed consent will be enrolled after completion of FOURIER.

The FOURIER OLE study requires laboratory assessments at day 1, week 12, and thereafter approximately every 6 months from day 1; the corresponding blood samples will be processed using a central laboratory.

Upon enrollment in FOURIER OLE study, subjects will receive evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM) according to their preference. Frequency and corresponding dose of administration can be changed at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. It is recommended that subjects continue the same background lipid-lowering therapy (LLT), including statin, as taken during FOURIER.

This study will continue for 260 weeks (approximately 5 years). Subjects ending administration of evolocumab should continue study assessments until the end of study.

All subjects will be followed and complete procedures/assessments from enrollment through the date of study termination unless the subject has withdrawn consent, irrespective of whether the subject is continuing to receive treatment. All deaths and cardiovascular events of interest will be reviewed by an independent external Clinical Events Committee (CEC), using standardized definitions.

Sample Size: Approximately 1600 subjects will be enrolled in this study.

Summary of Subject Eligibility Criteria: Subjects must have completed FOURIER (Study 20110118) while still receiving assigned investigational product and provided informed consent for this FOURIER OLE (20160250) study. Eligible subjects may not be currently receiving treatment in another investigational device or drug study, or have ended treatment on another investigational device or drug study(ies) within less than 4 weeks. Women cannot be

pregnant or breastfeeding or planning to become pregnant or planning to breastfeed during treatment with evolocumab and within 15 weeks after the end of treatment with evolocumab. Women of childbearing potential must be willing 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.

For a full list of eligibility criteria, please refer to Section 4.

Investigational Product

Amgen Investigational Product Dosage and Administration: Evolocumab will be administered using a handheld mechanical (spring-based) prefilled 1.0 mL auto-injector/pen (AI/pen) or an on-body electromechanical 3.5 mL personal injector (PI).

Evolocumab will be administered 140 mg subcutaneous (SC) Q2W (1 administration by prefilled AI/pen) or 420 mg SC QM (3 administrations by prefilled AI/pen or 1 administration by PI).

Subjects will choose whether to initiate treatment at the Q2W or QM schedule and will have the opportunity to switch between evolocumab Q2W and QM at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. Subjects who choose QM treatment will initiate treatment using the PI, provided the appropriate supply is available. If the PI is not available, then the AI/pen may be used. **Subjects will have the opportunity to switch between the AI/Pen and PI, at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available.**

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration: It is recommended that subjects continue the same background LLT, including statin, as taken while in FOURIER. Background LLT will not be provided by Amgen.

Procedures: Mandatory study visits will occur at day 1, week 12 and thereafter approximately every 6 months from day 1. Evolocumab resupply visits will be scheduled quarterly (every 12 weeks). **The last resupply of evolocumab will occur 12 weeks after the week 240 visit.** Evolocumab will be supplied directly to the site. The method of resupply will be determined based on local regulations as well as available infrastructure. Assessments and procedures include vital signs; physical examination; body weight; assessment of concomitant therapy, adverse events, adverse device effects, serious adverse events, and disease-related events; laboratory assessments, including fasting lipid panel, apolipoprotein A1, apolipoprotein B, and lipoprotein(a); serum pregnancy testing (women of childbearing potential only); and evolocumab administration. If evolocumab is administered at the site, the administration by SC injection will be done after blood draw and vital sign procedures have been completed.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 3).

Statistical Considerations: The primary and secondary endpoints will use the OLE safety subset (OLE study only) which includes all subjects who received at least 1 dose of open-label evolocumab in the OLE study.

Statistical analyses in this open-label study are descriptive in nature. No statistical inference or missing value imputation is planned. No formal hypothesis will be tested in this study, unless specified otherwise, the baseline value is defined as the subject's baseline value from the parent study (FOURIER). All analyses will be performed on the OLE safety analyses set. The primary analysis of all primary, secondary, and exploratory endpoints will use data from the OLE study only. Additional analyses combining the data from the OLE study and FOURIER study will be performed as applicable. For all endpoints, results will be summarized by the randomized treatment group from the FOURIER study and overall, unless specified otherwise.

Exposure-adjusted subject incidence rates of all treatment-emergent adverse events, serious adverse events, fatal adverse events, adverse events leading to withdrawal from evolocumab, device-related adverse events, and disease-related events will be tabulated for the overall OLE study period. These events will also be presented by yearly subject exposure time intervals. **All adverse event summaries for the primary analysis of the primary endpoint will include a**ll

treatment-emergent events **reported on the Event electronic case report form (eCRF),** including CEC reviewed events **and disease related events**. All CEC reviewed events will be reported.

Adverse event data from the OLE study will also be combined with FOURIER study data as an additional analysis and positively reviewed events will not be included in the adverse event analysis to remain consistent with FOURIER adverse event reporting.

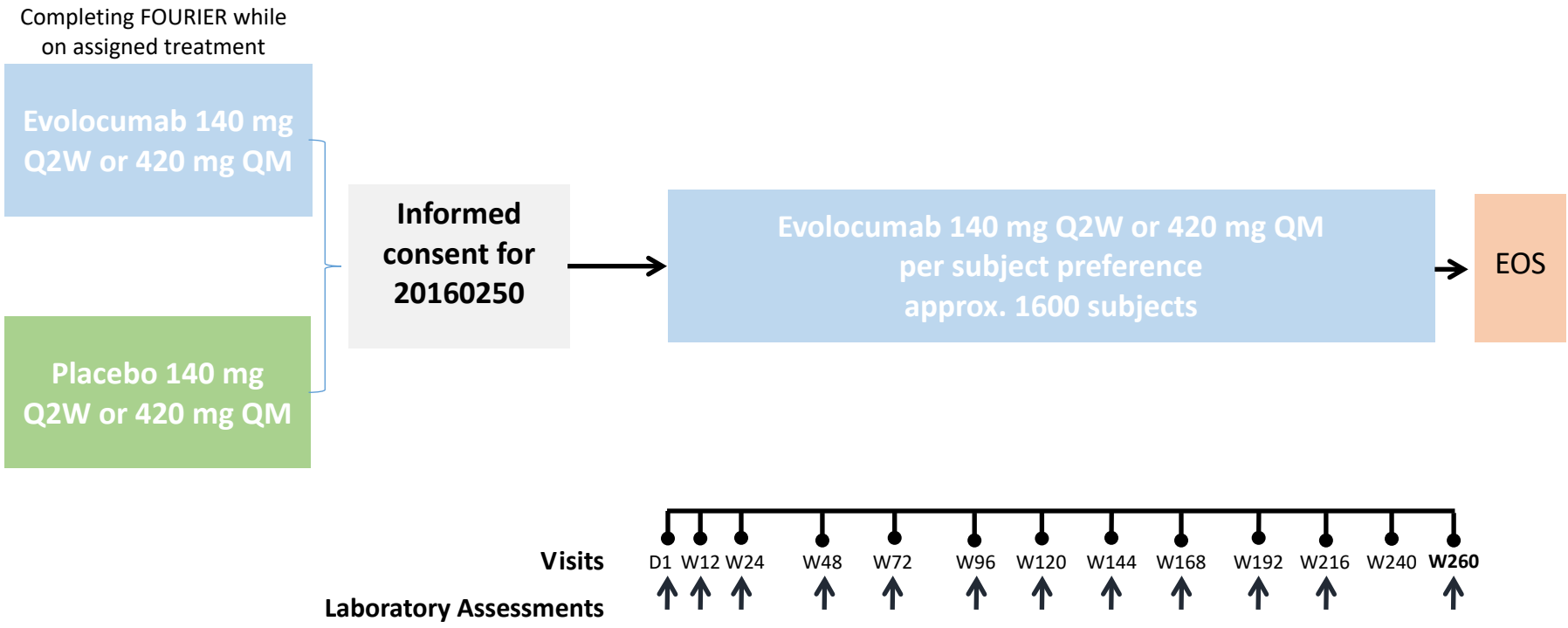
Summary statistics of the secondary endpoints (percent change of LDL-C from baseline and achieving an LDL-C < 40 mg/dL) will be provided.

