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

Evolocumab (AMG 145)

Amgen Protocol Number 20130295

EudraCT number 2015-004780-36

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FOURIER-OLE

Further Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk **O**pen-**l**abel **E**xtension

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Amendment 1 20 November 2017

Amendment 2 08 April 2019

Amendment 3 26 February 2020

Confidentiality Notice

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 Patients With Clinically Evident Cardiovascular Disease," dated **26 February 2020**, and agree to abide by all provisions set forth therein.

I agree to comply with the International **Council for** Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) 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 Patients With Clinically Evident Cardiovascular Disease

Study Phase: 3b

Indication: Dyslipidemia

Primary Objective: The primary objective is to describe the safety and tolerability of long-term administration of evolocumab.

Secondary Objectives: 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.

Hypotheses: 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 long-term safety of evolocumab in subjects who completed the FOURIER study (Study 20110118), a randomized placebo-controlled study of evolocumab in subjects with clinically evident atherosclerotic CVD on stable effective statin therapy. Eligible subjects at sites participating in this study who have signed the informed consent for this OLE may be enrolled at the completion of the FOURIER study. Enrollment of eligible subjects may be limited at the site level to maintain a 1:1 ratio between the following subject populations:

- subjects with ≥ 2 years of study exposure in FOURIER and
- subjects who have less than 2 years of study exposure in FOURIER and did not participate in the EBBINGHAUS study (Study 20130385)

Eligible subjects from EBBINGHAUS may participate in this study regardless of FOURIER study exposure.

This study (FOURIER OLE) requires laboratory assessments at week 12 and thereafter approximately every 24 weeks from day 1; the corresponding blood samples will be processed using a central laboratory. To preserve the integrity of FOURIER blinding, no local lipid assessments may be performed until either FOURIER is unblinded or at least 12 weeks after a subject's last administration of FOURIER investigational product (evolocumab or placebo), whichever is first.

Upon enrollment in this study (FOURIER OLE), subjects will receive evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM), according to the subject's preference. The 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 5000 subjects will be enrolled, including approximately 2000 subjects with ≥ 2 years of study exposure in FOURIER.

Summary of Subject Eligibility Criteria: Subjects must have completed FOURIER (Study 20110118) while still receiving assigned investigational product and provided informed consent for this OLE 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 4.1 through Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Evolocumab will be administered using a handheld mechanical (spring-based) prefilled 1.0 mL autoinjector/pen (AI/Pen) or an on-body electromechanical injection 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 unless required by local regulations.

Procedures: Mandatory study visits will occur at week 12 and thereafter approximately every 24 weeks from day 1. Evolocumab resupply visits will be scheduled quarterly (every 12 weeks). Evolocumab will be supplied to the subject at 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 targeted concomitant therapy, adverse events, device-related adverse effects, serious adverse events, and disease-related events; Cambridge Neuropsychological Test Automated Battery (CANTAB) assessments (only in subjects from EBBINGHAUS [Study 20130385]); laboratory assessments, including fasting lipid panel, apolipoprotein A1, apolipoprotein B, and lipoprotein(a); serum (or urine) 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 1).

Statistical Considerations: The primary and secondary endpoints will use the OLE safety analysis set (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 will be descriptive in nature. No statistical inference or missing value imputation is planned. No formal hypotheses 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/EBBINGHAUS 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 using the OLE safety analysis set. These events will also be presented by yearly subject exposure time intervals. All events, including CEC reviewed events will be tabulated.

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. The analysis will be performed using the long-term safety analysis set.

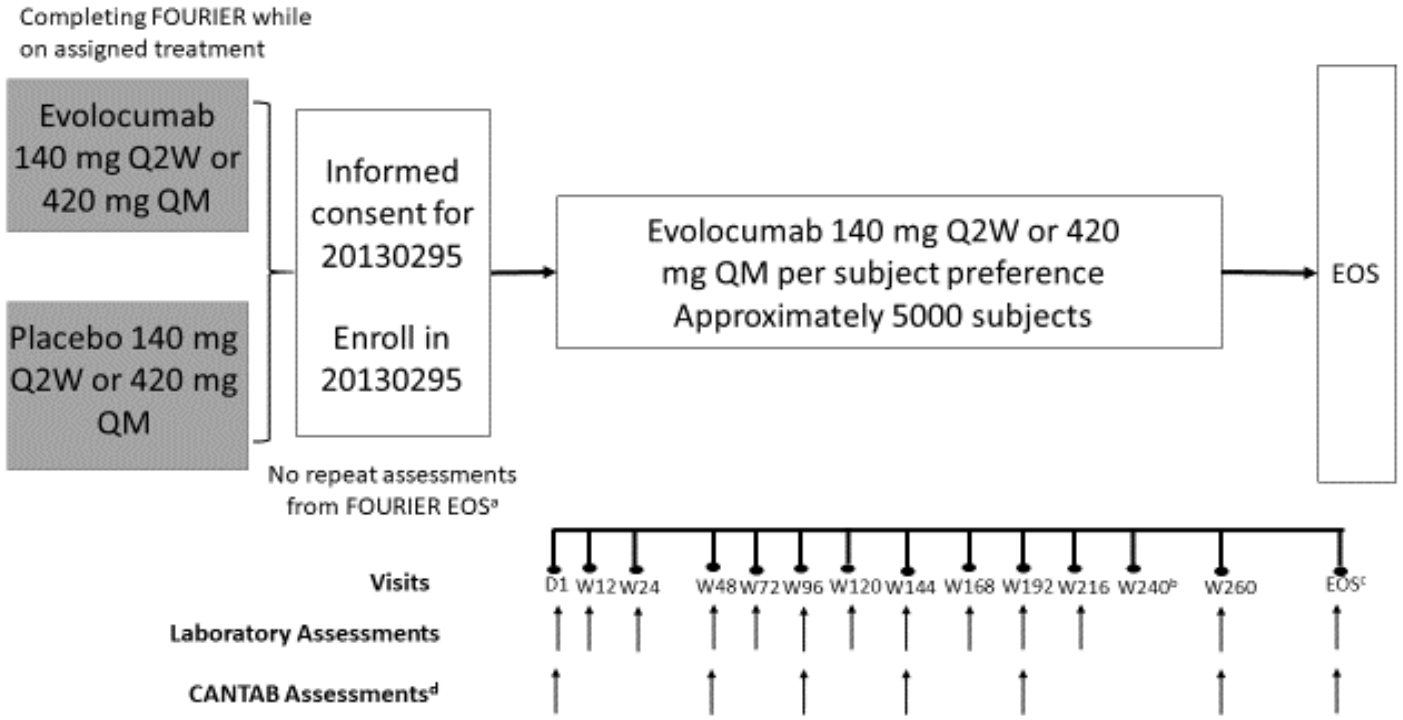
Summary statistics of the secondary endpoints (percent change of LDL-C from baseline and achieving an LDL-C < 40 mg/dL) will be provided.

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

Sponsor: Amgen

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

Study Design and Treatment Schema



CANTAB = Cambridge Neuropsychological Test Automated Battery; D = day; EOS = end of study; Q2W = every 2 weeks; QM = monthly; W = week

[a] Assessments do not need to be repeated except when the day 1 visit of this open-label extension study occurs > 90 days after the FOURIER EOS visit.

[b] Subjects may be contacted by phone.

[c.] Subject 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] CANTAB assessments will only be performed for subjects from the EBBINGHAUS study.

