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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Eileen M. Craig, MD
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Established Name	Evolocumab
(Proposed) Trade Name	Repatha
Therapeutic Class	proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
Applicant	Amgen, Inc.
Formulation(s)	Subcutaneous (SC) injection
Dosing Regimen	Primary hyperlipidemia or mixed dyslipidemia: 140 mg SC every 2 weeks (Q2W) or 420 mg SC every month (QM) Homozygous Familial Hypercholesterolemia (HoFH): 420 mg SC QM or 420 mg SC

	Q2W
Indication(s)	Lipid-altering therapy: (1) Primary Hyperlipidemia/ Mixed Dyslipidemia: to reduce LDL-C), TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp[a], and to increase HDL-C and ApoA1 in combination with other lipid lowering therapies and as monotherapy; (2) HoFH: to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies
Intended Population(s)	(1) Primary Hyperlipidemia or Mixed Dyslipidemia: Adults (2) HoFH: Adults and Children > 11 years

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1 Executive Summary

1.1 Recommendation on Regulatory Action

Based on data showing robust LDL-C reductions and an acceptable safety profile, this reviewer recommends approval for the following indications:

Evolocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with:

- Primary hyperlipidemia with established clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of low density lipoprotein cholesterol (LDL-C)
- Heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C

Evolocumab is indicated as an adjunct to diet and other lipid lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The indication should include the following limitations of use:

(1) the effect of evolocumab on cardiovascular morbidity and mortality has not been determined.
(2) evolocumab is not indicated for the treatment of patients with primary hyperlipidemia without established clinical atherosclerotic CVD.

The mean LDL-C reduction achieved with the uptitration from the 420 mg every 4 weeks to every two weeks dose of evolocumab in patients with HoFH was small and there was limited data to evaluate the safety of this dose. Some members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) stated that the risk for cardiovascular events is extremely high in this HoFH population and that the potential cardiovascular benefit from this 420 mg Q2W dose may outweigh the risk in this HoFH population who do not achieve adequate LDL-C lowering with the 420 mg every 4 week dose. In my assessment, the limited amount of safety and efficacy data provided in this submission for the 420 mg every 2 week dose is insufficient to support approval at this time, especially as this dosing regimen could be used in children.

The applicant's proposed indication included evolocumab to be given in combination with statin therapy in patients with primary hyperlipidemia and mixed dyslipidemia as well as monotherapy use in patients unable to take a statin. I do not believe that the benefit-risk assessment of evolocumab supports such a broad indication in the absence of positive data from a cardiovascular outcomes trial (CVOT). This reviewer's recommended indication targets patients in whom the benefit-risk is likely to be

favorable in the absence of confirmatory CV outcomes data and a relatively limited pre-marketing safety database.

1.2 Risk Benefit Assessment

BACKGROUND
Repatha® (evolocumab) is a human monoclonal immunoglobulin G2 (IgG2) antibody directed proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface. This action prevents PCSK9-mediated LDLR degradation, which leads to increases in LDLR, and results in decreases in serum LDL-C.

The efficacy of evolocumab (also referred to as AMG145 or EvoMab in this document) was assessed in four double-blind, randomized, placebo- or ezetimibe-controlled Phase 3 trials of 12 weeks duration and one 52-week placebo-controlled trial. The four 12-week trials evaluated evolocumab in four different patient populations: (1) monotherapy in a population at low CV risk (10-year Framingham risk score of 10% or less) (N=614); (2) in combination with statins (N=1896); (3) in 'statin-intolerance' (N=307); and, (4) in heterozygous familial hypercholesterolemia (HeFH) (N=329). The 52-week trial (DESCARTES, N=901: 599 EvoMab; 302 placebo) also evaluated evolocumab in four different patient populations whose background therapy was based upon their screening LDL-C, NCEP ATP III risk category, and statin therapy: (1) no drug therapy required - diet alone; (2) low dose drug therapy required - diet plus atorvastatin 10 mg; (3) high dose drug therapy required - diet plus atorvastatin 80 mg; and, (4) maximal drug therapy required - diet plus atorvastatin 80 mg plus ezetimibe 10 mg.

The overall safety database included a total of 5710 participants exposed to any dose of evolocumab.The safety of evolocumab for the indication of primary hyperlipidemia was assessed in eight phase 2 and phase 3 lipid-lowering trials, a phase 2 trial done in Japan, two device clinical home-use studies, one 52-week placebo-controlled trial and two open-label extension (OLE)[1] trials.

The indication for individuals with homozygous familial hypercholesterolemia (HoFH) is supported by two trials, trial 20110233 (placebo-controlled, N=49) and ongoing open-label extension trial 20110271 (N=96). Trial 20110233 used an evolocumab dose of 420

1 After participating in any of the phase 2 or phase 3 trials, participants could enroll in a phase 2 (Study 20110110) or phase 3 (Study 20120138) open-label extension trial, respectively. In these trials, participants were randomized for the first year of the trial to a standard of care (SoC) control arm versus SoC plus evolocumab, followed by open-label evolocumab therapy for all participants beginning in the second year. In Study 20110110, participants received either evolocumab 420 mg QM plus SoC or SoC alone in Year 1, and then switched to evolocumab 420 mg QM starting in Year 2. In Study 20120138, participants received either evolocumab (140 mg Q2W or 420 mg QM) plus SoC or SoC alone in Year 1, and then switched to evolocumab 140 mg Q2W or 420 mg QM starting in Year 2.

mg QM and ongoing trial 20110271 used doses of 420 mg QM and 420 mg Q2W. The duration of exposure is 12 weeks in trial 20110233 and 84 weeks in trial 20110271.

The applicant (Amgen) proposes indications to reduce low-density lipoprotein cholesterol (LDL-C), as well as changes in other lipid parameters, in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia

- in combination with a statin
- in combination with a statin plus other lipid lowering therapies
- as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant, and
- as monotherapy or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

The applicant is also proposing an indication to reduce LDL-C, as well as to reduce other lipid parameters, in adults and adolescents aged 12 years and over with HoFH in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

The proposed evolocumab dosage for marketing is either 140 mg every 2 weeks or 420 mg once monthly for the primary hyperlipidemia and mixed dyslipidemia indication. The proposed dosage is 420 mg either once monthly or 420 mg every 2 weeks in patients with HoFH. Patients on apheresis are instructed to initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

EFFICACY SUMMARY

Primary Hyperlipidemia

In the integrated analysis of efficacy of the four 12-week trials for primary hyperlipidemia, the mean age at baseline was 58 years and approximately 49% of participants were female. Most participants were white (92%) and non-Hispanic (95%). Approximately 52% of participants were enrolled at sites in Europe, 40% in North America and 8% Asia Pacific. Approximately 30% (n = 958) of participants were ≥ 65 years old.

Approximately 20% of participants in the integrated efficacy analysis population had a prior diagnosis of CAD and 10% had a diagnosis of cerebrovascular or peripheral arterial disease. Approximately 300 (10%) participants had a history of myocardial infarction; only 69 (2%) participants had a history of stroke at baseline. Approximately 4% (136) had a history of congestive heart failure, with 1.7% of participants having CHF NYHA class I and 2.6% having CHF NYHA class II. Additional baseline characteristics include 12% had Type 2 diabetes mellitus; 49% had hypertension; approximately 34% were high CHD risk by NCEP ATP-III risk categories, 10% were moderately-high and 29% were moderate CV risk. Thus, less than 45% (1370 participants) were at moderate-high or higher CHD risk at baseline.