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

Sponsor: Amgen

Data Element Standards Version(s)/Date(s): Version 5, 20 March 2015

Figure 1. Study Design and Treatment Schema



EOS = end of study; Q2W = every 2 weeks; QM = monthly

W240: Subjects may be contacted by phone at week 240.

EOS: safety follow-up phone call. A follow-up phone call is scheduled to occur at least 30 days (+ 3 days) after the last administration of evolocumab.

Evolocumab resupply visits will be scheduled quarterly (every 12 weeks).

Study Glossary

Abbreviation or Term	Definition/Explanation
AI/pen	auto-injector/pen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
AST	aspartate aminotransferase
CBC	complete blood count
CEC	Clinical Events Committee
CPK	creatine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
CRF	case report form
CVD	cardiovascular disease
CYP	cytochrome P450
day 1	defined as the first day that protocol-specified investigational product/protocol-required therapies are administered to the subject
DILI	drug-induced liver injury
eCRF	electronic case report form
EDC	electronic data capture
eSAE	electronic serious adverse event
electronic source data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a study
end of study	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s), for the purpose of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
end of study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint
end of treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOI	event of interest
EoIP	end of investigational product administration
EOS	end of study for individual subject; defined as the last day that protocol-specified procedures are conducted for an individual subject
EU	European Union
FOURIER	Study 20110118; the parent study for this open-label extension study

Abbreviation or Term	Definition/Explanation
FOURIER OLE	open-label extension study of the FOURIER study
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFU	instructions for use
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IVR	Interactive Voice Response
IWR	Interactive Web Response
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LKM1	liver kidney microsomal antibody 1
LLT	lipid-lowering therapy
Lp(a)	lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NASH	nonalcoholic fatty liver disease including steatohepatitis
non-HDL-C	non-high-density lipoprotein cholesterol
OLE	open-label extension
PCSK9	proprotein convertase subtilisin/kexin type 9
PI	personal injector
POR	proof of receipts
Q2W	every 2 weeks
QM	monthly

Abbreviation or Term	Definition/Explanation
SC	subcutaneous
source data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.
STEMI	ST segment elevation myocardial infarction
TBL	total bilirubin
TIA	transient ischemic attack
UA	unstable angina
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

To describe the safety and tolerability of long-term administration of evolocumab.

1.2 Secondary

The secondary objectives are the following:

- to describe the effects of long-term administration of evolocumab on low density lipoprotein cholesterol (LDL-C) levels
- to describe the effects of long-term administration of evolocumab in subjects achieving an LDL-C level of < 40 mg/dL (1.03 mmol/L)

1.3 Exploratory

The exploratory objectives are the following:

- To describe the effects of long-term administration on non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol, lipoprotein(a) (Lp[a]), triglycerides, high-density lipoprotein cholesterol (HDL-C), LDL-C, very low-density lipoprotein cholesterol (VLDL-C), and apolipoprotein A1 (ApoA1) levels.
- **To describe the effects of long-term administration of evolocumab on subject incidence of death and cardiovascular events of interest**

2. BACKGROUND AND RATIONALE

2.1 Cardiovascular Disease

Collectively, cardiovascular diseases (CVD) are regarded as a world-wide epidemic; and though over the last 2 decades CVD mortality has declined (primarily in developed countries), it still represents the leading cause of death and disability in the world, as well as over 10% of the global total disease burden. In 2008, the World Health Organization (WHO) estimated 57 million deaths world-wide, of which 36 million were due to non-communicable causes. CVD accounted for over 17 million of these deaths, nearly 80% of which were due to heart attacks and strokes alone (responsible for 7.3 million and 6.2 million deaths, respectively).

A large proportion of CVD is preventable, and the investment in prevention measures has been regarded as the most sustainable solution for dealing with the CVD epidemic. Elevated cholesterol is among the leading risk factors for cardiovascular deaths (sixth), with an estimated prevalence of 39% globally among all adults (even greater in high-income countries). Cardiovascular disease perhaps represents the single leading threat to the health of the world; the unmet medical need in this arena is immense (World Health Organization, 2011).

Dyslipidemia is a major modifiable risk factor for the development of CVD. It is estimated that approximately 100 and 34 million Americans have a total cholesterol in excess of 200 mg/dL (approximately 5.2 mmol/L) and 240 mg/dL (approximately 6.2 mmol/L), respectively. In Europe, up to 50% of the population aged 35 to 64 years has total cholesterol > 250 mg/dL (6.5 mmol/L) (Tolonen et al, 2005). This high prevalence of dyslipidemia translates into a significant cardiovascular morbidity and mortality, as described above. Dyslipidemia is associated with more than 50% of the global cases of coronary heart disease and more than 4 million deaths per year worldwide.

To decrease the morbidity and mortality associated with CVD, over 50 million patients in the United States, Europe, and Japan are currently treated with dyslipidemia therapies. The rationale for treatment of dyslipidemia, particularly elevated LDL-C, extends from extensive clinical trial data in both primary and secondary prevention that demonstrates the reduction in total cholesterol, non-HDL-C, and most importantly, LDL-C through pharmacological therapies, particularly statins, lowers the risk of CVD events (Kannel, 1995; Kannel et al, 1979; Kannel et al, 1974). The most recent Cholesterol Treatment Trialists' Collaboration (2010) meta-analysis which included 21 randomized controlled trials of statin versus control involving nearly 170 000 patients showed that for every approximately 1 mmol/L reduction of LDL-C, there was an approximately 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction [MI], coronary revascularization, or stroke). Importantly, this meta-analysis, which also evaluated 5 trials that compared more versus less intensive statin therapy, did not find a LDL-C threshold for risk reduction; additional vascular risk reduction is possible in patients with low LDL-C. The opportunity for further cardiovascular risk reduction is also consistently seen in the numerous primary and secondary prevention studies where subjects are treated with statins to their LDL-C goal, the results of which have manifested in durable, dramatic changes in medical practice and have consequently saved millions of lives.

Despite achieving their LDL-C goals, approximately two-thirds of these patients on lipid reduction therapy still have cardiovascular events (Libby and Theroux, 2005). While it is unlikely that this residual risk is entirely due to the additional LDL-C reduction needed beyond the LDL-C goal articulated in recent treatment guidelines (Grundy et al, 2004; National Cholesterol Education Program, 2002), Cholesterol Treatment Trialists' Collaboration (2010) data suggest that novel agents that are capable of providing

additional LDL-C lowering on top of statins may further reduce cardiovascular morbidity and mortality. Furthermore, some individuals are intolerant to statin therapy and cannot achieve their respective LDL-C goals (eg, Bruckert et al, 2005; Franc et al, 2003). Non-statin treatment options are currently available (eg, ezetimibe, bile acid sequestrants, plant stanols, niacin) to lower LDL-C but their potency is limited, such that LDL-C reductions occur on the order of 15% to 20%.