Study Glossary

Abbreviation or Term	Definition/Explanation
AI/Pen	autoinjector/pen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
AST	aspartate aminotransferase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CEC	Clinical Events Committee
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
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
EBBINGHAUS	Study 20130385; a substudy of FOURIER
eCRF	electronic case report form
EDC	electronic data capture
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 evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
end of study (primary completion)	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
end of treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	end of study for individual subject; defined as the last day that protocol-specified procedures are conducted for an individual subject
FOURIER	Study 20110118; the parent study for this open-label extension study
FOURIER OLE	open-label extension study of the FOURIER study (ie, the study described by this protocol)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCV	hepatitis C virus

Abbreviation or Term	Definition/Explanation
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IFU	instructions for use
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LLT	lipid-lowering therapy
Lp(a)	lipoprotein(a)
MI	myocardial infarction
OLE	open-label extension
PAL	Paired Associates Learning
PCSK9	proprotein convertase subtilisin/kexin type 9
PI	**personal injector**
Q2W	every 2 weeks
QM	monthly; defined as every 4 weeks
RTI	Reaction Time
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.
SWM	Spatial Working Memory
TIA	transient ischemic attack
TBL	total bilirubin
ULN	upper limit of normal
US	United States
VLDL-C	very low-density lipoprotein cholesterol

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1. OBJECTIVES

1.1 Primary

The primary objective is 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 < 40 mg/dL (1.03 mmol/L)

1.3 Exploratory

The exploratory objectives in subjects who completed the EBBINGHAUS study (Study 20130385) are the following:

- to evaluate long-term change over time in executive function, as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) strategy index of executive function
- to evaluate long-term change over time in working memory, as assessed by the CANTAB SWM test between-errors score
- to evaluate long-term change over time in memory function, as assessed by the CANTAB Paired Associates Learning (PAL) test
- to evaluate long-term change over time in psychomotor speed, as assessed by the CANTAB Reaction Time (RTI) test

The exploratory objective**s** in all subjects are:

- to describe the effects of long-term evolocumab administration on non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol, lipoprotein(a) (Lp[a]), triglycerides, HDL-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 worldwide epidemic; although CVD mortality has declined over the last 2 decades (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 estimated 57 million deaths worldwide, of which 36 million were due to noncommunicable causes. Cardiovascular diseases accounted for over 17 million of

these deaths; nearly 80% of which were due to heart attacks and strokes alone (responsible for 7.3 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 area 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 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 (US), Europe, and Japan are currently treated with dyslipidemia therapies. The rationale for treatment of dyslipidemia, particularly elevated LDL-C, extends from extensive clinical study 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 studies 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, nonfatal myocardial infarction [MI], coronary revascularization, or stroke). Importantly, this meta-analysis, which also evaluated 5 studies that compared more versus less intensive statin therapy, did not find an 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 were 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 patients on lipid reduction therapy still have cardiovascular events (Libby, 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 (National Cholesterol Education Program, 2002; Grundy et al, 2004), Cholesterol Treatment Trialists Collaboration (2010) data suggest that novel agents capable of providing additional LDL-C reduction 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). Nonstatin 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%.

The IMPROVE-IT study evaluated cardiovascular outcomes (cardiovascular death, MI, hospital admission for unstable angina, 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 MI or non-ST segment elevation MI or unstable angina less than 10 days before enrollment (Cannon, 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 nonstatin therapy, ezetimibe.

Considering the remaining cardiovascular risk despite the availability of statin therapy and given that nonstatin 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 nonstatin agent that will get a significant proportion of patients to their 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 an MI, nonhemorrhagic stroke, **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 suggest the 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 Evolocumab Investigator's Brochure for more information on evolocumab.

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 5000 subjects will be enrolled. Approximately 2000 subjects with 2 or

more years of study exposure in FOURIER will be enrolled in this OLE to provide safety and tolerability for subjects with 7 years of total study exposure (from the start of FOURIER to completion of the OLE). Assuming approximately 50% of these 2000 subjects were on evolocumab in FOURIER, approximately 1000 subjects will have 7 years of total evolocumab exposure. Additionally, subjects participating in the EBBINGHAUS study (Study 20130385; a substudy of FOURIER) will be provided the opportunity to enroll in the OLE so that additional long-term assessments of cognitive function will be performed, using the CANTAB.

The FOURIER OLE sites will be a subset of FOURIER sites. The FOURIER OLE study population will comprise the following subject groups:

a) subjects who have at least 2 years of study exposure in FOURIER
b) subjects from EBBINGHAUS, regardless of study exposure
c) subjects who have less than 2 years of study exposure in FOURIER and did not participate in EBBINGHAUS

Enrollment of eligible subjects may be limited at the site level, to maintain a 1:1 ratio between subject groups “a” and “c” (ie, subjects who have ≥ 2 years of study exposure in FOURIER and subjects who have less than 2 years of study exposure in FOURIER and did not participate in EBBINGHAUS) or to manage overall recruitment into the OLE.

2.4 Clinical Hypotheses

The primary 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, open-label extension study designed to assess the long-term safety of evolocumab in subjects who completed the FOURIER study, a randomized placebo-controlled study of evolocumab in subjects with clinically evident atherosclerotic CVD on stable effective statin therapy. Eligible subjects at sites participating in FOURIER OLE who have signed the FOURIER OLE informed consent may be enrolled at the completion of FOURIER. Enrollment of eligible subjects may be limited at the site level to maintain a 1:1 ratio between the following subject populations:

- subjects with ≥ 2 years of study exposure in FOURIER and
- subjects who have less than 2 years of study exposure in FOURIER and did not participate in EBBINGHAUS

In this study, laboratory assessments will be performed at week 12 and thereafter approximately every 24 weeks from day 1 (see Section 7.2); the corresponding blood samples will be processed using a central laboratory. To preserve the integrity of FOURIER blinding, no local lipid assessments may be performed until either FOURIER is unblinded or at least 12 weeks after a subject's last administration of FOURIER investigational product (evolocumab or placebo), whichever is first. Upon enrollment in this study (FOURIER OLE), 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 at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 250 centers will participate in this study in North America and Eastern Europe. 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 5000 subjects will be enrolled, including approximately 2000 subjects with ≥ 2 years of study exposure in FOURIER.

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 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, safety follow-up), as applicable.

4. SUBJECT ELIGIBILITY

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

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

102 Subject has completed FOURIER (Study 20110118) while still receiving assigned investigational product.

4.1.2 Exclusion Criteria

201 Investigational product was permanently discontinued during FOURIER for any reason, including an adverse event or serious adverse event.

202 Subject is currently receiving treatment in another investigational device or drug study, or ended treatment on another investigational device or drug study(ies) within less than 4 weeks. Other investigational procedures while participating in this study are excluded.

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

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

206 Female subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment with evolocumab and within 15 weeks after the end of treatment with evolocumab.

207 Female subjects of childbearing potential who are not 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 are excluded.

Female subjects of non-childbearing potential are not required to use contraception during the study and include those who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal. Postmenopausal is defined as 12 months of spontaneous and continuous amenorrhea in a woman ≥ 55 years old; or age < 55 years but no spontaneous menses for at least 2 years; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone [FSH] levels > 40 IU/L), postmenopausal estradiol levels (< 5 ng/dL), or according to the definition of postmenopausal range for the laboratory involved.

Acceptable methods of effective birth control include true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject; periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception), bilateral tubal ligation/occlusion, vasectomized partner (provided the vasectomized male has received medical assessment of surgical success), use of hormonal birth control methods (oral, intravaginal, transdermal, injectable, or implantable), intrauterine devices, intrauterine hormonal releasing system, or 2 barrier methods (each partner must use one barrier method) and the female partner must use spermicide in addition to a barrier method (men must use a condom; women must choose either a diaphragm, cervical cap, or contraceptive sponge [a female condom is not an option because of the risk of tearing when both partners use a condom]). If spermicide is not commercially available in the country or region, the 2-barrier method without spermicide is acceptable. Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require the use of highly effective methods of contraception, an increase in the number of contraceptive methods, a change in type of contraceptive methods, and/or an increase in the length of time that contraception is to be utilized or length of time that breastfeeding is to be avoided. The investigator is to discuss these contraceptive changes with the study subject.

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). All subjects 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. The investigator is to document this decision and date, in the subject's medical record and on the enrollment electronic case report form (eCRF).

Each subject who signs the IRB/IEC-approved ICF is to be assigned the same subject identification number for this OLE study as the parent study (FOURIER) 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.

5.1 Treatment Assignment

All subjects will receive open-label evolocumab.

6. TREATMENT PROCEDURES

6.1 Classification of Products and/or Medical Devices

The Amgen investigational medicinal product used in this study is evolocumab (AMG 145). In several countries, investigational product is referred to as investigational medicinal product. In this document, investigational medicinal product will be referred to as investigational product (evolocumab).