In the four 12-week trials, 72% of the participants were on statins: 32% were using high-intensity, 38% were using moderate-intensity and 2% were on low-intensity statin therapy. Mean serum concentration of LDL-C at baseline was 129 mg/dL, mean HDL-C was 54 mg/dL and median triglyceride was 119 mg/dL. These four trials that provide the efficacy data were heterogeneous and explored the use of evolocumab in four distinctly different patient populations: low CV risk not on background statin therapy, in combination with statins, 'statin-intolerant' and HeFH. Of note, participants who were not on concomitant statin therapy included individuals at low CV risk that did not warrant any lipid-lowering therapy as well as individuals at increased CV risk who did need to be on lipid-lowering therapy but had not tolerated statins in the past.

The integrated analyses from the four phase 3 12-week trials demonstrated statistically significant reductions in reflexive[2] LDL-C for both dosing regimens (evolocumab 140 mg Q2W and 420 mg QM dosing) (multiplicity-adjusted $p < 0.001$), with random-effects treatment differences (SE) that ranged from reductions of 60% (2%) for the 420 mg QM dose to 67% (3%) for the 140 mg Q2W dose compared with placebo.

The evolocumab 140 mg Q2W dose and the 420 mg QM dose yield similar LDL-C reductions but different pharmacodynamic profiles over the dosing interval (QM results in a sawtooth pattern compared to the more-stable LDL-C reduction achieved with Q2W dosing). The two different dosing regimens were designed by the applicant to cater to the patient's preference of taking the injectable every two weeks versus every four weeks and not to allow titration of the magnitude of LDL-C reduction.

The persistence of efficacy (420 mg QM dose) was demonstrated in the 52-week trial (20110109, DESCARTES). The mean age at baseline was 56 years and 52% of participants were female. Most participants were white (80%) and non-Hispanic (94%). Approximately 27% of participants were enrolled at sites in Europe, 58% in North America and 15% Asia Pacific. Approximately 23% of participants were ≥ 65 years old. As classified by NCEP ATP III criteria, the majority of participants (64%) were at moderate or low CHD risk and only 26% were considered at high risk for coronary heart disease. Only 15% of participants had a medical history of coronary artery disease, with <8% having a history of prior myocardial infarction. Additional baseline characteristics include 12% of participants who had Type 2 diabetes mellitus; 49% had hypertension; 4% had a medical history of cerebrovascular or peripheral arterial disease, with <1% having a history of prior stroke. Mean serum concentration of LDL C at baseline was 104 mg/dL, mean HDL-C was 53 mg/dL and median triglyceride was 108 mg/dL.

The percent change in LDL-C from baseline to Week 52 for evolocumab 420 mg QM compared with placebo QM using ultracentrifugation (UC)/directly measured, reflexive

2 In the LDL-C reflexive approach, the calculated LDL-C values are used, unless the value is < 40 mg/dL or triglycerides are > 400 mg/dL, in which case, the calculated LDL-C value was replaced with the ultracentrifugation/directly measured (UC) LDL-C value from the same blood sample, if available.

LDL-C, or calculated LDL-C values resulted in treatment differences of -57%, -58%, and -59%, ($p < 0.001$), respectively, when added to protocol-determined background lipid-lowering therapy. Evolocumab was effective across all subgroups with no significant differences; however, there was a trend toward greater LDL reduction with lower BMI.

Homozygous Familial Hypercholesterolemia (HoFH)

In the placebo-controlled HoFH trial 20110233, 51% of participants were male, 90% were white, and the mean age was 31 years, with a range from 13 years to 57 years. Ten (20%) participants were ≥ 12 to < 18 years of age at baseline. Twenty-one (43%) participants had coronary artery disease, and 4 (8%) had cerebrovascular or peripheral arterial disease. Twenty-four (49%) participants had homozygous genetic defects, 24 (49%) participants had compound heterozygous genetic defects and one had heterozygous genetic defects. Baseline therapy included a statin for all participants and the doses were rosuvastatin ≥ 10 mg QD or atorvastatin ≥ 40 mg QD for all except 1 in the evolocumab group. In this trial, which did not allow lipid apheresis treatment, evolocumab, compared to placebo, significantly reduced LDL-C from baseline to Week 12 by 31%. The mean change from baseline to Week 12 within the evolocumab arm alone was -23% and within the placebo arm alone was +8%. This 12-week, placebo-controlled trial included 10 adolescents, ages 13 to 17 years old, with HoFH. In this trial, 7 adolescents received evolocumab 420 mg subcutaneously once monthly and 3 adolescents received placebo. The treatment difference between evolocumab and placebo in mean % change in LDL C from baseline to Week 12 was -26.7%. The LDL-C reduction seen in this trial is similar to what has been observed with statin+ezetimibe, somewhat greater than what was observed with statin monotherapy (-22% mean reduction with rosuvastatin) and mipomersen[3] but less than that observed with lomitapide[4] (mean, -40%; median, -50%) and LDL apheresis (~ -50%, time-averaged).[5]

3 Mipomersen (once weekly subcutaneous injection), approved by FDA in January 2013, is an oligonucleotide inhibitor of apo B-100 synthesis, which is the principal apolipoprotein of LDL and VLDL. Mipomersen treatment led to mean 25% reduction in LDL-C compared to baseline and mean 21% reduction compared to placebo. Mipomersen, like lomitapide, promotes hepatic steatosis (with or without elevations in transaminases). Injection site reactions are also common (84% of patients, according to PI) and resulted in discontinuation of therapy in 5% of patients in phase 3 trials. Flu-like symptoms were reported in 30% of patients, resulting in discontinuation in 3% of patients in phase 3 trials.

4 Lomitapide (daily oral dosing) is an inhibitor of microsomal transfer protein (MTP), which participates in the formation of VLDL particles (a precursor to LDL), that was approved in December 2012. As a result of its mechanism of action, this drug promotes hepatic steatosis (with or without elevations in transminases) and fat malabsorption, leading to recommendations for monitoring hepatic transaminases and supplementation with essential fatty acids + Vitamin E, respectively. Gastrointestinal tolerability is an issue given the drug-induced fat malabsorption, although 23 of 29 patients in the 78-week pivotal trial remained on drug throughout.

5 Cuchel M, Bruckert E, Ginsberg HN et al, Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014 June 13; 35:2146-57.

There were 96 HoFH participants in the open-label extension trial 20110271, of which 81% were white, 47% were women and the mean age at baseline was 34 years. Eighty-three (87%) participants were ≥ 18 years of age and 13 (14%) were less than 18 years of age. More apheresis participants than non-apheresis participants with HoFH had a history of coronary artery disease (52% vs 43%), and cerebrovascular or peripheral arterial disease (32% vs 8%). Mean serum concentration of UC LDL-C at baseline in subjects with HoFH was 339 mg/dL in non-apheresis participants and 283 mg/dL in apheresis participants. Evolocumab resulted in UC LDL-C reductions of 19% at Week 12 and 23% at Week 24 in the HoFH analysis set. Increasing the frequency of dosing from 420 mg QM to 420 mg Q2W in participants with HoFH resulted in approximately 6% greater reduction of LDL-C. Participants who were being treated with apheresis had a reduced response to evolocumab (-20%) compared to the non-apheresis participants (-25%) at Week 24.

SAFETY SUMMARY

The overall safety database includes a total of 5710 participants exposed to any dose of evolocumab. At the time of database cutoff (1 April 2014), 5416 evolocumab-dosed participants had been on study for at least 3 months, 1824 evolocumab-dosed participants had been on study for at least 12 months, and 614 evolocumab-dosed participants had been on study for 2 years or more. Participants with the following characteristics have been treated with any dose of evolocumab for at least 1 year: 345 with established CVD; 183 with diabetes; 463 on concomitant high intensity statin; and 439 participants ≥ 65 years old.