Recently, the IMPROVE-IT study evaluated cardiovascular outcomes (cardiovascular death, MI, hospital admission for unstable angina [UA], or coronary revascularization) for ezetimibe combined with a statin, compared with a statin alone, in approximately 18 000 subjects who had been hospitalized for ST segment elevation myocardial infarction (STEMI), or non-STEMI or UA, less than 10 days before enrollment (Cannon et al, 2015). At 1 year, mean LDL-C was 70 mg/dL with a statin alone and 53 mg/dL with ezetimibe combined with a statin (a 24% reduction in LDL-C). Over the duration of the study, the addition of ezetimibe to a statin significantly reduced the event rate for the primary combined endpoint from 34.7% to 32.7% ($p = 0.016$). Reductions in individual event rates included a 21% relative risk reduction for ischemic stroke and 13% relative risk reduction for MI. Thus, despite the fact that mean LDL-C with a statin alone was 70 mg/dL, a level that is often used as a goal for lipid-lowering therapy (LLT), significant additional cardiovascular benefit was obtained by lowering LDL-C further with the addition of the non-statin therapy, ezetimibe.

Considering the remaining cardiovascular risk despite the availability of statin therapy and given that non-statin treatment options have modest efficacy and/or are poorly tolerated (niacin and bile acid sequestrants), there is an unmet medical need for a potent, effective non-statin agent that will get a significant proportion of patients to LDL-C goal and further reduce cardiovascular risk. This need is especially evident among individuals at high risk for future cardiovascular events; namely, those who have already suffered from a MI, non-hemorrhagic stroke, or **coronary or** peripheral arterial revascularization procedure or amputation due to atherosclerotic disease.

Evolocumab has demonstrated consistent, significant, and durable reduction in LDL-C with favorable effects on other lipid parameters across a robust clinical development program in more than 6000 subjects with primary hyperlipidemia and mixed dyslipidemia. In these studies, evolocumab reduced LDL-C by approximately 55% to 75% compared with placebo and by approximately 35% to 45% compared with ezetimibe. In subjects with homozygous familial hypercholesterolemia, evolocumab

reduced LDL-C by approximately 30% compared with placebo. Reduction of LDL-C was maintained with long-term treatment. The adverse event profile for evolocumab was similar overall to that of the control groups, including placebo. Extensive analyses have not identified major safety issues, including for low LDL-C, with evolocumab therapy.

Recently published data suggests potential for evolocumab to have beneficial effects on outcomes of CVD (Sabatine et al, 2015). This could potentially be confirmed with the results of FOURIER, the clinical outcomes study with evolocumab.

2.2 Amgen Investigational Product Background

Recycling of the hepatic cell surface low-density lipoprotein receptor (LDLR) plays a critical role in regulating serum LDL-C levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the LDLR and downregulates hepatic cell surface LDLR, which, in turn, leads to increased levels of circulating LDL-C. Humans with PCSK9 loss-of-function mutations have cholesterol levels lower than normal and reduced incidence of coronary heart disease (Abifadel et al, 2003). Evolocumab is a fully human monoclonal immunoglobulin G2, developed at Amgen Inc., that specifically binds to PCSK9 preventing its interaction with the LDLR. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

Refer to the specific section of the Evolocumab (AMG 145) Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Rationale

This 5-year open-label extension (OLE) study is being conducted to provide additional safety data on the long-term administration of evolocumab. These additional safety data include the long-term effects of LDL-C < 40 mg/dL (< 1.03 mmol/L). A total of approximately 1600 subjects will be enrolled.

2.4 Clinical Hypothesis

The clinical hypothesis is that long-term exposure of evolocumab will be safe and well tolerated in subjects with clinically evident atherosclerotic CVD.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, OLE study designed to assess the extended long-term safety of evolocumab in subjects who have completed the FOURIER (Study 20110118) trial.

FOURIER is a randomized, placebo-controlled study of evolocumab, in patients with clinically evident atherosclerotic CVD on stable effective statin therapy. After signing the informed consent, subjects should be enrolled within 7 days. Subjects at sites participating in FOURIER OLE who are eligible and have signed the FOURIER OLE informed consent will be enrolled after completion of FOURIER.

The FOURIER OLE study requires laboratory assessments at day 1, week 12, and thereafter approximately every 6 months from day 1 (see Section 7.2); the corresponding blood samples will be processed using a central laboratory. Upon enrollment in FOURIER OLE study, subjects will receive evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM) according to their preference. Frequency and corresponding dose of administration can be changed at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. It is recommended that subjects continue the same background LLT, including statin, as taken during FOURIER. This study will continue for 260 weeks (approximately 5 years). Subjects ending administration of evolocumab should continue study assessments until the end of study (EOS).

All subjects will be followed and complete procedures/assessments from enrollment through the date of study termination unless the subject has withdrawn consent, irrespective of whether the subject is continuing to receive treatment. All deaths and cardiovascular events of interest (MI, stroke, **coronary** revascularization, hospitalization for unstable angina, hospitalization for heart failure, and transient ischemic attack [TIA]) will be reviewed by an independent external Clinical Events Committee (CEC), using standardized definitions.

The overall study design is described by a study schema (Figure 1) at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 100 centers will participate in this study in selected European countries (Belgium, Denmark, Germany, France, Italy, Portugal, and Sweden). Sites that do not enroll subjects within 3 to 6 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 1600 subjects will be enrolled in this study.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The study will continue for 260 weeks (approximately 5 years).

3.5.2 End of Study

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

The primary completion date is the date when the last subject has completed the assessments for EOS/Safety Follow-up.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

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

4. SUBJECT ELIGIBILITY

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

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures.

102 Subject had completed FOURIER (Study 20110118) while still receiving assigned Investigational Product.

4.2 Exclusion Criteria

201 Permanent discontinuation of Investigational Product during FOURIER for any reason including an adverse event or serious adverse event.

202 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

203 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

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

205 Subject has known sensitivity to any of the active substances or excipients (eg, sodium acetate) to be administered during dosing.

206 Females who are pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment with evolocumab and for an additional 15 weeks after treatment with evolocumab discontinues.

207 Female subjects of childbearing potential unwilling to use an acceptable method of effective contraception during treatment and for an additional 15 weeks after the last dose of protocol-required therapies. Refer to Section 6.8 for additional contraceptive information.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). Subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved ICF before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria, documents and dates this decision in the subject's medical record, and contacts the IVR/IWR system to enroll the subject.

Each subject who enter into the screening period for the study (after signing the IRB/IEC-approved ICF) are to be assigned the same subject identification number as the parent study (FOURIER Study 20110118) before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment.

5.1 Treatment Assignment

All subjects will receive open-label evolocumab.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment case report form (CRF).

6. TREATMENT PROCEDURES

6.1 Classification of Product(s), Medical Device(s) and/or Combination Product(s)

The Amgen investigational product used in this study includes: evolocumab.

The non-Amgen non-investigational products used in this study includes: background LLTs, including a statin.

The investigational medical devices used in this study includes: prefilled auto-injector/pen (AI/pen) or personal injector (PI).

Note: Non-investigational medical devices (ie, medical device[s] not under study) or medicinal products will be described in Section 6.5.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of evolocumab and the investigational medical devices used in this study.

6.2 Investigational Product

6.2.1 Amgen Investigational Product - Evolocumab

Evolocumab will be manufactured and packaged by Amgen Inc., and distributed using Amgen clinical study drug distribution procedures. Evolocumab will be presented as follows:

- an AI/pen, as a single-use, disposable, handheld mechanical (spring-based) device for fixed dose, subcutaneous (SC) injection of a 1.0-mL deliverable volume of 140 mg/mL evolocumab
- a PI, as a single-use, disposable, on-body electromechanical injection device that is copackaged with a prefilled Crystal Zenith cartridge containing a 3.5-mL deliverable volume of 120 mg/mL evolocumab

Evolocumab should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required). Evolocumab

should be handled per the instructions provided in the IPIM and the instructions for use (IFU) for the prefilled AI/pen or PI.