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

Evolocumab will be provided by prefilled autoinjector/pen (AI/Pen) or **personal injector (PI)**.

Note: Ancillary devices (ie, medical devices not under study) are described in Section 6.6.

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 information about background LLT and the investigational medical devices used in this study.

6.2 Investigational Product - Evolocumab

Evolocumab (AMG 145) will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product distribution procedures. Evolocumab will be provided 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 to the subject at 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 eCRF. Subjects should return used evolocumab for reconciliation by the site.

6.2.1 Dosage, Administration, and Schedule

Evolocumab will be administered SC for approximately 260 weeks in accordance with the instructions in the IPIM and IFU. 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.

If evolocumab is 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.

Subjects 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. The first self-administration after switching the dose and frequency (140 mg Q2W to 420 mg QM or vice versa) 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.

If a subject dose of evolocumab is missed, administration should occur as soon as possible if there are more than 7 days 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.

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.

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

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

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.

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.

Stopping and rechallenge rules due to hepatotoxicity are provided in Section 6.4.

6.3 Non-Amgen Non-investigational Products - Background Lipid-lowering Therapy

Non-Amgen non-investigational products, including background LLT, will also be used in this study. Additional details regarding the products are provided in the IPIM.

6.3.1 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, and frequency of 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. These therapies will not be provided or reimbursed by Amgen (except if required by local regulation).

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

6.3.2 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.

If a subject has elevated ad hoc laboratory values (Section 6.4) 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.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of evolocumab, statins, and other applicable lipid background therapies as specified in the Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation (July 2009). Hepatic laboratory assessments are not required for this study. However, the following guidelines apply for elevations noted during ad hoc tests.

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

Amgen investigational product (evolocumab), statins, and other applicable lipid background therapies should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL ≥ 2 x ULN
- AND increased AST or ALT > 3 x ULN if baseline values were less than the ULN
- AND ALP < 2 x ULN
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; 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
- nonhepatic causes (eg, rhabdomyolysis, hemolysis)

6.4.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of evolocumab outlined above and have no underlying liver disease, the following rules are recommended for withholding of evolocumab, statins, and other applicable lipid background therapies:

- elevation of either AST or ALT according to the following:
  - > 8 x ULN at any time
  - > 5 x ULN but < 8 x ULN for ≥ 2 weeks
  - > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule
  - > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (eg, right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice)
- OR TBL > 3 x ULN at any time
- OR ALP > 8 x ULN at any time

Evolocumab, statins, and other applicable lipid background therapies should be withheld pending investigation into alternative causes of DILI. If evolocumab is withheld, the subject is to be followed according to recommendations in Appendix A for possible 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 6.4.3).

6.4.3 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 Section 6.4.1) should never be rechallenged.

6.5 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 6.8.

Targeted 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
- 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 targeted 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 1). Concomitant therapies are to be collected from informed consent through the end of safety follow-up period.

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.

6.6 Medical Devices

Evolocumab will be provided by prefilled AI/Pen or **PI** (Section 6.2).

Other medical devices, which are not considered test articles, may be used in the conduct of this study as part of standard 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.

6.7 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 drug or devices provisioned and/or repackaged/modified by Amgen. Drug or devices includes evolocumab, AI/Pen, and **PI**.

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

6.8 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.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Eligible subjects who have signed the ICF and meet the inclusion/exclusion criteria requirements for this FOURIER OLE study will be enrolled at the completion of the FOURIER study. Subject identification numbers will be the same as those in FOURIER. Assessments done for the FOURIER/EBBINGHAUS (as applicable) EOS visit do not need to be repeated for this study, unless day 1 in this study (FOURIER OLE) occurs > 90 days after the FOURIER EOS visit. Baseline data for participating subjects will be carried over from the FOURIER study.

Table 1. Schedule of Assessments

Time Point	Treatment Period (± 14 days)													Safety Follow-up
	Day 1[a]	Wk12	Wk24	Wk48	Wk72	Wk96	Wk120	Wk144	Wk168	Wk192	Wk216	Wk240[b]	Wk260	EOS[c]
GENERAL AND SAFETY ASSESSMENTS														
Informed consent	X													
Targeted concomitant therapy	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Device-related adverse effects	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease-related events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[d]												X	
Vital signs[e]	X[d]	X	X	X	X	X	X	X	X	X	X		X	
Body weight	X[d]	X	X	X	X	X	X	X	X	X	X		X	
Coronary revascularization procedure and death information[f]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
NEUROCOGNITIVE ASSESSMENTS														
CANTAB SWM test[g]	X[d]			X		X		X		X			X	
CANTAB PAL test[g]	X[d]			X		X		X		X			X	
CANTAB RTI test[g]	X[d]			X		X		X		X			X	
LABORATORY ASSESSMENTS[h]														
Fasting lipid panel	X[d]	X	X	X	X	X	X	X	X	X	X		X	
ApoA1, ApoB, Lp(a)	X[d]	X	X	X	X	X	X	X	X	X	X		X	
Pregnancy test[i]	X	X	X	X	X	X	X	X	X	X	X		X	
FSH[j]	X													
DOSING														
Administration at study site[k]	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense/reconcile evolocumab[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes defined on next page of the table

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; CANTAB = Cambridge Neuropsychological Test Automated Battery; **eCRF = electronic case report form;** EOS = end of study; FSH = follicle-stimulating hormone; Lp(a) = lipoprotein(a); PAL = Paired Associates Learning; Q2W = every 2 weeks; QM = monthly; RTI = Reaction Time; SWM = Spatial Working Memory; Wk = week

Mandatory study visits will occur at week 12 and thereafter approximately every 24 weeks from day 1. Resupply visits will be scheduled quarterly (every 12 weeks).

[a] Day 1 is the day of first administration of evolocumab in this study (FOURIER open-label extension).

[b] Subjects may be contacted by telephone at week 240.

[c] Subject 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] FOURIER/EBBINGHAUS (as applicable) EOS assessments should not be duplicated, except when day 1 occurs > 90 days after the FOURIER EOS visit.

[e] Vital signs include sitting blood pressure and heart rate.

[f] **Coronary revascularization procedure and death information for cardiovascular events of interests must be collected in the eCRF. Sites will be prompted for this information when necessary.**

[g] CANTAB assessments will only be performed in subjects from the EBBINGHAUS study. In addition to the scheduled assessments, all CANTAB assessments should be performed if a subject from the EBBINGHAUS study reports a neurocognitive adverse event. Assessment should be conducted at appropriate time after the subject has been allowed to eat and drink.

[h] To preserve the integrity of FOURIER blinding and database locking, no local lipid assessments may be performed until either FOURIER is unblinded or at least 12 weeks after the subject's last administration of FOURIER investigational product (evolocumab or placebo), whichever is earlier. Subjects must be fasting for ≥ 9 hours before each study visit where fasting lipid samples are obtained. Blood samples for these assessments will be processed at a central laboratory. Additional laboratory assessments that may be deemed necessary to evaluate (serious) adverse events will be processed locally.

[i] Serum (or urine) pregnancy test will be performed in women of childbearing potential only. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.

[j] Only if needed to establish postmenopausal status (see Exclusion Criterion 207).

[k] Administration at the study site is recommended if the study visit is within the dosing schedule for the subject.

[l] Evolocumab will be supplied to the subject at the site. Subjects will administer evolocumab on a Q2W or QM schedule and will have the opportunity to switch between Q2W and QM at any scheduled time point when evolocumab is supplied to the subject, provided the appropriate supply is available. Subjects should continue evolocumab for the entire 260-week treatment period. **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.**

7.2 General Study Procedures

Mandatory study visits will occur at week 12 and thereafter approximately every 24 weeks from day 1. Evolocumab resupply visits will be scheduled quarterly (every 12 weeks). Evolocumab will be supplied to the subject at the site. The method of resupply will be determined based on local regulations as well as available infrastructure. Assessments and procedures will be conducted per the schedule of assessments (Table 1) and include vital signs; physical examinations; body weight; assessment of targeted concomitant therapy, adverse events, device-related adverse effects, serious adverse events, and disease-related events; CANTAB assessments (only in subjects from EBBINGHAUS); laboratory assessments, including fasting lipid panel, ApoA1, ApoB, and Lp(a); serum (or urine) pregnancy testing (women of childbearing potential); and evolocumab administration.