The population included in the integrated parent studies[6] had a mean age of 58 years, approximately 83% were white and approximately 51% female. Approximately 19% and 8% had a prior diagnosis of CAD and cerebrovascular or peripheral arterial disease, respectively. Approximately 13% had Type II diabetes mellitus, 51% had hypertension and 11% had renal impairment (eGFR < 60 mL/min/1.73m^2) while 44% of participants were at high or moderately-high risk by ATP-III. At baseline, approximately 30% of participants were using high-intensity statin therapy (per ACC/AHA definition statins such as atorvastatin 40-80 mg or rosuvastatin 20-40 mg) and 38% were using moderate intensity statin therapy (such as atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg). The mean duration of evolocumab exposure in the 140 mg Q2W and 420 mg QM treatment groups was 2.6 months and 5.3 months, respectively. The greater duration of exposure in the QM dose was due to trial 20110109, which was 52 weeks in duration and participants were administered only the 420 mg QM dose. The median duration of evolocumab exposure in the 140 mg Q2W and 420 mg QM treatment groups was 2.8 months.

6 The Integrated Parent Analysis Set (IPAS) comprises integrated data from the 12-week phase 2 and phase 3 trials in addition to the 52-week study (20110109)

The exclusion criteria in the phase 2 and 3 trials included poorly controlled or newly diagnosed diabetes; New York Heart Association CHF class III or IV; uncontrolled serious cardiac arrhythmia; uncontrolled hypertension; hypo/hyperthyroidism; severe hepatic impairment (Child-Pugh class C); estimated glomerular filtration rate (eGFR) < 30mL/min/1.73m^2; ALT/AST > 2 x ULN; creatine kinase (CK) > 3 x ULN; myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass, or stroke within 3 months prior to randomization; and malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years. Thus, individuals with these conditions were not represented in the trials.

Deaths: There were 15 deaths reported during the clinical program. Four deaths occurred during the parent trials [1/2080 (0.05%) any control; 3/3946 (0.08%) any EvoMab], 7 deaths occurred during the open-label extension year 1 standard of care (SoC)-controlled period [4 (0.3%) SoC; 3 (0.1%) EvoMab], 2 deaths (0.3% EvoMab) occurred during the year 2+ OLE uncontrolled period, and 2 deaths occurred after the end of study (1 on placebo and 1 on EvoMab). A total of 11 deaths were deemed to be cardiovascular: 2 (0.1%) in any control and 4 (0.1%) in any EvoMab group of the integrated parent studies; 3 (0.1%) deaths in the evolocumab plus SoC group and 1 (0.1%) death in the SoC alone group of the year 1+ SoC-controlled period; and 1 (0.1%) death in the year 2+ OLE period.

Nonfatal Serious Adverse Events: In the integrated parent studies, serious adverse events (SAEs) were reported by 95 (3.0%) participants in the EvoMab Q2W/QM group, 36 (2.4%) participants in the Any Placebo group, and 43 (2.1%) participants in the Any Control (i.e., placebo or ezetimibe) groups. The most common SAEs (any EvoMab and any control groups, respectively) were myocardial infarction (0.1% and 0%), angina pectoris (0.1% in both groups), and pneumonia (0.1% and 0%). Although the numbers were small, there was a numeric increase in the evolocumab group in the incidence of cardiac disorders (particularly angina and myocardial infarction), pancreatitis, appendicitis, pneumonia and back pain.

Adverse Events Leading to Discontinuation: In the integrated parent studies, the incidence was slightly higher in the EvoMab group as compared to the placebo group for both dosing frequencies: 29 (2.3%) participants in the EvoMab 140mg Q2W group and 10 (1.7%) participants in the placebo Q2W group and 42 (2.1%) participants in the EvoMab 420mg QM group and 14 (1.5%) participants in the placebo QM group reported an adverse event leading to discontinuation of IP. Small increases in discontinuations in the EvoMab group as compared to the any control group include cardiac disorders (4, 0.1% and 1, <0.1%), CPK increased (4, 0.1% and 1, <0.1%), and nausea (6, 0.2% and 3, 0.1%).

Common Adverse Events: In the integrated parent trials, the incidences of adverse events in the evolocumab 140 mg Q2W (43.6%) and the placebo Q2W groups (41.0%)

were similar as well as for evolocumab 420 mg QM group (54.0%) and placebo QM groups (54.6%). The most common adverse events, where there is a notable increase in the EvoMab group (any evolocumab and any control groups, respectively), were nasopharyngitis (5.9% and 4.8%), upper respiratory tract infection (3.2% and 2.7%), back pain (3.0% and 2.7%), and nausea (2.1% and 1.8%).

Adverse Events of Special Interest: The safety assessment of evolocumab was focused on concerns known to occur with other lipid-lowering therapies (such as diabetes, liver, muscle and neurocognitive events), those associated with other injectable protein therapies (such as hypersensitivity events, injection site reactions), those occurring in participants with LDL-C levels < 40 mg/dL, those that could theoretically be associated with PCSK9 inhibition/LDL receptor upregulation (hepatitis C events), as well as notable adverse events found during the review.

Cardiovascular Disorders: In the integrated parent studies, cardiac disorder adverse events were reported in 77 (2.4%) participants in the evolocumab group (140 mg Q2W or 420 mg QM) and 29 (1.4%) participants in the any control group. The most common adverse events in the evolocumab group and any control group were palpitations (0.6% and 0.3%), angina pectoris (0.3% and 0.2%), and ventricular extrasystoles (0.3% and 0.1%). Serious cardiac adverse events were reported in 21 (0.7%) participants in the evolocumab group and 5 (0.2%) participants in the any control group. The most common serious cardiac events in the evolocumab group and any control group were myocardial infarction (0.1% and 0%), angina pectoris (0.1% and 0.1%), and acute myocardial infarction (0.1% and 0%).

Pancreatitis: An imbalance was observed in cases of pancreatitis. At the 120-Day Safety Update (data cut-off date of 01 July 2014), there were 7 participants with 8 events of pancreatitis. Six events occurred while the participants were receiving evolocumab or evolocumab plus standard of care (SoC) and 2 events occurred while the subjects were receiving SoC alone. All 7 participants recovered from the 8 events: 3 events resolved while the participant continued to receive evolocumab and 2 events resolved while the participant continued to receive SoC alone. While one cannot rule out evolocumab as a contributing factor in these cases, other risk factors in these cases included concurrent alcohol use, diabetes, gallstones and concomitant medications associated with pancreatitis.

Renal Disease/Proteinuria: An imbalance was observed in cases of serious renal disorders and proteinuria in statin-intolerant and diabetic subjects. In the parent trials, serious adverse events were reported in 4 (0.1%) participants in the any evolocumab group (glomerulonephritis acute, glomerulonephritis minimal lesion, IgA nephropathy, and renal failure acute) and no participants in the any control group. In the year 1 SoC-controlled period, 6 (0.2%) participants reported a serious adverse event in the evolocumab plus SoC group [nephrolithiasis (2 subjects), urinary incontinence (2 subjects), calculus ureteric and renal failure acute] and 1 (0.1%) participant in the SoC

alone group (renal failure acute). In the year 1 SoC-controlled period, there was a small but greater incidence of proteinuria in statin-intolerant and diabetic subjects who had no baseline proteinuria in the evolocumab plus SoC group, compared with the SoC alone group. Both the EvoMab and SoC alone group had additional confounding factors for the development of proteinuria, such as hypertension, diabetes and concomitant medications. It is not known if evolocumab was a contributing factor in these increased renal disorder and proteinuria cases.