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

Evolocumab will be supplied directly to the site. The method of resupply will be determined based on local regulations as well as available infrastructure. The investigator may be required to record the box number of evolocumab (prefilled AI/pen or PI) on the subject's Drug Administration electronic case report form (eCRF). Subjects should return used evolocumab for reconciliation by the site.

6.2.1.1 Dosage, Administration, and Schedule

Evolocumab will be administered SC Q2W or QM for approximately 260 weeks in accordance with the instructions in the IPIM and IFU. **The last resupply of evolocumab will occur 12 weeks after the week 240 visit.** The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency at administration of SC injections before self-administration is permitted. The first self-administered dose by the subject (or designee, if not a healthcare professional) may be administered at the site under the supervision of a healthcare provider at day 1. In this study, evolocumab will be administered by self-administration by the subject, designee, or a qualified healthcare professional in a non-investigator site setting (eg, at home). In exceptional circumstances, SC administration of evolocumab by a qualified healthcare professional in a clinic setting will also be allowed.

When evolocumab is scheduled to be administered at the study site, the date and completion time of administration, the body location of the injection, whether the injection was fully or partially administered, and box number are to be recorded on each subject's eCRF.

When evolocumab is administered at a non-investigator site location, at a minimum, the dates the devices were dispensed and the used devices returned, the number of devices returned, box numbers, and for each device whether it was returned fully or partially used are to be recorded on each subject's eCRF.

It is suggested that the evolocumab administration is done by the subject under site staff supervision at each of the regular study visits to ensure continued proper use of the

injection device. Evolocumab administration at a scheduled visit, if applicable, is to be performed after completion of the blood draws and vital signs.

Details of preparing evolocumab, the injection procedures, and device disposal are included in the IPIM and IFU provided by Amgen before the start of the study.

Evolocumab will be administered either at 140 mg in 1.0 mL (1 administration by prefilled AI/pen) Q2W or at 420 mg in 3.0 mL or 3.5 mL (3 administrations by prefilled AI/pen or 1 administration by PI, respectively) QM. The 3 injections for the QM administration, if applicable, can be administered into different injection sites. The SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

The effects of overdose of this product are not known.

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

No dose adjustments of evolocumab will be allowed in this study.

Evolocumab is administered on a Q2W or QM schedule. Subjects will have the opportunity to switch between **the AI/pen and PI,** at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. **The first self-administration after switching the device should be done at a regularly scheduled visit under the supervision of the investigator or qualified study center staff.** Subjects who choose QM treatment will initiate treatment using the PI, provided the appropriate supply is available. If the PI is not available, then the AI/pen may be used. Additionally, subjects taking 420 mg evolocumab QM will have the opportunity to switch drug administration (3 administrations by prefilled AI/pen or 1 administration by PI) at any scheduled time point. The reason for dose change of evolocumab is to be recorded on each subject's eCRF(s).

If, in the opinion of the investigator, a subject is unable to tolerate evolocumab, that subject will discontinue evolocumab but should continue to return for all other study procedures and measurements until the EOS.

If a subject dose of evolocumab is missed or late, administration should occur as soon as possible if there are 7 days or more until the next scheduled dose. If there are less than 7 days before the next scheduled dose, the missed dose should be omitted and the next dose should be administered according to the original schedule.

The decision to rechallenge the subject after therapy changes should be discussed and agreed unanimously by the subject, investigator, and Amgen. If signs or symptoms

recur with rechallenge of evolocumab, then evolocumab should be permanently discontinued.

Information on when to stop Amgen investigational product due to hepatotoxicity is provided in Section 6.3.

6.2.2 Non-Amgen Non-investigational Product

Non-Amgen non-investigational products including background LLT (including statin), will also be used in this study. These therapies will not be provided or reimbursed by Amgen.

6.2.2.1 Non-Amgen Non-investigational Product – Background Lipid-lowering Therapy

6.2.2.1.1 Dosage, Administration, and Schedule

It is recommended that subjects continue the same background LLT, including statin, as taken while in FOURIER (Study 20110118). All background LLT adjustments must be clearly documented and recorded on the appropriate eCRF page and in the source documents. The dose, start date/time, stop date/time, frequency, and non-Amgen non-investigational product are to be recorded on each subject's eCRF. Background LLT will not be provided by Amgen unless required by local regulations. Recommendations for background LLT are provided in Appendix D.

All other drugs that are allowed per protocol and that are prescribed for the subject must be commercially available and used at dosages approved by local regulatory authorities.

Subjects should consult the investigator if they miss a dose of background statin.

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

The investigator should consult the local product label for information on dose adjustments, delays, withholding, restarting, or permanent discontinuation of background LLT, including statins. The reason for dose change of non-Amgen non-investigational product is to be recorded on each subject's eCRF(s).

If a subject has elevated ad hoc laboratory values (Section 6.3) and is receiving background LLT, including statins, that may result in such elevations (eg, ezetimibe, fenofibrate, or niacin), the additional therapies should be evaluated for a potential role in the elevated laboratory values and considered for discontinuation. If a subject has elevations in triglycerides > 500 mg/dL (5.65 mmol/L) and is concomitantly receiving a

bile acid binding resin, the bile acid binding resin should be evaluated for discontinuation.

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

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Routine hepatic laboratory assessments are not required for this study. However, the guidelines (Section 6.3.1) apply for elevated liver enzymes noted during ad hoc tests.

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms

- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

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

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.2).

Table 1. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

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

If signs or symptoms recur with rechallenge, then evolocumab, statins, and other applicable lipid background therapies should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 1) should never be rechallenged.

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7. Concomitant therapies are to be collected from informed consent through the end of safety follow-up period.

Concomitant therapy and medications will be recorded on the eCRF. The following groups of concomitant medications will be recorded:

- cardiovascular medications
- analgesics/antipyretics
- anticoagulants/antiplatelets
- antibiotics
- antidepressants
- vitamins
- hormone replacement therapy (HRT)
- oral corticosteroids

For antibiotics, the therapy name, indication for use, class of medication, date first taken, and route of administration will be collected. For other concomitant medications, the investigator, or designee, should record whether the therapy was being taken at the time points indicated in the schedule of assessments **(Table 3)**.

For concomitant therapy being taken to treat an event collect therapy name, indication, dose, unit, frequency, start date, and stop date.

Subjects should adhere to the National Cholesterol Education Program Adult Treatment Panel III therapeutic lifestyles changes diet or an equivalent diet. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting or long runs) 48 hours prior to each visit.

6.5 Medical Devices

The following investigational medical devices, prefilled AI/pen or PI, will be used in this study and provided by Amgen (Section 6.2). Additional details for each medical device is to be provided in the IPIM.

The evolocumab AI/pen is a single use disposable, handheld mechanical "spring-based" device for fixed dose SC injection of 140 mg/mL evolocumab in 1.0 mL deliverable volume.

The evolocumab PI is a single use, disposable, on-body electromechanical injection device that is copackaged with a prefilled Crystal Zenith cartridge containing 120 mg/mL evolocumab in a 3.5 mL deliverable volume.

Other non-investigational medical devices may be used in the conduct of this study as part of standard of care. These devices that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.6 Product Complaints

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

This includes any drugs, devices or combination products provisioned and/or repackaged/modified by Amgen. Drugs or devices includes investigational product (evolocumab), AI/pen, and PI.

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

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

Treatment with any investigational therapies other than study-provided evolocumab is not permitted during the study.