Time gaps between the completion of FOURIER and day 1 of this OLE study should be minimized. It is recommended that the day 1 FOURIER OLE visit occurs on the same day as the FOURIER EOS visit. If this is not possible (eg, last evolocumab dose in FOURIER is less than 7 days from the first dose in this study), the day 1 visit should occur no later than 90 days after the FOURIER EOS visit. All on-study visits and dosing should be scheduled from FOURIER OLE study day 1 (day of first administration of evolocumab in this 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 1). If a study visit is missed or late, including visits outside the visit window, subsequent visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits. 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 performed. The risks and benefits of participating in the study will be verbally explained to each potential subject before 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 1). If performed at the site, evolocumab administration must be after completion of blood draw and vital sign procedures.

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

Laboratory Assessments

Subjects must be fasting for ≥ 9 hours before each study visit where fasting lipid samples are obtained. To preserve the integrity of FOURIER blinding and database locking, no local lipid assessments may be performed until either FOURIER is unblinded or at least 12 weeks after the subject's last administration of FOURIER investigational product (evolocumab or placebo), whichever is earlier. On-study laboratory samples will be analyzed using a central laboratory. Additional laboratory assessments that may be deemed necessary to evaluate (serious) adverse events will be processed locally.

The following laboratory assessments will be performed at the time points listed in the schedule of assessments (Table 1):

- fasting lipid panel:
  - total cholesterol
  - triglycerides
  - LDL-C
  - HDL-C
  - VLDL-C
  - non-HDL-C
- ApoA1
- ApoB
- Lp(a)
- serum or urine pregnancy test (women of childbearing potential only)
- FSH (if needed [see Exclusion Criterion 207])

Vital Signs

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.

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.

7.2.1 Enrollment and Baseline Procedures (Day 1)

Subjects who sign the ICF and meet eligibility criteria will be enrolled. Day 1, defined as the day of the first administration of evolocumab in this study, should occur on the same day as the FOURIER EOS visit. If this is not possible, subjects will return to the study site for day 1 procedures while continuing their background LLT.

Enrollment will be managed at a site level to allow the following subjects to enroll if eligibility criteria are met:

a) subjects who have at least 2 years of study exposure in FOURIER
b) subjects from EBBINGHAUS, regardless of study exposure
c) subjects who have less than 2 years of study exposure in FOURIER and did not participate in EBBINGHAUS

Enrollment of eligible subjects may be limited at the site level, to maintain a 1:1 ratio between subject groups “a” and “c” (ie, subjects who have ≥ 2 years of study exposure in FOURIER and subjects who have less than 2 years of study exposure in FOURIER and did not participate in EBBINGHAUS) or to manage overall recruitment into the OLE.

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. Demographic data (except age) will be carried over from the parent study. Demographic data, including sex, age, race, and ethnicity, may be used to study their possible association with subject safety and treatment effectiveness.

The following procedures are to be completed during day 1; however, assessments performed at the FOURIER/EBBINGHAUS (as applicable) EOS visit should not be repeated unless day 1 is > 90 days after the FOURIER EOS visit. If administered at the site, evolocumab is to be administered after completion of the blood draws and vital signs.

- confirmation that the ICF has been signed
- review of targeted concomitant therapy
- review of adverse events, serious adverse events, device-related adverse effects, and disease-related events. Any events that occurred between FOURIER EOS and day 1, if applicable, will be recorded on the Event eCRF.
- physical examination
- vital signs (sitting blood pressure and heart rate)
- body weight
- **coronary revascularization procedure and death information (sites will be prompted for this information when necessary)**
- CANTAB SWM, PAL, and RTI tests (subjects who participated in the EBBINGHAUS study only)
- blood draws for fasting lipids (≥ 9-hour fasting sample), ApoA1, ApoB, Lp(a), and FSH (only if required to ensure menopause [see Exclusion Criterion 207])
- blood draw or urine sample for a serum or urine pregnancy test (women of childbearing potential only)
- 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 **PI**s), if applicable

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 1). If administered at the site, evolocumab is to be administered after completion of the blood draws and vital signs.

- review of targeted concomitant therapy
- review of adverse events, serious adverse events, device-related adverse effects, and disease-related events
- vital signs (sitting blood pressure and heart rate)
- body weight
- **coronary revascularization procedure and death information (sites will be prompted for this information when necessary)**
- CANTAB SWM, PAL, and RTI tests (subjects who participated in the EBBINGHAUS study only)

- blood draws for fasting lipids (≥ 9-hour fasting sample), ApoA1, ApoB, and Lp(a)
- blood draw or urine sample for a serum or urine pregnancy test (women of childbearing potential only)
- 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 **PI**s), if applicable

The investigator should instruct the subject to report to the site (eg, by telephone call) any adverse events, device-related adverse effects, serious adverse events, or 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 1) for collection of adverse events, device-related adverse effects, serious adverse events, or disease-related events.

In addition to the time points listed in the schedule of assessments (Table 1), all CANTAB assessments should be performed if a subject from the EBBINGHAUS study reports a neurocognitive adverse event.

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 until 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 end of investigational product administration procedures should be completed at the time of withdrawal.

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/End of Study Visit

The safety follow-up/EOS visit is to be scheduled at least 30 days (+ 3 days) after the last dose of evolocumab, unless they are continuing their participation in the study after ending evolocumab prior to study completion. This safety follow-up will be done by phone. The following procedures are to be completed during the EOS visit:

- review of targeted concomitant therapy

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

7.3 Cambridge Neuropsychological Test Automated Battery Tests

The CANTAB is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, administered to subjects who participated in EBBINGHAUS (Study 20130385) using a touch screen computer. The following 3 tests will be completed:

- SWM
- PAL
- RTI

These 3 tests assess the key cognitive domains of working memory/executive function, episodic memory, and psychomotor speed/attention. Completion of this test battery will take approximately 25 minutes at each time point.

The CANTAB platform has been used in interventional clinical studies to test (and demonstrate) both cognitive impairment and enhancement (Attwood et al, 2007; Elliott et al, 1997; Greig et al, 2005; Harmer et al, 2001; Jäkälä et al, 1999; Rusted and Warburton, 1988; Ryan et al, 2006) and was used in the EBBINGHAUS study. The subtests of the CANTAB selected for this study have established sensitivity to cognitive dysfunction in amnestic clinical syndromes such as mild cognitive impairment and Alzheimer's disease (Egerhazi et al, 2007) and have also been used to demonstrate cognitive safety for drug therapy (eg, Kollins et al, 2011).

The results of the cognitive tests will not be communicated to the investigator.

Additional information about the CANTAB SWM, PAL, and RTI tests administered in this study is provided in Appendix F.

7.3.1 Spatial Working Memory

The SWM test assesses the subject's ability to retain spatial information and manipulate it in working memory. This test of working memory and executive function is particularly sensitive to dorsolateral prefrontal cortical functioning. It is a self-ordered task that also measures strategy and is sensitive to frontal lobe and executive dysfunction (Manes et al, 2002; Owen et al, 1996; Owen et al, 1990). A number of colored boxes are presented on the screen, and the computer hides a token in these boxes one at a

time. The subject is instructed to touch the boxes in turn to search for the token that has been hidden. When a token is found it should be placed in a home area on the right side of the screen. The subject then searches for more tokens until the same number of tokens as the number of colored boxes has been found. The key task instruction is that the computer will never hide a token in the same box twice in the same problem. As the test progresses, the task becomes more difficult, up to a maximum of 8 boxes.