Diabetes: To explore the potential for diabetes, the incidence of new onset diabetes among all patients, patients with baseline impaired fasting glucose (IFG) and patients with baseline normoglycemia were performed. In the integrated parent studies, using a 3-component definition of new onset diabetes (AEs consistent with diabetes, initiation of anti-diabetic medication or at least 2 consecutive post-baseline FBG measurements ≥ 126 mg/dL), in the group with IFG (defined as 100 ≤ FBG < 126 mg/dL), there was a small increase in post baseline new onset diabetes in the EvoMab group (29, 3.1% in EvoMab vs 11, 2.6% in Placebo vs 11, 1.9% in Any Control). Using a 4-component definition of new onset diabetes (3-component plus any post baseline HbA1c ≥ 6.5%), in the group with IFG, there was no difference among the groups in post baseline new onset diabetes (42, 4.5% in EvoMab vs 23, 5.4% in Placebo vs 23, 4.1% in Any Control). In the group with baseline normoglycemia, regardless of using the 3- or 4-component definition of new onset diabetes, the incidence was small but there was no increase seen in the EvoMab group compared to placebo or control.

During the year 1 SoC-controlled period and using the 3-component definition of new onset diabetes mellitus, the subject incidence of new onset diabetes mellitus during the year 1 SoC-controlled period was slightly higher in subjects with IFG at parent study baseline who received evolocumab plus SoC (29, 3.3%) compared with those who received SoC alone (10, 2.4%). This was also seen using the 4-component definition in the IFG group: evolocumab plus SoC (53, 6.3%) compared with those who received SoC alone (21, 5.2%). In the group with baseline normoglycemia, regardless of using the 3- or 4-component definition of new onset diabetes, the incidence was small but there was no increase seen in the EvoMab plus SoC group compared to SoC alone.

Musculoskeletal Adverse Events: In the integrated parent trials, adverse events for the Musculoskeletal and Connective Tissue Disorders system organ class were reported in 466 (14.6%) participants in the evolocumab group (140mg Q2W or 420 mg QM) and 284 (13.7%) participants in the any control group. The most common adverse event, where there is an increase in the evolocumab group, was back pain (3.1% in the EvoMab group vs 2.7% in the any control group). In the year 1 SoC-controlled period, 541 (19.1%) participants and 216 (15.2%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were arthralgia (3.4% and 2.5%), back pain (3.1% and 2.5%), myalgia (2.5% and 2.4%), and pain in extremity (2.5% and 1.5%).

In the phase 2 and phase 3 integrated trials, 14 participants during the integrated parent studies [9 (0.2%) in the any evolocumab group and 5 (0.2%) in any control group], 13 during the year 1 SoC-controlled period [5 (0.2%) in the evolocumab plus SoC group and 8 (0.6%) in the SoC alone group], and 6 (0.6%) during the year 2+ OLE period had a postbaseline CK > 10 x ULN. Most of these participants had confounding factors (such as concurrent hypothyroidism, muscle and joint injuries, tendonitis, and concomitant statin therapy) that may have contributed to the events. However, in the phase 1 studies, there were 3 reports of rhabdomyolysis and/or CK> 10 x ULN in healthy individuals not on concomitant statin therapy suggesting that evolocumab may contribute to such muscle symptoms or CK increases when used as monotherapy.

Liver-related Findings: The participant incidence of transaminase and bilirubin abnormalities was low and similar in the parent and extension trials for both the control and evolocumab groups. In the integrated parent studies, 5 (0.2%) participants in the evolocumab group (140 mg Q2W or 420 mg QM) and 7 (0.3%) participants in the any control group had ALT or AST > 5 x ULN at any postbaseline visit. No participant in the parent studies had both (ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR > 1.5) at any study visit. Three (0.1%) participants in the evolocumab plus SoC group of the year 1 SoC-controlled period had transaminase levels 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5: one case occurred 3 days after the participant admitted himself to rehabilitation for alcohol detoxification; one case had a normal bilirubin but an elevated INR due to warfarin and the transaminases declined despite continuation of evolocumab treatment; and in the last case, the participant was being treated for a urinary tract infection with nitrofurantoin and was also on simvastatin. Liver biopsy in this participant was consistent with drug-induced hepatitis. LFTs eventually normalized after suspending nitrofurantoin, evolocumab, simvastatin and other medications.

Neurocognitive Findings: One of the theoretical safety issues is related to cognitive function in patients who achieve very low levels of circulating LDL-cholesterol with PCSK9 therapy. Of note, it is believed that the blood-brain barrier limits access of monoclonal antibody products such as evolocumab to the central nervous system. In addition, brain cholesterol is derived by de novo synthesis, as the blood-brain barrier prevents access to cholesterol carrying lipoproteins from the circulation.[7] This should allow the brain to remain largely independent from circulating levels of cholesterol. Nevertheless, to examine this potential cognitive safety issue more thoroughly, a search was done of neurocognitive-related adverse event terms that included deliria (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception and mental impairment disorders. For the integrated parent trials, 11 participants reported neurocognitive adverse events: 5 (0.1%) were in the any evolocumab group and 6 (0.3%) were in the any control group.

7 Bjo¨rkhem I, Meaney S. Brain Cholesterol: Long Secret Life Behind a Barrier. Arterioscler Thromb Vasc Biol. 2004;24:806-815.)

For the year 1 SoC-controlled period, 16 (0.6%) participants in the evolocumab plus SoC group and 3 (0.2%) in the SoC alone group reported 22 neurocognitive adverse events. Exploratory analyses of the neurocognitive adverse events were performed for LDL-C subgroups defined by post-randomization values. In the year 1 SoC-controlled period, the LDL-C < 40 mg/dL EvoMab subgroup had an incidence of 0.7% (9/1369) compared with 0.5% (7/1427) in the LDL-C ≥ 40 mg/dL EvoMab subgroup. A review of the participants in the Year 1 SoC-Controlled period, who had neurocognitive events and an LDL-C < 40 mg/dL in the parent study or the extension study, showed that many of these cases were confounded by other conditions or medications that could also affect cognitive function. Many of these participants also had an LDL-C > 40 mg/dL just prior to the event.

Anti-evolocumab Antibody Formation: From the 14 integrated phase 2 and phase 3 studies supporting the indication in patients with primary hyperlipidemia and mixed dyslipidemia, 0.1% (7 out of 4846) of subjects developed binding antibodies after at least one dose of evolocumab. No subject developed neutralizing antibodies. There does not appear to be a temporal correlation between the development of binding antibodies and specific adverse events such as hypersensitivity.

Hypersensitivity: The incidence of potential hypersensitivity events was low overall but higher in the evolocumab group compared to placebo or to any control: in the integrated parent trials (evolocumab: 3.2%; any placebo: 2.4%; any control 2.4%), the year 1 SoC-controlled period (evolocumab plus SoC: 4.4%; SoC alone: 3.3%), and the year 2+ OLE period (5.7%). Five participants (all on evolocumab) reported adverse events of angioedema; some of these cases may have been confounded by use of another medication that may have contributed to the angioedema.

Injection Site Reactions: The incidence of injection site reactions was low and similar between treatment groups in the integrated parent studies (any evolocumab: 3.3%; any control 3.0%), the year 1 SoC-controlled period (evolocumab plus SoC: 3.7%; SoC alone did not receive injections), and the year 2+ OLE period (3.1%). The most common injection site reaction adverse events were injection site erythema, injection site pain, and injection site bruising. There was a total of nine participants who discontinued evolocumab due to injection site reactions (5 had recurring events and 4 had single events).

Hepatitis C: Because of the theoretical potential for increased HCV infectivity in participants treated with a PCSK9 inhibitor, analyses were performed to assess potential cases of hepatitis C. The incidence of hepatitis C was low: no subjects in the parent studies; in the year 1 SoC-controlled period (evolocumab plus SoC: 0%; SoC alone: 1, 0.1%) and the year 2+ OLE period (1, 0.1%).

CONCLUSIONS

Evolocumab (420 mg QM) results in statistically significant reductions in LDL-C of approximately 60% after 12 and 52 weeks of treatment. Evolocumab, at doses of 140 mg Q2W and 420 mg QM, yield similar LDL-C reductions. Evolocumab was effective across all subgroups with no significant differences. In patients with HoFH, evolocumab (420 mg QM), compared to placebo, significantly reduced LDL-C from baseline to Week 12 by 31%. The mean change from baseline to Week 12 within the evolocumab arm alone was -23% and within the placebo arm alone was +8%. Efficacy findings were similar in adult and adolescent patients with HoFH.