Medications or foods that are known potent inhibitors of cytochrome P450 (CYP) 3A (eg, itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, human

immunodeficiency virus [HIV] or hepatitis C virus [HCV] protease inhibitors, antidepressant nefazodone, and grapefruit juice in large quantities [> 1 quart daily; approximately 1 L]) are not recommended during the study because of their potential impact on metabolism of certain statins (see Appendix E).

If a subject is enrolled and subsequently requires a treatment that is not recommended based on their particular statin (eg, a strong CYP3A4 inhibitor in a subject on atorvastatin), the treating physician should give consideration to using an equivalent concomitant drug (eg, a drug that does not inhibit CYP3A4 so that the subject can continue taking statin background therapy). If this is not possible, it may be necessary to withdraw or change statin background therapy while the concomitant drug is required.

There is no need to discontinue treatment with evolocumab should a subject require a nonrecommended drug (eg, a strong CYP3A4 inhibitor) since monoclonal antibody therapeutics are not metabolized through CYP and, thus, are unaffected by the use of CYP inhibitors.

The use of antacids is not recommended within the period of 2 hours before and 2 hours after dosing with statins.

6.8 Contraceptive Requirements

Females of Childbearing Potential

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

Female in the following categories are not considered of child bearing potential:

1. Premenopausal female with 1 of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

    Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.
2. Premenarchal female

3. Postmenopausal female

    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

    b. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

6.8.1 Female Subjects

Female subjects of childbearing potential must agree to use an acceptable method of effective contraception (as described in Table 2 below) during treatment and for an additional 15 weeks after the last dose of protocol-required therapies.

Table 2. Acceptable Methods of Effective Contraception for Female Subjects

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

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

6.8.2 Male Subjects

Male subjects are not required to use contraception while taking evolocumab.

6.8.3 Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant during treatment and for 15 weeks after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. The investigator must discuss these contraceptive changes with the subject.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 3. Schedule of Assessments

Time point/Frequency	Screening	D1	W12	W24	W48	W72	W96	W120	W144	W168	W192	W216	W240[a]	W260[b]	EOS[c]
General Procedures															
Informed consent	X														
Medical history	X														
Vital signs	X		X	X	X	X	X	X	X	X	X	X		X	
Review for AEs/ADEs/SAEs/DREs		Continually throughout entire study													
Concomitant therapy	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X													X	
Body weight	X		X	X	X	X	X	X	X	X	X	X		X	
Coronary revascularization procedure and death information[h]		**Continually throughout entire study**													
Laboratory[d]															
Fasting lipid panel and ApoA1, ApoB, Lp(a)		X	X	X	X	X	X	X	X	X	X	X		X	
Serum pregnancy (FSH)	X[e]	X (X)	X	X	X	X	X	X	X	X	X	X		X	
Evolocumab[f]															
Administration at study site[g]		X	X	X	X	X	X	X	X	X	X	X	X		
Evolocumab dispense/reconcile		X	X	X	X	X	X	X	X	X	X	X	X	X[b]	

Footnotes defined on next page

ADE = adverse device effect; AE = adverse event; **AI/pen = auto-injector/pen;** ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; BP = blood pressure; D1 = day 1 (first administration of evolocumab in FOURIER OLE study); DRE = disease-related events; **eCRF = electronic case report form;**EOS = end of study; FSH = follicle-stimulating hormone; HR = heart rate; Lp(a) = lipoprotein(a); **PI = personal injector;** SAE = serious adverse event; Q2W = every 2 weeks; QM = monthly; W = week.

Mandatory study visits will occur at day 1, week 12, and thereafter approximately every 6 months from day 1 (each site visit has a window of ± 2 weeks). Resupply visits will be scheduled quarterly (every 12 weeks). Evolocumab will be supplied directly to sites. **The last resupply of evolocumab will occur 12 weeks after the week 240 visit.**

[a] Subjects may be contacted by phone at week 240.

[b] No evolocumab to be dispensed; reconciliation only.

[c] Subjects will be contacted by phone at least 30 days (+ 3 days) after last evolocumab administration, unless they are continuing their participation in the study after ending evolocumab prior to study completion.

[d] On-study blood samples for these assessments will be processed at central laboratory. Additional laboratory assessments that may be deemed necessary to evaluate (serious) AEs will be processed locally. Serum pregnancy in females of childbearing potential. FSH only if needed to establish postmenopausal status.

[e] Screening pregnancy test to be completed within 7 days prior to enrollment by local institutional standard practice.

[f] Subjects administer evolocumab at a Q2W or QM schedule and will have the opportunity to switch between **the AI/Pen and PI,** at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. **The first self-administration after switching the device should be done at a regularly scheduled visit under the supervision of the investigator or qualified study center staff.**

[g] Recommended if study visit is within dosing schedule for the patient.

[h] **Coronary revascularization procedure and death information for cardiovascular events of interests must be collected in the eCRF that occur after signing the ICF through the EOS/Safety Follow-Up visit for this study, or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later. Sites will be prompted for this information when necessary.**

7.2 General Study Procedures

Mandatory study visits will occur at day 1, week 12 and thereafter approximately every 6 months from day 1 (each site visit has a window of ± 2 weeks). Resupply visits will be scheduled quarterly (every 12 weeks)**. The last resupply of evolocumab will occur 12 weeks after the week 240 visit**. Evolocumab will be supplied directly to the site. Method of resupply will be determined based on local regulations as well as available infrastructure. Assessments and procedures are per Schedule of Assessments (Table 3) and include vital signs, physical exam, body weight, concomitant therapy, adverse events/adverse device effects/serious adverse events/disease-related events assessments, fasting lipid panel, serum pregnancy testing (females of childbearing potential), and evolocumab administration. If evolocumab is administered at the site, the administration by SC injection will be done after all other procedures have been completed.

All on-study visits and dosing should be scheduled from FOURIER OLE study day 1 (day of first administration of evolocumab in FOURIER OLE study). When it is not possible to perform the study visit at the specified time point, the visit should be performed within the visit window in the Schedule of Assessments (Table 3). If a study visit is missed or late, all attempts should be made to bring the subject in to complete required assessments. If the visit occurs outside the visit window, subsequent visits should resume on the original visit schedule. If possible, all study procedures for a visit should be completed on the same day.

It is the responsibility of the investigator to ensure that all procedures are performed according to the protocol. 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 study visit are described below and the timing of the procedures is provided in the Schedule of Assessments (Table 3). If performed at the site, evolocumab administration must be after completion of blood draw procedures, as applicable.

The investigator should instruct the subject to report to the site (eg, telephone call) any adverse events, adverse device effects, serious adverse events, or disease-related events at any time (ie, between scheduled visits).

7.2.1 Screening, Enrollment, and Study Day 1

Subjects who meet eligibility criteria will be enrolled and within 3 days of enrollment will complete study day 1 procedures (as listed in Table 3), while continuing their background LLT. Day 1 is defined as the day of first administration of evolocumab in the FOURIER OLE study.

Subjects of childbearing potential are required to have a pregnancy test within 7 days prior to enrollment. This test is to be performed locally per institutional standard practice. Results are to be reviewed and documented before the subject can be enrolled.

For prior therapies, refer to Section 6.4.

The following procedures are to be completed during the screening period or study day 1 at time points designated in the Schedule of Assessments (Table 3):

- confirmation that the ICF has been signed
- age and other demographic data (including sex, race, and ethnicity, that will be carried over from the parent study) may be used to study their possible association with subject safety and treatment effectiveness
- medical/surgical history
- vital signs (eg, sitting blood pressure and heart rate)
- adverse event/serious adverse event/adverse device effect/disease-related event reporting
- concomitant therapy
- physical examination as per standard of care (including medical/surgical history). Physical examination findings should be recorded on the appropriate eCRF (eg, medical history, event).
- body weight
- **coronary revascularization procedure and death information (sites will be prompted for this information when necessary)**
- laboratory assessments including local and central laboratories, as applicable
- blood draw for a serum pregnancy test (women of childbearing potential only by central laboratory per local institutional standard practice)
- administration of evolocumab at study site (see Section 6.2.1 for instruction and supervision of subjects), if applicable
- dispensing evolocumab (prefilled AI/pens or PIs)

7.2.2 Treatment

The following procedures will be completed during the 5-year (260 week) treatment period at the times designated in the Schedule of Assessments (Table 3).