Exploratory endpoints of the study are the SWM strategy index of executive function and SWM between-errors score. An efficient strategy for completing the task is to follow a planned search sequence, beginning with a specific box and then returning to start each new search sequence with that same box as soon as a token has been found. The strategy score represents the number of times a subject begins a search with a different box, with a high score representing an inefficient use of strategy and planning and a low score representing an efficient use of strategy (Owen et al, 1990). The between-errors score is the number of times that the subject revisited a box in which a token had previously been found. A lower score indicates better performance.

7.3.2 Paired Associates Learning

The PAL test assesses visuospatial episodic memory. This test is particularly sensitive to changes in medial temporal lobe functioning. Boxes are displayed on the screen and open in turn to reveal a number of patterns. Subjects are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomized order, and the subject touches the box in which the pattern was located. If an error is made, the patterns are presented again to remind the subject of their locations. As the test progresses, the stages become more difficult as the number of patterns to be remembered increases, up to a maximum of 8 patterns. For subjects who fail to complete all levels, an adjusted score is calculated that allows for errors predicted in the stages that were not attempted.

The exploratory endpoint of PAL total errors adjusted is comprised of the number of errors committed by the subject plus an adjustment for the estimated number of errors he/she would have made on any stages that were not reached. A lower score indicates better performance.

7.3.3 Reaction Time

The RTI test assesses psychomotor speed and attention. The RTI test is a direct analogue of the rodent 5-choice serial reaction time test, one of the best studied

behavioral paradigms. In humans, the CANTAB RTI test has been extensively studied and shows differential sensitivity to pharmacological manipulation and to clinical impairment associated with a range of conditions, including mild cognitive impairment and Alzheimer's disease. The subject holds down a button until a spot appears in 1 of 5 circles on the screen. As soon as possible after the spot flashes, the subject lifts his/her finger from the button and touches the circle in which the spot appeared.

The exploratory endpoint of RTI median 5-choice reaction time is the median duration between the onset of the stimulus and the release of the button. A lower score indicates better performance.

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 can decline to continue receiving evolocumab 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 evolocumab or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the schedule of assessments (Table 1) 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 evolocumab and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

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(s) from evolocumab 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 (evolocumab) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria [see Section 6.2.2], pregnancy)
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- death
- 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 nonserious) anticipated to occur in the study population due to the underlying disease. **All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.** 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, myocardial infarction, 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 and/or disease-related outcomes that do not qualify as serious adverse events include:

- 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.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product (evolocumab)/protocol required-therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

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.

A device-related adverse effect is any adverse event related to the use of a medical device. Device-related adverse effects include adverse events resulting from insufficient or inadequate IFU, 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 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

- the investigator believes a causal relationship exists between the investigational medicinal product/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

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.

The criteria for grade 4 in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading differ from the regulatory criteria for serious adverse events. It will be left to the investigator's judgment to also report these grade 4 abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record.

9.2 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 the FOURIER EOS visit through the EOS visit for this study (FOURIER OLE) or 30 days (+ 3 days) after the last administration of evolocumab, whichever is later, are **recorded** using the Event eCRF. Additionally, the investigator is required to report a fatal disease-related event on the Event eCRF.

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.

Events assessed by the investigator to be related to the investigational product (evolocumab)/protocol-required therapies, and determined to be serious, require reporting of the event on the Event eCRF.

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 observed by the investigator or reported by the subject that occur after the FOURIER EOS visit through the EOS 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 is responsible for ensuring that all device-related adverse effects observed by the investigator or reported by the subject that occur after the FOURIER EOS visit through the EOS 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 all of 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

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is described in Appendix A. 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 investigator must assess whether the adverse event is possibly related to investigational medicinal product (evolocumab). 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?

The investigator must assess whether the adverse event is possibly related to the prefilled AI/Pen or **PI** investigational device 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 study-mandated statin background therapy. 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 study-mandated statin background therapy?

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

The investigator is 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 the FOURIER EOS visit through the EOS visit for this OLE 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 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/electronic Serious Adverse Event Contingency Report Form. If the first notification of a serious adverse event is reported to Amgen via the electronic Serious Adverse Event 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 any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by a study activity/procedure?

The investigator is 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 after knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the 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 procedures and statutes.

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 after the protocol-required reporting period or after the EOS. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union member states), investigators are required to report serious adverse events that they become aware of after the EOS. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

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

9.2.2.4 Reporting a Safety Endpoint as a Study Endpoint

Not applicable.

9.2.2.5 Serious Adverse Events That Are Not To Be Reported in an Expedited Manner

Not applicable.

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies and for an additional 15 weeks after the end of treatment with 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. The pregnancy should be reported 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 lactation case occurs while the female subject is taking protocol-required therapies, the lactation case should be reported to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies and for an additional 15 weeks after the end of treatment with evolocumab.

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

Amgen is sponsoring 2 prospective, observational studies of pregnant women who have been exposed to Repatha® (evolocumab) at any point during pregnancy and/or breastfeeding. One study registry is conducted in the US and Canada, and the other one 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 20130295 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. To learn more about the study in the US and Canada, you can go to MotherToBaby.org or call at 877.311.8972. 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 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 in subjects who completed the EBBINGHAUS study are the following:

- SWM strategy index of executive function
- SWM between-errors score
- PAL total errors adjusted
- RTI median 5-choice reaction time

The exploratory endpoints in all subjects are the following:

- change and percent change from baseline at each scheduled visit in each of the following lipid parameters:
  - total cholesterol
  - triglycerides
  - LDL-C
  - HDL-C
  - VLDL-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 revascularization
    - hospitalization for unstable angina
    - hospitalization for heart failure
    - TIA

10.1.2 Analysis Sets

The long-term safety analysis set (FOURIER and OLE studies) includes all subjects who were randomized to and received evolocumab or placebo in the FOURIER study regardless of whether the subjects enrolled in the OLE study.

The OLE safety analysis set (OLE study only) includes all subjects who received at least 1 dose of open-label evolocumab in the OLE study.

The OLE CANTAB analysis set (OLE study only) includes all subjects who enrolled in the EBBINGHAUS study and received at least 1 dose of open-label evolocumab in the OLE study.

10.1.3 Covariates and Subgroups

The planned covariates and subgroups include the following:

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

10.2 Sample Size Considerations

It is estimated approximately 5000 subjects who completed the FOURIER study will be enrolled. Based on a sample size of 5000 subjects, Table 2 lists the width of 95% confidence intervals for a range of various underlying adverse event rates.

Table 2. Confidence Interval Width for Adverse Event Rates

Percent Underlying Adverse Event	Width of 95% Confidence Interval
0.01%	0.056%
0.05%	0.124%
0.10%	0.176%
1.00%	0.552%
2.00%	0.776%
3.00%	0.946%
4.00%	1.086%
5.00%	1.208%

10.3 Planned Analyses

10.3.1 Interim Analyses

Interim analyses will be performed to support safety data reporting and assessments of other listed endpoints. The study is not anticipated to stop early unless an unexpected safety signal is detected that is assessed by Amgen Safety to warrant study stop.

10.3.2 Primary Analysis

The primary analysis activities are commenced based on achieving the end of study 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 will be descriptive in nature. No statistical inference or missing value imputation is planned. No formal hypotheses 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/EBBINGHAUS).

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/EBBINGHAUS 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 version at the time of 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 evolocumab, device-related adverse events, and disease related events will be tabulated for the overall OLE study period using the OLE safety analysis set. 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 all treatment-emergent** events **reported on the Event eCRF**, including CEC reviewed events **and disease related events**.

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. The analysis will be performed using the long-term safety analysis set.

10.4.3 Secondary 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 Endpoints

Summary statistics for CANTAB assessments, including SWM strategy index of executive function, SWM between-errors score, PAL total errors adjusted, and RTI median 5-choice reaction time, will be provided based on the OLE CANTAB analysis set.

Summary statistics for percent change from baseline at each scheduled visit for each exploratory lipid parameter will be summarized.

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 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 study manager to the investigator. The written informed consent document 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 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.

The acquisition of informed consent is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject 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.

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 (evolocumab).

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, the age at time of enrollment must be included.
- 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 federal regulations/International Conference on Harmonisation (ICH) GCP guidelines, it is required that the investigator and institution permit authorized representatives of the company, 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 multicenter studies, the coordinating investigator.