The effect of evolocumab on cardiovascular morbidity and mortality in any population has not been determined.

The safety database for the 140 mg Q2W dose and the 420 mg QM dose is adequate but limited in long-term, placebo-controlled data. The 52-week placebo-controlled trial enrolled many participants at low or moderate CV risk. Thus, the overall trial population does not represent a population at high CV risk with substantial CVD burden on maximally tolerated statin therapy—arguably, the most appropriate patient population for add-on therapy to a statin.

The limited amount of safety and efficacy data is a concern for the 420 mg Q2W dose, especially as this dosing regimen could potentially be used in children aged 12 years or older.

Potential safety issues identified in this review could be adequately addressed in labeling and by appropriate monitoring and treatment by health care providers. If evolocumab is approved, these issues should be thoroughly explored in on-going studies. These safety concerns include an observed imbalance of pancreatitis which may or may not be related to evolocumab; an imbalance of proteinuria (in statin-intolerant and diabetic subjects), which may or may not be related to evolocumab; the possible increased incidence of new onset diabetes in patients with baseline impaired fasting glucose; musculoskeletal adverse events and CK elevations, which may have been confounded by statin use; transaminase elevations and hepatobiliary AEs, which may have been confounded by concomitant use of statins and other medications; a potential for neurocognitive adverse events with long-term use; hypersensitivity and skin-related adverse reactions; injection site adverse reactions, as well as any adverse reactions that may be related to chronic, extremely low levels of LDL-C induced by a drug that have yet to be identified.

The evolocumab development program was presented at the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 10 June 2015. One of the issues discussed at the meeting was the use of LDL-C as a surrogate endpoint for the demonstration of efficacy in certain patient populations. For statins, LDL-C reduction as a surrogate for reduced CV risk reduction has been confirmed through multiple randomized controlled trials involving several statins and in patient populations with

varying degrees of baseline risk and LDL-C values. Recently, however, several controlled clinical trials have demonstrated that favorable changes in lipid parameters do not always translate into the expected cardiovascular benefit. One example is the ILLUMINATE trial[8], which showed that treatment with torcetrapib decreased LDL-C by 25% and increased HDL-C levels by 72% but also increased the risk for death and CVD. Other examples include trials that have focused on lipid endpoints other than LDL-C, such as the FIELD study[9], Action to Control Cardiovascular Risk in Diabetes – Lipid (ACCORD-Lipid),[10] Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial,[11] and Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)[12], which have failed to show cardiovascular benefits despite favorable lipid biomarker changes (predominantly changes in TG and HDL-C). This experience has led us to reassess previous assumptions about lipid-related surrogate endpoints in general.

Regarding the safety profile of evolocumab, the general consensus of the advisory committee was that evolocumab had a reassuring safety profile, although some adverse reactions may emerge after a larger number of individuals had been exposed for a longer duration. There was no convincing evidence that low LDL-C levels were harmful, however the consequences of long-term exposure to very low LDL-C levels was unknown and therefore it was difficult to define a threshold for low LDL-C levels or to provide guidance to health care providers on how this should be managed. The committee did agree that statin dose reduction was not an appropriate solution given that statins have positive CV risk reduction data.

One of the questions that the committee was asked to opine on was whether evolocumab-induced LDL-C lowering is sufficient to substitute for demonstrating its effect on clinical outcomes (i.e., to substitute for investigation in a CV outcomes trial) in one or more populations (e.g., different degrees of CV risk, familial vs. non- familial etiologies of hyperlipidemia, use with or without concomitant statins, etc.). Some committee members commented that LDL as a surrogate is mechanism dependent. Evolocumab's mechanism of action through upregulation of LDL receptors is reassuring as it is similar to the mechanism of action for statins. In addition, the data from

8 Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109-2122.
9 Keech A, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. Lancet. 2005; 366(9500): 1849-61.
10 ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. NEJM 2010; 362:1563.
11 The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255-67.
12 The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203-12.

individuals who have genetic mutations resulting in a loss of PCSK9 function is somewhat reassuring, although limited.

The committee voted 11 to 4 that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval in one or more patient populations (excluding HoFH). While some of the committee members believed that the trials were too short and small in size to assess safety, the majority believed that approval is acceptable for some populations, such as HeFH, high CV risk for secondary prevention and, for some panelists, high risk CVD with increased LDL on maximally tolerated statin therapy. The panelists also expressed that evolocumab should not be used in low CV risk populations prior to showing positive CVOT results and that it was important to convey that evolocumab-induced low LDL levels should not be managed by reducing or eliminating statin therapy. There was consensus that the ongoing CVOT should be completed in a timely manner and members were concerned that approval may derail the ongoing trial. The majority of members did not believe that the CVOT needed to be completed prior to approval.

The committee voted 15 to 0 that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval in the HoFH patient population. The panelists commented that the optimal dose and dosing schedule is not clear. While some panelists did not support the 420 mg Q2W dose, others felt that the unique need of this HoFH population justified the uncertainty with this dose as this would likely be used by experts in HoFH management.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division of Risk Management (DRISK) does not recommend that a REMS be required for evolocumab at this time. DRISK believes that labeling, including a Medication Guide, is sufficient to mitigate the risks associated with evolocumab. This reviewer concurs with DRISK's assessment.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of completing this review, the following studies have been recommended as postmarket requirements (PMR) and postmarket commitments (PMC). Details regarding the final language remain under discussion.

PMRs

1. Conduct a large, randomized controlled long-term trial in which the incidence and severity of new onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity and adverse events potentially related to demyelination with evolocumab treatment will be evaluated.

2. Conduct a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with evolocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect

3. Conduct an efficacy and safety study evaluating evolocumab in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. The study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C ≥ 130 mg/dL.

   Of note, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred under Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). To meet this requirement, the following studies are planned to fulfill the pediatric study plan (PSP):

- Study 20120123: Double-blind, randomized, multicenter, placebo-controlled, parallel study to characterize the efficacy, safety, and tolerability of 24 weeks of evolocumab for LDL-C reduction, as add-on to diet and lipid-lowering therapy, in pediatric subjects from 10 to 17 years of age with HeFH.

(b) (4)

4. Conduct a prospective observational study of pregnant women exposed to evolocumab to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

(b) (4)

PMCs

5. To establish the evolocumab drug substance (DS) stability acceptance criteria for the 9- and 12-month stability timepoints at the (b) (4)°C condition based on available stability data. The acceptance criteria and supporting data will be submitted as a CBE.
6. To demonstrate that the identity by ELISA assay performed at Amgen Thousand Oaks (ATO) for evolocumab drug product (DP) lot release testing functions within the parameters identified for the validated assay prior to releasing evolocumab lots tested for identity at ATO.
7. To re-evaluate the evolocumab drug substance (b) (4) limit (b) (4). The final report should include the corresponding data, the analysis and statistical plan used to evaluate (b) (4) limits, and any proposed changes to the limits.
8. To re-evaluate the evolocumab DP acceptance criteria (b) (4) s specified in PMC 7. The DP lots will include the lots which were used in the analysis of specifications submitted in the BLA and subsequent drug product lots manufactured. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the (b) (4) limits, and any proposed changes to the limits. The analysis should also include linkage to the drug substance (b) (4) limits for (b) (4) based on the re-evaluation specified in PMC 7.
9. To re-evaluate the evolocumab drug product release and stability acceptance criteria for the prefilled syringe and autoinjector presentations after the manufacture of DP lots from an additional 2 DS manufacturing campaigns. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the results and acceptance criteria, and any proposed changes to the criteria.