Administration of evolocumab is to be administered after completion of the blood draws and vital signs during each visit that it is required.

- vital signs (eg, sitting blood pressure and heart rate)
- review of adverse events/serious adverse events/adverse device effects/disease-related events
- review of concomitant therapy
- body weight
- **coronary revascularization procedure and death information (sites will be prompted for this information when necessary)**
- blood draws for fasting lipids (≥ 9-hour fasting sample), ApoA1, ApoB, and Lp(a)
- blood draw for a serum pregnancy test (women of childbearing potential only by central laboratory per local institutional standard practice)
- administration of evolocumab at study site (see Section 6.2.1 for instruction and supervision of subjects), if applicable
- reconciliation of used evolocumab, and dispensing evolocumab (prefilled AI/pens or PIs), if applicable

The investigator should instruct the subject to report to the site (eg, by telephone call) any adverse events, serious adverse events, adverse device effects, disease-related events at any time (ie, between scheduled visits). In addition, subjects will be contacted by telephone as designated in the schedule of assessments (Table 3) for collection of adverse events, serious adverse events, adverse device effects, disease-related events.

If, in the opinion of the investigator, a subject is unable to tolerate evolocumab, that subject will discontinue evolocumab but will continue to return for all other study procedures and measurements through the EOS.

If a subject withdraws from the study early, investigators should make every effort to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, the **week 260** procedures should be completed at the time of withdrawal (see Section 7.2.3).

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

7.2.3 Safety Follow-up Visit/End of Study Visit

A safety follow-up is scheduled to occur at least 30 days (+ 3 days) after last administration of evolocumab. This safety follow-up will be done by phone (Table 3).

The study required procedures during the EOS visit are outlined below:

- review of adverse events/serious adverse events/adverse device effects/disease-related events
- review of concomitant therapy
- **coronary revascularization procedure and death information (sites will be prompted for this information when necessary)**

7.2.4 Description of Study Procedures

7.2.4.1 Medical History

Ongoing adverse events from the end of the parent study (FOURIER), whether they have resolved or not at the time of signing the informed consent for the OLE (now classified as medical history) will be collected in the relevant medical history eCRF page. Medical history from prior to the date of enrollment into the parent study will not be collected in the OLE with the exception of heterozygous familial hypercholesterolemia (HeFH) diagnostic evidence. Any medical history on local diagnoses of HeFH (ie, criteria outlined by the Simon Broome Register Group [Scientific Steering Committee, 1991], the Dutch Lipid Clinic Network [World Health Organization, 1999], MEDPED [Williams et al, 1993]) or confirmed by genotyping, will be collected.

7.2.4.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure and heart rate.

Use of an automated oscillometric device for blood pressure measurement is preferred and recommended. Blood pressure should be recorded using the same arm as in FOURIER. The appropriate size cuff should be used. Blood pressure and heart rate measurements will 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 multiplied by 2 to obtain heart rate.

Record all measurements on the vital signs eCRF.

7.2.4.3 Review of Safety Events

All adverse events, serious adverse events, adverse device effects, and disease-related events must be recorded on the subject's eCRF that occur after signing the ICF through the EOS/Safety Follow-Up visit for this study, or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later. All reported adverse events are followed until resolution or stabilization.

During the independent review of deaths and cardiovascular events of interest, investigators may be prompted to provide additional information.

7.2.4.3.1 Coronary Revascularization Procedure and Death Information

Coronary revascularization procedure and death information for cardiovascular events of interests must be collected in the eCRF that occur after signing the ICF through the EOS/Safety Follow-Up visit for this study, or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later. Sites will be prompted for this information when necessary.

7.2.4.4 Physical Examination

A complete physical examination is to include examination of cardiovascular and respiratory systems, abdominal examination, and general neurologic examination.

7.2.4.5 Physical Measurements: Weight

Weight in kilograms should be measured without shoes.

7.2.4.6 Laboratory Assessments

Subjects must be fasting for ≥ 9 hours before each study visit where fasting lipid samples are obtained. On-study laboratory samples will be analyzed centrally as noted in the Schedule of Assessments (Table 3). Additional laboratory assessments that may be deemed necessary to evaluate (serious) adverse events will be processed locally.

Table 4 outlines the specific analytes that will be assessed during the study.

Table 4. Laboratory Analyte Listing

Laboratory Chemistry	Laboratory Coagulation	Laboratory Urinalysis	Laboratory Hematology	Other Labs
None	None	None	None	Fasting lipid panel: • Total cholesterol • Triglycerides • LDL-C • HDL-C • VLDL-C • non-HDL-C ApoA1 ApoB Lp(a) Pregnancy test (females of childbearing potential) FSH (if applicable)

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; FSH = follicle-stimulating hormone; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); non-HDL-C = non-high-density lipoprotein cholesterol; VLDL-C = very low-density lipoprotein cholesterol

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Assessments (Table 3) and collection of data, including endpoints and adverse events and must document this decision in the subject's medical records. The investigator must discuss the different options of follow up (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other treating physicians, from review of the medical records or public records as permitted by applicable law). Such public record searches may be conducted by the site or vendors approved by the site. Subjects who have discontinued investigational product, device, and/or protocol required therapies as well as study assessments or procedures should not be automatically

removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria [see Section 6.2.1.2], pregnancy)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

8.4 Lost to Follow-up

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

The site must attempt to contact the subject at each scheduled visit and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study. These contact attempts are to be documented in the subject's medical record.

For subjects who are lost to follow-up, the investigator (or vendors approved by the site) can search publicly available records as permitted by applicable law to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, subjects have hyperlipidemia and clinically evident atherosclerotic CVD. Therefore, disease-related events include the following: manifestations and complications of atherosclerotic vascular disease such as coronary artery disease, angina, MI, ischemic stroke, TIA, carotid artery disease, peripheral vascular disease (including complications such as claudication), and testing suggesting progression of atherosclerotic vascular disease. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

Disease-related events that do not qualify as adverse events or serious adverse events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.
- Death due to the disease under study is to be recorded on the Event eCRF.

Disease-related events that would qualify as an adverse event or serious adverse event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product (evolocumab)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

Disease-related events will be collected through OLE duration including the safety follow-up visit, and will be **recorded** using the Event eCRF **per Section 9.2.1**.

9.1.2 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 or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) 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 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.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a disease-related event as defined in Section 9.1.1):

- 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

A disease-related event (eg, angina) is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria.

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, DILI (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-Related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after signing the ICF through the EOS/Safety Follow-Up visit for this study, or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later, are recorded on the Event eCRF as a disease-related event.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product (evolocumab)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event eCRF as serious adverse events.

Additionally, the investigator is required to report a fatal disease-related event on the Event eCRF as a disease-related event.

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events and adverse device effects observed by the investigator or reported by the subject that occur after signing the ICF through the EOS/Safety Follow-Up visit for this OLE study, or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later, are reported using the Event eCRF.

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- dates of onset and resolution (if resolved)
- severity
- assessment of relatedness to investigational product (evolocumab and/or the medical devices [prefilled AI/pen or PI]), any study-mandated activity or procedure, or other protocol-required/study-mandated therapies)
- action taken

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event eCRF.