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The 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 to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator 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 should include:

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

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 Amgen 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 Compliance Auditing 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 before the completion of all protocol-required visits and are unable or unwilling to continue the schedule of assessments (Table 1), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

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

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages 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 Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, 2013, updated 2014), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for 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 J-P, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154-156.

Attwood AS, Higgs S, Terry P. Differential responsiveness to caffeine and perceived effects of caffeine in moderate and high regular caffeine consumers. *Psychopharmacology (Berl).* 2007;190:469–477.

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; the IMPROVE IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387-2397.

Cholesterol Treatment Trialists' (CTT) Collaborators. 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.

Egerházi A, Berecz R, Bartók E, Degrell I. Automated neuropsychological test battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:746–751.

Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology (Berl).* 1997;131:196–206.

Amgen. Evolocumab Investigator's Brochure, version 9.0.

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.

Greig NH, Sambamurti K, Yu Q, Brossi A, Bruinsma GB, Lahiri DK. An overview of phenserine tartrate, a novel acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. *Curr Alzheimer Res*. 2005;2:281–290.

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.

Harmer CJ, McTavish SFB, Clark L, Goodwin GM, Cowen PJ. Tyrosine depletion attenuates dopamine function in healthy volunteers. *Psychopharmacology (Berl).* 2001;154:105–111.

International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals 2013: http://www.icmje.org/

Jäkälä P, Riekkinen M, Sirviö J, Koivisto E, Riekkinen P. Clonidine, but not guanfacine, impairs choice reaction time performance in young healthy volunteers. *Neuropsychopharmacology*. 1999;21:495–502.

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

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

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, DC, Dept of Health, Education, and Welfare, Publication No. (NIH) 74-599, 1974.

Kollins SH, López F, Vince BD, et al. Psychomotor functioning and alertness with guanfacine extended release in subjects with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2011;21:111–120.

Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol*. 2005;46:1225-1228.

Manes F, Sahakian BJ, Clark L, et al. Decision making processes following damage to the prefrontal cortex. *Brain*. 2002;125:624–639.

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.

Owen AM, Evans AC, Petrides M. Planning and spatial working memory: a positron emission tomography study in humans. *Eur J Neurosci*. 1996;8:353–364.

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*. 1990;28:1021–1034.

Rusted JM, Warburton DM. Original investigations The effects of scopolamine on working memory in healthy young volunteers. *Psychopharmacology (Berl)*. 1988;96:145–152.

Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MWJ. Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care*. 2006;29:345–351.

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 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.

When an adverse event cannot be graded by CTCAE version 4.0 the following severity grade may be used:

1 MILD: aware of sign or symptom, but easily tolerated

2 MODERATE: discomfort enough to cause interference with usual activity

3 SEVERE: incapacitating with inability to work or do usual activity

4 LIFE-THREATENING: refers to an event in which the subject was, in the view of the investigator, at risk of death at the time of the event (This category is not to be used for an event that hypothetically might have caused death if it was more severe.)

5 FATAL

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL according to the criteria specified in Section 6.4 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 eCRF (eg, Event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.3.

Additional Clinical Assessments and Observation

All subjects in whom evolocumab or protocol-required therapies are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4.1 and Section 6.4.2 or who have AST or ALT elevations > 3 x ULN 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:

- AST, ALT, ALP, and bilirubin (total and direct) are to be repeated within 24 hours.
- In cases of TBL > 2 x ULN, retesting of liver tests and bilirubin (total and direct) 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 evolocumab and/or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Investigation of alternative causes for elevated AST or ALT and/or elevated TBL is to be initiated:
  - Complete blood count with differential is to be obtained to assess for eosinophilia.
  - Serum total immunoglobulin immunoglobulin G, anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody 1 are to be obtained to assess for autoimmune hepatitis.
  - Serum acetaminophen (paracetamol) levels are to be obtained.
  - A more detailed history of the following is to be obtained:
    - 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 nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies are to be obtained.
  - Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear are to be obtained.
  - Appropriate liver imaging is to be performed, if clinically indicated.
- Appropriate blood sampling is to be obtained for pharmacokinetic analysis.
- Hepatology consult is to be obtained (liver biopsy may be considered in consultation with an hepatologist).
- The subject and the laboratory tests (ALT, AST, and TBL) are to be followed until all laboratory abnormalities return to baseline or normal. The close observation period is to continue for a minimum of 4 weeks after discontinuation of all evolocumab 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 eCRFs.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20130295 evolocumab (AMG 145)	Electronic 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

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. ADVERSE EVENT

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

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/drug under study	**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/drug under study or an Amgen device used to administer the IP/drug under study?							**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
							evolocumab (AMG 145)		Prefilled Autoinjector/ Pen(AIPen)		Automated MiniDoser (AMD)				
							No✓	Yes✓	No✓	Yes✓	No✓	Yes✓			
				☐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; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN
Study # 20130295
evolocumab (AMG 145)

Electronic 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/Drug/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product: 01 Still being Administered; 02 Permanently discontinued; 03 Withheld	Lot # and Serial #
evolocumab (AMG 145)	☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AI/Pen) device	☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
Automated Mini-Doser (AMD) device	☒ 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 # 20130295 evolocumab (AMG 145)	Electronic 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

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Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: 20130295

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

Pregnant female's LMP mm_____ / dd_____ / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____ / yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____ / yyyy_____

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN® Lactation 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: 20130295

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject 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.

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Appendix D. Recommended Lipid-lowering Background Therapy

It is recommended that subjects continue the same background 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 6.8. 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, HIV or 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

Appendix F. Cambridge Neuropsychological Test Automated Battery Tests

The CANTAB SWM, PAL, and RTI will be completed by subjects who completed the EBBINGHAUS study (Study 20130385).

Brief descriptions with screenshots for these 3 tests are provided on the pages below. Interactive test demos can be accessed at the following website:

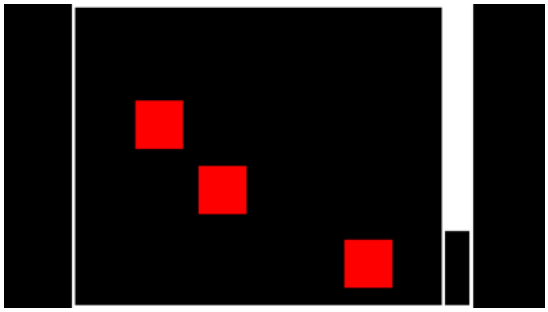
http://www.cambridgecognition.com/clinicaltrials/cantabsolutions/tests

Spatial Working Memory

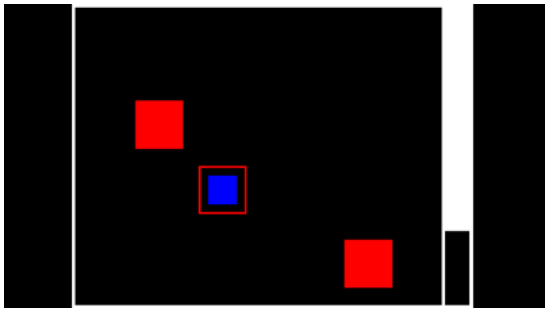
A number of colored boxes are presented on the screen, and the computer hides a token in these boxes one at a time. The subject is instructed to touch the boxes in turn to search for the token that has been hidden. When a token is found, it should be placed in a home area on the right side of the screen. The subject then searches for more tokens until the same number of tokens as the number of colored boxes has been found. The key task instruction is that the computer will never hide a token in the same box twice. As the test progresses, the task becomes more difficult, with up to a maximum of 8 boxes. The color and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.

Step-by-step Example

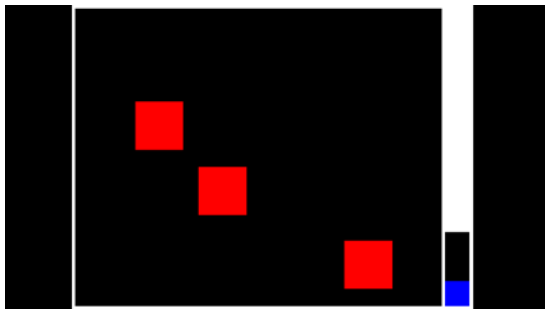
Colored boxes are shown on the screen. One of the boxes contains a token. The subject chooses 1 box and opens it by touching the box on the screen. If the box is empty, the box closes after a few seconds and another box needs to be touched.