2 Introduction and Regulatory Background

2.1 Product Information

The non-proprietary name of this product is evolocumab (previously referred to as AMG 145). Proposed tradenames at the time of this review encompass 2 combination product presentations (biologic/device) that include the biologic evolocumab and 2 separate device presentations (pre-filled syringe and autoinjector/pen). Amgen initially submitted the proposed proprietary names, (b) (4) on March 26, 2014 to the IND (105188). However, the applicant formally withdrew the request for proprietary name review and subsequently submitted the names, Repatha,

Repatha SureClick, and Repatha RelyTouch, for review to the IND on May 27, 2014. In the BLA submission (BLA #125522), the sponsor submitted the names, Repatha and Repatha SureClick, for review on September 16, 2014. The applicant is seeking to use this trade name in all regions. The proposed proprietary names for the two combination products are:

- Repatha, for the pre-filled syringe (PFS) – This device itself will not be associated with a proprietary name.
- Repatha SureClick®, for the AI/pen – This device will use the previously trademarked name, SureClick®.

The Office of Prescription Drug Promotion (OPDP) determined the proposed root name, Repatha, is acceptable from a promotional perspective. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Metabolism and Endocrinology Products (DMEP) concurred with the findings of OPDP's promotional assessment of the proposed root name. OPDP noted that the device name "SureClick" is already part of an approved product, Enbrel SureClick, from the same applicant. Therefore, while OPDP found the proposed proprietary name, Repatha SureClick, problematic from a promotional perspective, OPDP did not object to the name. DMEPA and DMEP concurred with the findings of OPDP's promotional assessment of the proposed device name.

Evolocumab (also known as AMG 145) is a new molecular entity. Its pharmacological categories include (1) monoclonal antibody, (2) cholesterol-lowering agent and (3) inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab, a human monoclonal immunoglobulin G2 (IgG2) directed against PCSK9, binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface. This action prevents PCSK9-mediated LDLR degradation, which leads to increases in LDLR, and results in decreases in serum LDL-C.

The applicant proposes indications for primary hyperlipidemia and mixed dyslipidemia as well as HoFH, which are discussed in more detail in the next section.
Evolocumab will be available in one product strength of 140 mg/mL. The route of administration is subcutaneous. There are 2 devices in this application. The prefilled syringe (PFS) is a prefilled, single-use, disposable, handheld, injection device that is provided ready to use. The autoinjector (AI)/pen is a prefilled, single-use, disposable, handheld, mechanical (spring-based) injection device that is provided ready to use, pre-assembled with the prefilled syringe.

The applicant's proposed dosage and administration instructions are as follows:

> Primary Hyperlipidemia and Mixed Dyslipidemia:
> "The recommended dose for [TRADENAME] is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.

One single-use prefilled syringe (PFS) or single-use prefilled SureClick® Autoinjector delivers the 140 mg every 2 week dose, and 3 single-use prefilled syringes or 3 single-use prefilled SureClick® Autoinjectors administered consecutively within 30 minutes delivers the 420 mg once monthly dose."

Homozygous Familial Hypercholesterolemia:
"The recommended dose for [TRADENAME] is 420 mg either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Three single-use prefilled syringes or 3 prefilled SureClick® Autoinjectors administered consecutively within 30 minutes deliver the 420 mg once monthly or 420 mg every 2 weeks dose."

Dosage in patients with renal impairment
"No dosage adjustment is necessary in patients with mild to moderate renal impairment."

Dosage in patients with hepatic impairment
"No dose adjustment is necessary in patients with mild to moderate hepatic impairment."

Dosage in geriatric patients
"No dosage adjustment is necessary in geriatric patients."

2.2 Tables of Currently Available Treatments for Proposed Indications

Primary Hyperlipidemia and Mixed Dyslipidemia
The applicant is seeking the following indication for evolocumab in primary hyperlipidemia and mixed dyslipidemia: indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides(TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

The following drugs are currently approved for patients with primary hyperlipidemia or mixed dyslipidemia

- atorvastatin, simvastatin, pitavastatin, lovastatin, fluvastatin, pravastatin, niacin extended-release, fenofibrate (to reduce elevated TC, LDL-C, Apo B, and TG and to increase HDL-C)
- rosuvastatin, atorvastatin/ezetimibe and simvastatin/ezetimibe (to reduce elevated TC, LDL-C, Apo B, TG and non-HDL-C and to increase HDL-C)

Of note, there are no approved lipid-altering therapies that have been granted the following lipid parameter changes proposed by Amgen in their indication: to reduce TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), and lipoprotein (a) (Lp[a]), and to increase ApoA1. Also, the approved therapies for primary hyperlipidemia/mixed dyslipidemia state they are indicated to reduce *elevated* lipid parameters (such as TC and LDL-C); Amgen's proposed indication does not include this.

In addition, there are no approved lipid-altering therapies that have been granted indications for patients who are 'statin-intolerant' or for whom 'a statin is not considered clinically appropriate.'

Homozygous Familial Hypercholesterolemia
The applicant is seeking the following indication for evolocumab in HoFH: indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

The following drugs are currently approved for the reduction of elevated total cholesterol and LDL-C specifically for patients with HoFH: lomitapide, mipomersen, simvastatin, atorvastatin, rosuvastatin, ezetimibe, atorvastatin/ezetimibe and simvastatin/ezetimibe. Rosuvastatin, lomitapide and mipomersen are also approved for the reduction of apolipoprotein B in the HoFH population. Lomitapide and mipomersen are also approved for the reduction of non-HDL-C in the HoFH population.

Of note, the indicated population for the currently approved therapies is 'patients' without reference to adult or adolescent even for drugs that included some adolescent subjects in the clinical trials. Some of these drugs (such as rosuvastatin, atorvastatin, simvastatin) have specific indications for HeFH in pediatric subjects where a dedicated trial was done in children.

2.3 Availability of Proposed Active Ingredient in the United States

Evolocumab is not currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Evolocumab is the second drug in this class. Alirocumab (Praluent™), approved on 24 July 2015, is the first PCSK9 inhibitor to be approved in the US. Praluent™ is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Safety concerns include hypersensitivity/allergic reactions and injection site reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial IND (IND 105188) was submitted on 15 May 2009 by Amgen with an aim to develop the drug for hypercholesterolemia.

On 10 June 2009, IND 105188 was placed on partial clinical hold (PCH) for multiple dose studies. The applicant was informed that single dose studies were allowed to proceed but multiple dose studies were on clinical hold. They were advised that they needed to obtain and submit repeat-dose toxicity data from a second species before multiple dose studies would be permitted to proceed. The FDA explained that given that this compound acts through a novel mechanism, was associated with immune system perturbation in 50% of monkeys treated with 300 mg/kg/week AMG 145 (evolocumab), and was associated with early sacrifice of one monkey at this dose, it was considered that toxicity data from a second species were needed to better evaluate the toxicity profile of AMG 145 before repeat-dose studies were conducted in humans. In order to address the partial clinical hold for repeat-dose clinical studies, a repeat-dose toxicity study was to be conducted in a pharmacologically relevant rodent species (e.g. hamster). A four-week study was recommended. It was suggested that a two-week interim sacrifice group could be included if there was concern that a test item-inactivating immune response may have been elicited in the rodent. In addition, the FDA noted that there was evidence in the six-week monkey toxicity study that AMG 145 may perturb the immune system (lymphoid hyperplasia and increased mass of the spleen, lymphoid hyperplasia of the pylorus, and involution of the thymus). It was recommended that an evaluation of the immunotoxicological potential of AMG 145 should be conducted.