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

The investigator must assess whether the adverse event is possibly related to investigational medicinal product (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 the investigational medicinal product and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to the prefilled AI/Pen or PI investigational devices used to administer investigational medicinal

product (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 investigational device?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical devices and/or procedure including any screening procedures). 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 (eg, administration of investigational product, protocol-required therapies, use of medical devices), and/or 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) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2.2 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 the ICF through the EOS/Safety Follow-Up visit for this study, or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event eCRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/eSAE Contingency Report Form. For EDC studies where the

first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to investigational medicinal product (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 the investigational medicinal product and/or other protocol-required therapies?

The investigator must assess whether the serious adverse event is possibly related to the prefilled AI/Pen or PI investigational devices used to administer investigational medicinal product (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 investigational device?

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical devices and/or procedure including any screening procedures). 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 (eg, administration of investigational product, protocol-required therapies, use of medical devices), and/or procedure?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

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. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs

in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

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

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant while the subject is taking evolocumab report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur for an additional 15 weeks after the last dose of evolocumab.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

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

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

Amgen is sponsoring a prospective, observational study of pregnant women who have been exposed to Repatha® (evolocumab) at any point during pregnancy and/or breastfeeding. The registry is conducted in Europe, South Africa, and Australia. Participants are not asked to make any changes to their healthcare routine. While subjects who are pregnant are not eligible for the 20160250 study, if a site investigator/health care practitioner has a subject who becomes pregnant while receiving evolocumab, they will be advised to refer the subject to Amgen's evolocumab pregnancy registry according to the place of residency. More information on the pregnancy registry study in Europe, South Africa, and Australia is available in the respective study protocol (Protocol ID: 20150162 and the following websites; ClinicalTrials.gov and AmgenTrials.com.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

The primary endpoint is the subject incidence of adverse events.

10.1.1.2 Secondary Endpoints

The secondary endpoints for this study are the following:

- percent change of LDL-C from baseline at each scheduled visit
- achievement of an LDL-C < 40 mg/dL (1.03 mmol/L) at each scheduled visit

10.1.1.3 Exploratory Endpoints

The exploratory endpoints for this study are the following:

- Change and percent change from baseline at each scheduled visit in each of the following lipid parameters:
  - total cholesterol
  - triglycerides
  - HDL-C
  - VLDL-C
  - LDL-C
  - non-HDL-C
  - ApoA1
  - ApoB
  - Lp(a)
- Subject incidence of events positively reviewed by the CEC:
  - All deaths
  - Cardiovascular events of interest:
    - MI
    - Stroke
    - **Coronary r**evascularization
    - Hospitalization for unstable angina
    - Hospitalization for heart failure
    - TIA

10.1.2 Analysis Sets

The OLE safety analysis set includes all subjects who received at least 1 dose of open-label evolocumab in the OLE study. This analysis set will be used for all analyses.

10.1.3 Covariates and Subgroups

The planned covariates and subgroups include the following:

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- race

10.1.4 Handling of Missing and Incomplete Data

No missing value imputation is planned for primary, secondary, or exploratory endpoints.

10.2 Sample Size Considerations

It is estimated approximately 1600 subjects who completed the FOURIER trial will be enrolled. Based on sample size of 1600 subjects, Table 5 lists the width of 95% confidence interval (CI) for a range of various underlying adverse event rates.

Table 5. Confidence Interval Width for Adverse Event Rates

Underlying Adverse Event Rate (%)	Width of 95% Confidence Interval
0.01	0.098
0.05	0.219
0.10	0.310
1.00	0.975
2.00	1.372
3.00	1.672
4.00	1.920
5.00	2.136

10.3 Planned Analyses

10.3.1 Interim Analyses

There will be interim analyses to support safety data reporting and assessments of other listed endpoints. The study is not anticipated to stop early unless a major unexpected safety signal is detected.

10.3.2 Primary Analysis

Primary analysis activities are commenced based on achieving the EOS milestone described in Section 3.5.2.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Statistical analyses in this open label study are descriptive in nature. No statistical inference or missing value imputation is planned. No formal hypothesis will be tested in this study. 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. Unless specified otherwise, the baseline value is defined as the subject's baseline value from the parent study (FOURIER) and all analyses (primary, secondary, exploratory, and safety) will be performed on the OLE safety analysis set. For all endpoints, results will be summarized

by the randomized treatment group from the FOURIER study and overall, unless specified otherwise.

The primary analysis of all primary, secondary, and exploratory endpoints will use data from the OLE study only. Additional analyses combining the data from the OLE study and FOURIER study will be performed as applicable.

All deaths and cardiovascular events of interest (MI, stroke, **coronary** revascularization, hospitalization for unstable angina, hospitalization for heart failure, and TIA) will be reviewed by an independent external CEC, using standardized definitions. The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists) and medical reviewers trained on the clinical trial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC reviews events according to pre-specified criteria defined in the CEC charter. The CEC will be blinded to the original randomized treatment group from the FOURIER study.

10.4.2 Primary Endpoint

The current Medical Dictionary for Regulatory Activities (MedDRA) version at the time of the data lock will be used to code all adverse events **and disease related events** to a system organ class and preferred term. Exposure adjusted subject incidence rates of all treatment emergent adverse events, serious adverse events, fatal adverse events, adverse events leading to withdrawal from investigational product, device-related adverse events, and disease related events will be tabulated for overall OLE study period. These events will also be presented by yearly subject exposure time intervals . **All adverse event summaries for the primary analysis of the primary endpoint will include a**ll **treatment-emergent** events **reported on the Event eCRF**, including CEC reviewed events **and disease related events**. All CEC reviewed events will be reported.

Adverse event data from the OLE study will also be combined with FOURIER study data as an additional analysis and positively reviewed events will not be included in the adverse event analysis to remain consistent with FOURIER adverse event reporting.

10.4.3 Secondary Efficacy Endpoints

Summary statistics of the secondary endpoints (percent change of LDL-C from baseline and achieving an LDL-C < 40 mg/dL) will be provided.

10.4.4 Exploratory Efficacy Endpoints

Summary statistics of exploratory endpoints will be provided at each scheduled visit for each exploratory lipid parameter. Subject incidence of positively reviewed events (by an independent external CEC) will be summarized.

10.4.5 Additional Safety Analyses

Vital signs will be summarized using descriptive statistics at each scheduled visit. Concomitant medications of interest and exposure to evolocumab will also be summarized.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Manager to the investigator. The written ICF is to 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 or legally acceptable representative 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 product (evolocumab) is administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

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

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical

records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

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

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF 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 IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC 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 is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

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 eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

- For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental/International Conference on Harmonisation (ICH) GCP guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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 Clinical Trial Agreement. The investigator is to notify the IRB/IEC in

writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

12.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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

Elements to include:

- subject files containing completed eCRFs, ICFs, and subject identification list
- study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable.

In addition, all original source documents supporting entries in the eCRFs 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(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the eCRFs 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 Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs 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 is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying 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 (Table 3), the investigator can search publicly 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

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

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals (ICMJE, 2013), 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; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors 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 review. The Clinical Trial Agreement among the institution, 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 that is available as a separate document. Subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs), if permitted under applicable regional laws or regulatory guidelines.

13. REFERENCES

Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154-156.

Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403-414.

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372:2387-2397.

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681.

Evolocumab (AMG 145) Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Franc S, Dejager S, Bruckert E, Chauvenet M, Giral P, Turpin G. A comprehensive description of muscle symptoms associated with lipid-lowering drugs. *Cardiovasc Drugs Ther*. 2003;17:459-465.

Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

Kannel WB et al. The Framingham Study: An epidemiological investigation of cardiovascular disease, Section 30. Some characteristics related to the incidence of cardiovascular disease and death: The Framingham Study. 18-year follow-up. Washington, D.C., Dept. of Health, Education, and Welfare, Publication No. (NIH) 1974:74-599.

Kannel WB, Castelli WP, Gordon T. Lipoprotein cholesterol in the prediction of atherosclerotic disease: New perspectives based on the Framingham Study. *Ann Intern Med*. 1979;90:85-91.

Kannel WB. Range of serum cholesterol values in the population developing coronary artery disease. *Am J Cardiol*. 1995;76:69C-77C.

Libby, P and Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111:3481-3488.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.

Sabatine MS, Guigliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1500-1509.

Scientific Steering Committee of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ*. 1991;303(6807):893 896.

Tolonen H, Keil U, Ferrario M, Evans A, WHO MONICA Project. Prevalence, awareness and treatment of hypercholesterolaemia in 32 populations: results from the WHO MONICA Project. *Int J Epidemiol*. 2005;34:181-192.

Williams RR, Schumacher MC, Barlow GK, et al. Documented need for more effective diagnosis and treatment of familial hypercholesterolemia according to data from 502 heterozygotes in Utah. *Am J Cardiol*. 1993;72:18D-24D.

World Health Organization. Familial Hypercholesterolaemia (FH): Report of a second WHO consultation. Geneva 1999.

World Health Organization. Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. Geneva 2011; http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event grading and information. The CTCAE is available at the following link:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin (TBL) and/or international normalized ratio (INR) elevation according to the criteria specified in Section 6.3 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 1 or who experience AST or ALT elevations > 3x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

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

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - complete blood count (CBC) with differential to assess for eosinophilia
  - serum total immunoglobulin G, anti-nuclear antibody (ANA), anti-smooth muscle antibody, and liver kidney microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - serum acetaminophen (paracetamol) levels
  - a more detailed history of:
    - prior and/or concurrent diseases or illness
    - exposure to environmental and/or industrial chemical agents
    - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - prior and/or concurrent use of alcohol, recreational drugs and special diets
    - concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - viral serologies
  - creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
  - appropriate liver imaging if clinically indicated
- appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in corresponding electronic case report forms (eCRFs).

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20160250 Evolocumab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<< For competion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

and start date: Day ____ Month ____ Year ____

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Evolocumab: No / Yes Prefilled autoinjector pen (Aiper): No / Yes On-body 3.5 mL Personal Injector	Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No	☐Yes ☐No				
				☐Yes ☐No	☐Yes ☐No				
				☐Yes ☐No	☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability / incapacity; 06 Congenital anomaly / birth defect; 08 Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20160250 Evolocumab	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

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

IP/Amgen Device:		Prior to, or at time of Event: Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Prior to, or at time of Event: Dose	Prior to, or at time of Event: Route	Prior to, or at time of Event: Frequency	Action Taken with Product (01 Still being Administered; 02 Permanently discontinued; 03 Withheld)	Lot # and Serial #
Evolocumab	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AI/Pen)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
On-body / 3.5 mL Personal Injector	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

AMGEN Study # 20160250 Evolocumab	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

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)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20160250

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
Evolocumab				mm____/dd____/yyyy____

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

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

If yes, provide date of delivery: mm____ / dd____ / yyyy____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20160250

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
Evolocumab				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix D. Recommended Lipid-lowering Background Therapy

It is recommended that subjects continue the same background lipid-lowering therapy (LLT), including statin, as taken during FOURIER. Background LLT should be optimized for the individual subject consistent with local professional society guidelines. All subjects should receive at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended.

No other lipid therapy is required for the FOURIER OLE study. Ezetimibe and other commercially available lipid therapy at dosages approved by local regulatory authorities may be added to any of these regimens except excluded medication as per Section 6.7. These therapies, including statins, are not provided or reimbursed by Amgen (except if required by local regulation). Background LLT received at enrollment should remain unchanged throughout the entire duration of the study.

Appendix E. Drugs With Known Major Interactions With Statin Background Therapy

Atorvastatin:

- strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, human immunodeficiency virus (HIV) or hepatitis C virus (HCV) protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 L daily])

Simvastatin:

- strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 L daily])
- verapamil
- diltiazem
- danazol
- if simvastatin > 20 mg
  - amlodipine
  - amiodarone
  - ranolazine

Rosuvastatin:

- systemic cyclosporine
- and if rosuvastatin > 10 mg, HIV or HCV protease inhibitors

Pitavastatin:

- systemic cyclosporine
- erythromycin
- rifampin

Amendment 2

Protocol Title: A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries

Amgen Protocol Number (evolocumab) 20160250

EudraCT number 2016-004066-26

NCT number: NCT03080935

Amendment Date: 19 February 2020

Rationale:

This protocol is being amended to:

- Update safety language:
  - Safety Section updated to reflect that all serious drug-related events must be recorded and reported to the sponsor or designee within 24 hours
  - Included “coronary revascularization” throughout the protocol to identify the specific vascular territory of interest, which is the coronary circulation.
  - The identified Events of Interest (EOIs) were removed from the protocol and are no longer pre-specified.
- Update the Schedule of Assessments:
  - Added week 260 (replacing End of Investigational Product Administration [EoIP]) back into the schedule of assessments to realign with the 20130295 sister study and to clarify that the week 260 visit still applies.
  - Coronary revascularization procedure and death information added throughout to support the independent safety review of cardiovascular events of interest and deaths by the Clinical Events Committee.
- Clarify dosing details:
  - details regarding the switch frequency between auto-injector/pen (AI/pen) and personal injected (PI) were added, and
  - the last resupply of evolocumab will occur 12 weeks after the week 240 visit.
- Update the exploratory objectives in Section 1.3 to be consistent with exploratory endpoints in Section 10.1.1.3
- Remove language in the definition of Primary Completion to align with current protocol template.
- Administrative, typographical, and formatting changes were made throughout the protocol

Amendment 1

Protocol Title: A Multicenter, Open-label, Single-arm, Extension Study to Assess Long term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries

Amgen Protocol Number (evolocumab) 20160250

Amendment Date: 14 December 2018

Rationale:

The following changes are being made to the study for the reasons indicated:

- Financial disclosure statement text removed as this is not applicable to this study (only European sites will be participating)
- An independent external Clinical Events Committee was established and will review deaths and cardiovascular events of interest; cardiovascular events of interest to be reviewed were defined
- The term “targeted” concomitant therapy was removed throughout; all concomitant therapy will be assessed.
- Clarification of statistical considerations: primary analysis of all endpoints in the OLE study will only use OLE study data and how CEC events will be analyzed.
- Exposure time intervals were modified
- Clarifications of text or update with current template and Amgen standards:
    - Clarification of text to indicate that the lipid profiles are conducted at scheduled visits and not on a yearly basis
    - Self-evident correction text was removed as it is no longer an Amgen standard
    - Week 260 was removed as part of end of study definition for clarity
    - Concomitant therapy for disease under study, antibiotics, and then all other therapies: information collected was clarified
    - Male contraception language removed as not applicable.
    - Clarification of how data will be collected and defined when a subject transitions from parent to OLE study, including medical history and what data will be transferred to OLE was provided.
    - Definition of subject withdrawal updated throughout and aligned with current template.
    - Redundant text for subject withdrawal and concomitant therapy removed.
    - Resupply period was clarified
    - Lot number was changed to box number for accuracy

- Lost to follow up section added for clarity
- Figure 1 text modified for clarity
- Table 3: Schedule of Assessments text modified for clarity

Administration, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.