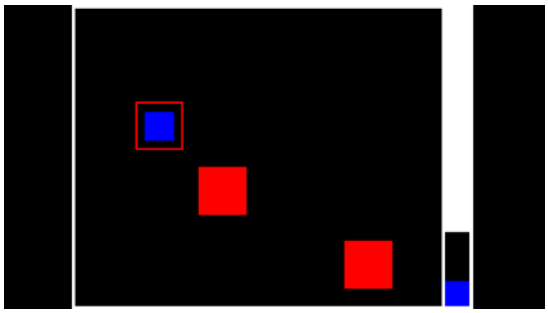
If a box contains a token, the box stays open until the token is transferred to the column on the right side of the screen.



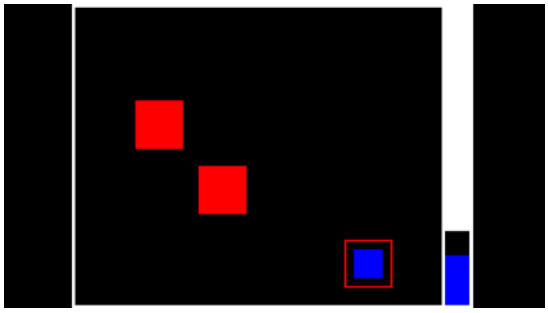
The token is transferred to the column on the right side of the screen by touching the column. The open box closes.



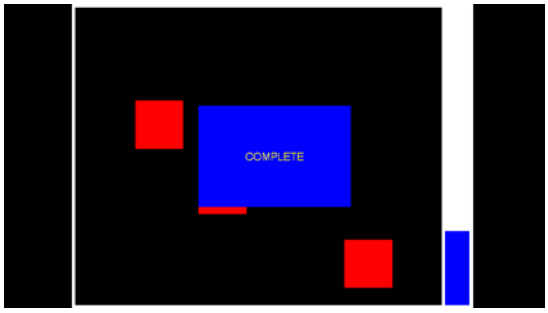
The next token needs to be found by touching another box.



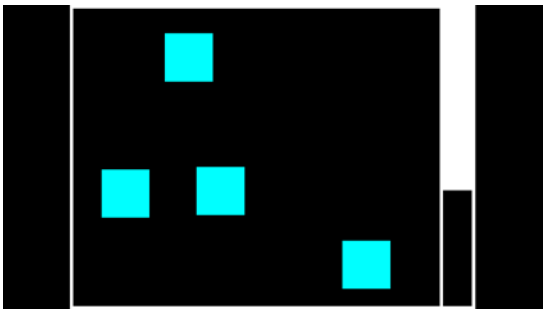
No box contains more than 1 token, so the subject needs to remember where she/he has found a token previously and try not to return to those boxes.



Upon completion a “complete” message is briefly displayed.



The test starts with practice problems with 3 boxes and becomes gradually more difficult with problems having 4 boxes, 6 boxes, and then 8 boxes at the most difficult stage.



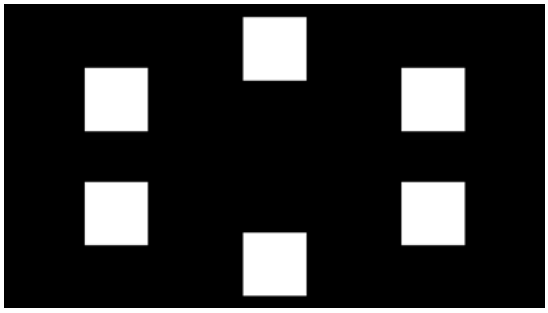
The SWM test ends after it has been completed with a total of 8 boxes on the screen.

Paired Associates Learning

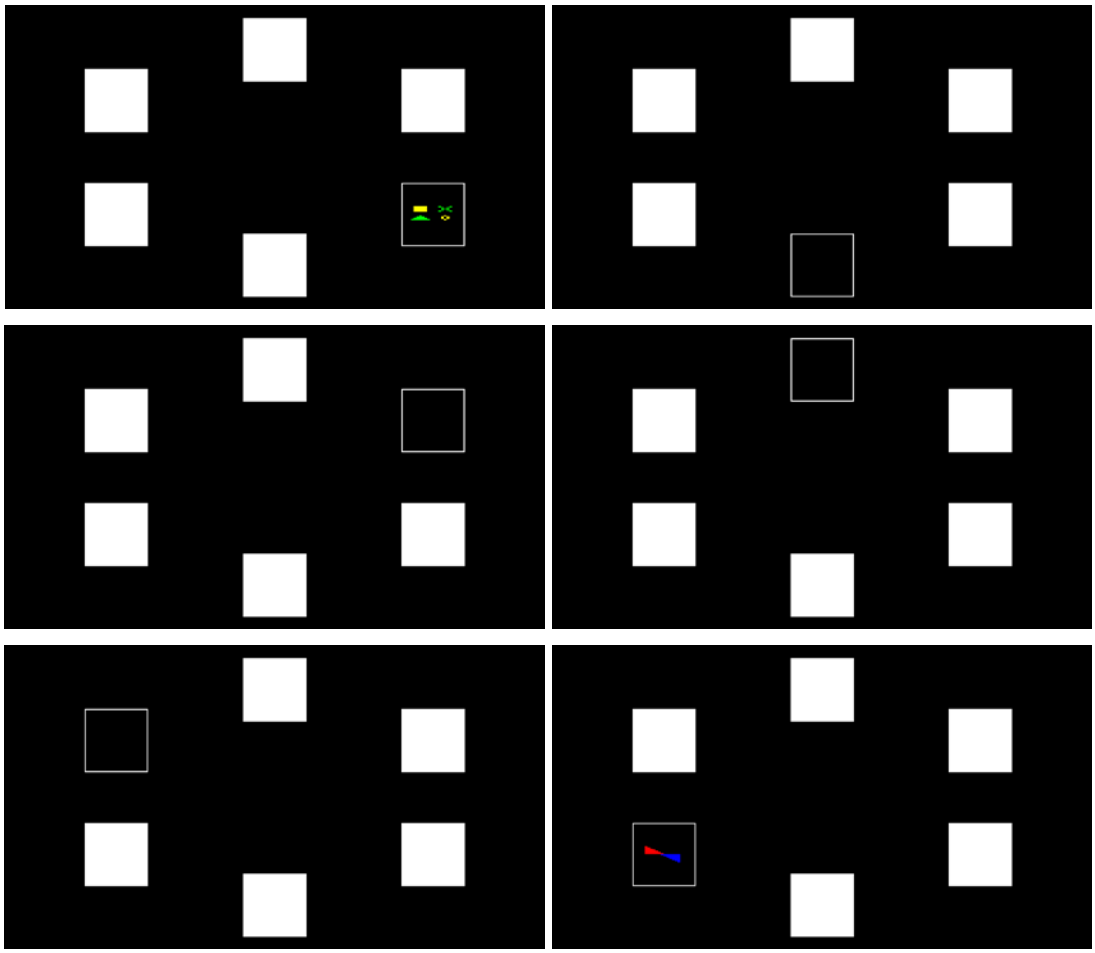
Boxes are displayed on the screen and open in turn to reveal a number of patterns. Subjects are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomized order, and the subject touches the box in which the pattern was located. If an error is made, the patterns are presented again to remind the subject of their locations. As the test progresses, the stages become more difficult as the number of patterns to be remembered increases, up to a maximum of 8 patterns.