On 10 March 2010, the applicant submitted a complete response to the partial clinical hold. Two study reports were submitted and reviewed: 1) results of the 28-Day toxicity study in the Golden Syrian Hamster and 2) results of the tissue cross-reactivity study in the Golden Syrian Hamster. There was no AMG 145-related toxicity in this study at any dose, and the NOAEL was considered to be 300 mg/kg/week (the highest dose tested). The hamster NOAEL provided a safety multiple of 43x to a weekly human dose of 420 mg. On 09 April 2010, after review of this submission, the partial clinical hold was removed and repeat-dose studies using AMG 145 under this IND were allowed.

On 12 September 2013, orphan drug designation was granted for the treatment of HoFH (designation # 13-4041).

The division held a face-to-face end-of-Phase 2 (EOP2) meeting with Amgen on 10 July 2012 to discuss the evolocumab development program. Topics of discussion included: (1) monotherapy and superiority to ezetimibe/statin claims would likely require cardiovascular outcomes trial (CVOT) data, (2) concerns regarding only taking two dosing regimens (Q2W and Q4W) into phase 3 that seemed to yield approximately the same degree of LDL-C lowering, (3) FDA did not agree with Amgen's proposed definition of statin-intolerance of failing 1 or more statins, (4) FDA expressed concerns with some of the proposed study populations who may not be taking the maximum tolerated dose of statin. The division expected that placebo-controlled studies, such as protocol 20110115 (combination with statins), would enroll patients who are not at goal despite taking the maximal tolerated dose of statin, with or without other lipid-modulating agents, (5) the design of the proposed CVOT, (6) accrual of a minimum of 25% of the planned first secondary endpoint events in the CVOT prior to BLA submission, (7) no dedicated studies to investigate drug-drug interactions would be required, but systemic exposure data was to be collected, (8) FDA agreed that a thorough QT study would not be required, but that safety ECGs be collected at baseline and at steady state and (9) FDA agreed that the nonclinical data package should be sufficient.

A pre-BLA clinical meeting was held on 10 April 2014. Clinical topics addressed during this meeting included: (1) FDA will accept the evolocumab BLA file, even if less than 25% of potential events have been accrued and adjudicated in the CVOT (FOURIER study) prior to filing of the BLA; (2) FDA reconfirmed that the FDA is unlikely to consider a monotherapy indication or an indication explicitly referencing "statin-intolerant" patients without positive outcomes data. FDA expected that the approvability of a PCSK9 inhibitor, in the absence of outcomes data, would be a topic for discussion with an advisory committee; (3) FDA communicated concerns about the sufficiency of the safety database and duration of exposure to support the proposed indications; (4) FDA stated that current estimates for the 1-year exposure would not constitute a complete file; therefore a different cutoff for the safety database was required; (5) FDA requested the submission of all available PK data from all the phase 1, 2 and 3 studies. FDA encouraged the inclusion of phase 3 studies in the population PK analysis; and (6) a subsequent proposal agreed upon by Amgen and the FDA included a safety database cutoff date of 01 April 2014, including updates to all case study reports (CSRs) and affected summaries.

BLA 125522 was received by the agency on 27 August 2014.

The table below presents a more extensive synopsis of the regulatory history.

Table 1: Summary of Key Regulatory Interactions

Meeting Date/ Type/	Notes
(b) (4)	
10 July 2012 End of Phase 2 (Clinical) To discuss the clinical development program	•FDA: With respect to your study populations, you are proposing to enroll subjects (b) (4), but we disagree. In contrast to some of the current designs, we would expect that placebo-controlled studies would enroll patients who are not at goal despite taking the maximal tolerated dose of statin, with or without other lipid-modulating agents. •FDA stated that it would inappropriate to use AMG 145 as monotherapy in the general population before cardiovascular (CV) outcomes data are available. Thus, with the possible exception of an indication for a "statin-intolerant" population, it is unlikely that we would entertain a monotherapy indication without CV outcomes data. •FDA stated that based on the currently proposed designs, you intend to make superiority claims to ezetimibe (b) (4) We would not include superiority claims to (b) (4) before CV outcomes data for AMG 145 are available.

	(b) (4)
	•FDA expressed concerns on having both 140 mg Q2W and 420 mg Q4W regimens. These dosing regimens seem to have approximately the same pharmacodynamic (PD) effect with regard to LDLC (b) (4) • Amgen suggested that both selected doses were more effective than other tested doses, were associated with more stable LDL levels, and were not associated with any higher incidence of adverse events or laboratory abnormalities. They noted that AMG 145 140 mg Q2W provides a lower drug exposure, based on AUC, than the 420 mg Q4W dose; therefore, these dosages ought to be sufficient to identify dose-related adverse effects. • FDA stated that we would prefer the duration of the studies to be 24 weeks.
	• FDA did not agree with Amgen's proposed definition of statin-intolerance of failing 1 or more statins. FDA recommended the following definition for muscle-related statin-intolerance: the inability to tolerate at least two previous statins at the lowest approved daily dose as a result of muscle-related symptoms that began or increased during statin therapy and stopped with the discontinuation of statin therapy. Symptoms could include aches, pain, cramping, and/or weakness but should exclude those thought to be the result of strain, exertion, or trauma. Historical information regarding previous statins, doses, and muscle-related events that led to the diagnosis of "statin intolerance" should be recorded. We would require a design that would incorporate a blinded statin re-challenge arm in order to provide convincing evidence that you have successfully identified a distinct patient population. We recognize that subjects with a history of certain serious adverse effects (e.g., documented myositis or rhabdomyolysis on statin therapy) could not be enrolled in such a trial. • FDA was in agreement with the general design of the proposed CVOT and recommended it be submitted as a SPA. FDA stated as a result of the division's experience with the development programs of non-statin LDL-C-lowering drugs, we will require that the trial has accrued a minimum of 25% of the planned 1630 first secondary endpoint events before submission. It is also possible that the results of the ongoing IMPROVE-IT trial, which is studying the incremental contribution of ezetimibe on CV outcomes beyond simvastatin alone, might alter the division's approach to non-statin lipid-modulating drugs. If IMPROVE-IT fails to demonstrate a favorable effect of ezetimibe on clinical outcomes, it is possible that results from your CV outcomes trial may be required prior to approval. • FDA agreed that no dedicated studies to investigate drug-drug interactions were required, but systemic exposure data should be collected •FDA agreed that a thorough QT study is not required, but that safety ECGs be collected at baseline and at steady state • Additional Topics discussed at the meeting: Amgen informed FDA that they intend to reclassify the phase 2 study 20110109 as a phase 3 study. Amgen confirmed that the phase 3 trials will be performed with the formulation of AMG 145 intended for the market.
	(b) (4)