Step-by-step Example

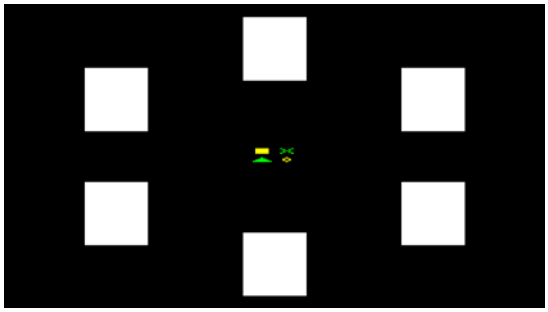
Six boxes are displayed on the screen.



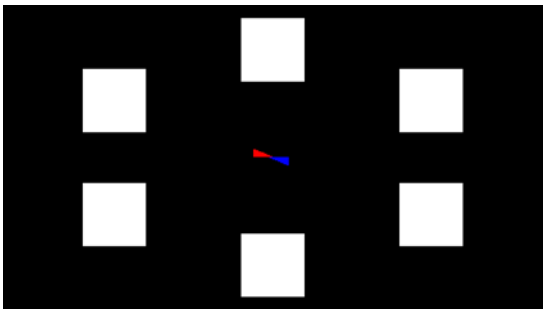
Two of the boxes contain a pattern. The boxes are opened in a random order to reveal the locations of the patterns.



After all the boxes have opened, 1 pattern is shown in the center of the screen. The subject touches the box in which he/she thinks the pattern was located.



The other pattern is shown in the center of the screen. The subject touches the box in which he/she thinks that pattern was located.



If the subject responds correctly, the test progresses to more difficult stages with 4 patterns, 6 patterns, then 8 patterns at the most difficult level. For the 8-pattern stage, 2 additional white boxes are included on the screen. If at any stage the subject does not respond correctly, the boxes re-open to remind the subject where the patterns are located. The subject can try again until the maximum number of attempts has been reached.

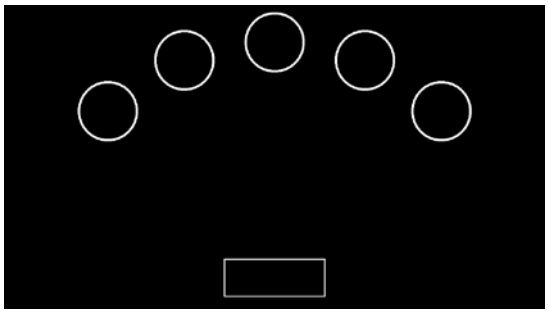
The PAL test ends when the 8-pattern stage has been completed or at an earlier stage if the maximum number of attempts has been reached and the subject has not responded correctly.

Reaction Time

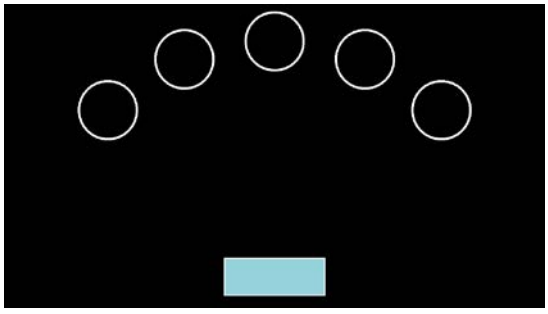
The subject holds down a button until a spot appears in 1 of 5 circles on the screen. As soon as possible after the spot flashes, the subject lifts their finger from the button and touches the circle in which the spot appeared.

Step-by-step Example

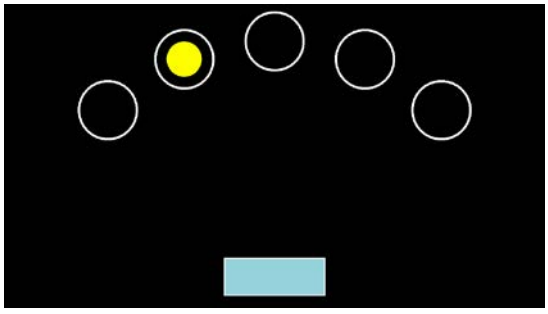
A button and 5 circles are displayed on the screen.



The subject holds down the button with the index finger of their dominant hand to initiate the trial.



A spot flashes in one of the circles. The subject releases the button and uses the same finger to touch inside the circle in which the spot appeared as quickly as possible.



The RTI test begins with 10 practice trials and is completed when 30 assessed trials have been performed.

Amendment 3

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

Amgen Protocol Number Evolocumab 20130295

NCT Number: 02867813

EudraCT Number: 2015-004780-36

Amendment Date: 26 February 2020

Rationale:

The 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.
- Update the Schedule of Assessments:
  - 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 (CEC).
- Clarify that all adverse event summaries for the primary analysis of the primary endpoint will include all treatment-emergent events reported on the Event electronic Case Report Form (eCRF), including CEC reviewed events and disease related events
- Replaced “automated mini-doser (AMD)” with “personal injector (PI)” to align with program-level naming convention:
- Administrative, typographical, and formatting changes were made throughout the protocol

Amendment 2

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

Amgen Protocol Number Evolocumab 20130295

NCT Number: 02867813

EudraCT Number: 2015-004780-36

Amendment Date: 08 April 2019

Rationale:

The protocol is being amended to:

- align the protocol with the evolocumab 20160250 study
- incorporate an independent external clinical events committee (CEC) to review all deaths and cardiovascular events of interest
- modify statistical considerations to clarify that the primary analysis will use data from the open-label extension (OLE) study only
- add exploratory endpoint “to describe the effects of long-term administration of evolocumab on subject incidence of death and cardiovascular events of interest”
- incorporate language about Amgen sponsoring of 2 prospective observational studies of pregnant women who have been exposed to evolocumab
- update the study glossary
- clarify and update text to align with the current template (FORM-001520) and Amgen standards
- clarify text to indicate that the secondary endpoints will be conducted at scheduled visits and not on a yearly basis
- remove self-evident corrections (SEC) text, as it is no longer an Amgen standard
- remove “week 260” from end of study (primary completion date) definition for clarity
- clarify language related to the collection of concomitant therapy
- clarify the evolocumab resupply period
- change “lot number” to “box number” for accuracy
- modify Table 1 footnote text to clarify that 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
- make editorial changes (including typographical, grammatical, and formatting) throughout the document.

Amendment 1

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

Amgen Protocol Number 20130295

EudraCT number 2015-004780-36

Amendment Date: 20 November 2017

Rationale:

This protocol is being amended to:

- Clarify that subjects will only be allowed to obtain investigational product at the study site (per supply chain, delivery methods are not a feasible option for this study). Sites are responsible for distributing investigational product to subjects and they may not have the adequate process to guarantee that investigational product will not be compromised during transportation.
- Primary completion and end of study language (Section 3.5.2) has been updated to align with current protocol template in order to clearly define these terms and when they occur
- Update the scheduled visit window from ±7 days to ±14 days for all visits in order to allow for subject flexibility as site visits are every 6 months
- Add an on-site administration and dispensation/reconciliation of investigational product at week 240 in order to ensure subjects have enough investigational product to last through week 260
- Separate the week 260 visit and end of study visit into 2 separate columns in the Schedule of Assessments, as the end of study visit is a phone call 30 days after the last dose of evolocumab that serves as a safety follow-up visit collecting targeted concomitant medications and adverse events (aligns with Section 9.2). This has also been clarified in Section 7.2.3.
- Clarify that subjects should be allowed to eat and drink between fasting bloodwork and CANTAB assessments
- Remove collection of temperature and respiratory rate from vital signs assessment as they were not collected during the parent study and thus do not need to be collected in this open-label extension study
- Clarify how demographic data and medical history will be defined and obtained at enrollment (rolled over from parent study)
- Provide clearer guidelines for obtaining a subject's vital status after discontinuation from the study

- Clarify the procedures that should be followed if a patient discontinues from treatment and/or the study
- Add instructions for handling subjects who are lost to follow-up to clarify when a subject would be considered a “lost to follow-up” in the study and define the site expectation to keep trying to contact with the “lost to follow-up” subjects until the end of the study
- Remove tabulation of disease-relate events from primary endpoint as the parent study did not collect the disease-related event data, thus it is not possible to do the tabulation involving parent data
- Make administrative and editorial corrections throughout the protocol