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15 July 2013 – Written Responses; To obtain FDA feedback on the proposed ISS and ISE	• The FDA found the proposed data standardization plan to be acceptable, but had questions regarding the primary endpoint for the phase 2 and phase 3 studies • FDA requested a discussion regarding the adjudication on reported adverse events, the process for positive adjudication, and a description of the adjudication packages to be submitted • FDA stated: "We note that you intend to (b) (4) in the integrated datasets. We would need further details regarding how you plan to analyze and interpret your results before agreeing that the inclusion of these studies is appropriate."
30 October 2013 - Tcon; advice on the data package to support the HoFH indication	• FDA noted the heterogeneity of response of HoFH subjects to evolocumab as a possible limitation. •Primary Endpoint: The FDA indicated that mean percent change in LDL-C from baseline to Week 12 is the expected primary endpoint for HoFH. FDA indicated that the "regulatory decision" will likely be based upon the mean percent change in LDL-C from baseline to Week 12 (currently a co-primary endpoint) for all 12 week Phase 3 trials. •An indication for HoFH would only be considered in parallel with or after an indication is granted for the general population with hyperlipidemia. The FDA stated that Amgen could pursue a Treatment IND to grant early access to the HoFH population pursuant to expanded access regulations
10 April 2014 – Pre-BLA (Clinical)	• FDA stated that we continue to believe that accrual of a minimum of 25% of MACE (with timely adjudication) prior to BLA submission is the appropriate method to encourage timely CVOT completion. If you decide to submit prior to reaching the 25% of endpoints threshold, you should include the number (%) of first secondary endpoint events that have been accrued, the number (%) that have been adjudicated and the results of adjudication (i.e., the number accepted as endpoints vs. rejected), and the number (%) of subjects that have been randomized at the time of BLA submission. • FDA reconfirmed that the FDA is unlikely to consider a monotherapy indication or an indication explicitly referencing "statin-intolerant" patients without positive outcomes data. FDA expects that the approvability of a PCSK9 inhibitor, in the absence of outcomes data, will be a topic for discussion with an advisory committee. • FDA stated that the proposed safety database was significantly less than what was estimated at the EOP2 meeting and we had concerns about the sufficiency of the safety database and duration of exposure to support the proposed indications. FDA stated that current estimates for the 1-year exposure would not constitute a complete file; therefore a new safety data-cut is required (01 April 2014 agreed to be the new data cut).
18 April 2014 post-Pre-BLA meeting information requests	FDA Request #3. The baseline characteristic data published in your NEJM report of the DESCARTES trial seem inconsistent with the "high-risk" population that you have indicated are most appropriate for evolocumab therapy. Specifically, more than half of the trial's population fall into the "diet alone" or "diet plus atorvastatin 10 mg" groups, which do not seem consistent with high-risk populations. Overall, it appears that only 271 patients were treated for a year with high-dose atorvastatin (with or without ezetimibe) combined with evolocumab. Considering the entire trial population, the majority (65%) of subjects were categorized as either low or moderate risk by the ATP-III classification. Furthermore, the mean baseline LDL-C among all patients was 104 mg/dL, which is quite well controlled and does not appear consistent with the population that you describe as having an unmet medical need (i.e., "high" LDL-C despite statin therapy). Especially since you believe that this trial represents the highest-quality safety data for your program, we continue to have concerns regarding long-term safety among the target population likely most appropriate for evolocumab before outcomes data are available. Thus, we anticipate having to rely substantially on data from your open-label controlled extensions that studied higher-risk populations. As we previously requested in the pre-BLA meeting preliminary comments, any information you can provide with regard to the numbers of patients that have been treated with evolocumab for at least one year in relevant categories of demographic or

	baseline characteristics would be helpful to guide our decisions regarding agreements with your safety database. Please let us know if, and when, you would be able to provide additional information. FDA Post-Meeting Comments: It is our understanding that a data cutoff on April 1, 2014 would provide (b) (4) patients with ≥361 days exposure to evolocumab. We also note that (b) (4) %) of these subjects would come from your phase 3 program (b) (4) of them from your DESCARTES trial) and (b) (4) %) would come from your phase 2 program. We still question whether the summary of baseline characteristics that you have provided are consistent with the "high-risk" population that you have indicated as most appropriate for evolocumab therapy. This is an issue of concern that will be discussed during the review of your application. As we mentioned previously, we anticipate having to rely substantially on data from your open-label controlled extensions that studied higher-risk populations. Therefore, the controlled data from the 120-day safety update should be incorporated into updated analyses of the controlled phases of these trials and should not be submitted solely as a separate data presentation. Provided that the 120-day safety update is submitted as described above, we do not anticipate that an April 1, 2014 data cutoff for Studies 20110110, 20120138, and 20120271 would preclude filing of a BLA for the proposed indications of primary hyperlipidemia and mixed dyslipidemia and HoFH. Whether the safety database will be sufficient for approval of the proposed indications will be a subject of review. Additional FDA Request: As noted above, you anticipate that (b) (4) % ((b) (4)) of the subjects with ≥361 days of evolocumab exposure will come from your phase 2 program and its open-label extension studies. We note that you administered evolocumab differently in phase 2 (total volume per administration drawn from six sterile vials) with a formulation (70 mg/mL) that you do not intend to market and that you did not use in phase 3. Please explain how you plan to bridge your phase 2 and phase 3 programs for the evaluation of clinical safety.
30 April 2014 firm responds via email to IR of 4/18/14	Amgen Response to FDA Request #3 (excerpts): In designing DESCARTES, Amgen and its academic collaborators endeavored to enroll an appropriate at-risk cardiovascular population where it would be ethical to evaluate the treatment of hyperlipidemia with evolocumab compared to placebo in a blinded fashion for 1 year. To facilitate this, background lipid-lowering therapy was optimized to one of four treatment groups (diet alone; diet plus atorvastatin 10 mg; diet plus atorvastatin 80 mg; and diet plus atorvastatin 80 mg plus ezetimibe 10 mg) for individual subjects based on their LDL-C and cardiovascular risk according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III risk categories. On optimized therapy, eligible subjects needed to have a fasting LDL-C greater than 75 mg/dL and less than 100 mg/dL for subjects with coronary heart disease or risk equivalent, or an LDL-C of less than 130 mg/dL for subjects without coronary heart disease or risk equivalent unless they had reached maximal therapy (ie, atorvastatin 80 mg plus ezetimibe 10 mg). It is the position of Amgen that DESCARTES enrolled an appropriate at-risk cardiovascular population to evaluate long-term safety, tolerability, and efficacy of evolocumab alone and in combination with high-intensity and moderate-intensity lipid-lowering therapy. In DESCARTES, 36% and 33% of the subjects were high/moderately high and moderate risk by ATP-III risk categories, respectively. Using the DESCARTES NCEP risk-based treatment approach, approximately 88% of the subjects enrolled in DESCARTES ended up on high-intensity (45%) and moderate-intensity (43%) statin therapy. Furthermore, it is striking that approximately 21% of the DESCARTES subjects had mean LDL-C values of 117-120 mg/dL after forced titration to atorvastatin 80 mg plus ezetimibe 10 mg. In subjects allocated to diet alone or diet plus atorvastatin 10 mg, approximately 42% and 42%, had hypertension, respectively. In the diet alone group, 18% and 37% were high/moderately high and moderate risk by ATP III, respectively. In the diet plus atorvastatin 10 mg group, 22% and 36% were high/moderately high and moderate risk by ATP III, respectively… The population encompassing the datasets using 01 April 2014 as a data cut-off date (Tables 4-7) has a mean

(SD) age of 57 (11) years and is approximately 54% female. Approximately 18% and 7% have a prior diagnosis of coronary artery disease and cerebrovascular or peripheral arterial disease, respectively. Approximately 11% have Type II diabetes mellitus while approximately one third have metabolic syndrome and mixed dyslipidemia. Approximately 40% are high and moderately-high risk by ATP-III; 31% are moderate risk. Given the evaluation of evolocumab monotherapy to determine the safety and efficacy of evolocumab in the absence of possible confounding factors from statins, as well as the evaluation of evolocumab in statin-intolerance, approximately 70% of the population studied was on lipid-lowering therapy at baseline with 69% on statins. Of the patients on statin therapy at baseline, approximately 37% and 48% were on high-and moderate-intensity statin, respectively. Please note that severe heart failure, type 1 diabetes, and poorly controlled, or newly diagnosed, type 2 diabetes are listed as exclusionary criteria for each of the phase 2 and 3 studies. (see table 7 below)

Table 7. Evolocumab-treated Subject Baseline Characteristics in Phase 3 Studies with ≥ 1 year Study Exposure (Exposure ≥361 days)

Report Topic	All Combined (Phase 2 and 3)	Any Phase 3	S109	S114	S115	S116	S117
Number of Subjects with ≥361 Days of Exposure	1761	650	566	58	5	19	2
Female – n (%)	945 (53.7)	341 (52.5)	295 (52.1)	32 (55.2)	4 (80.0)	9 (47.4)	1 (50.0)
Age (years), mean (SD)	56.7 (11.3)	56.3 (10.9)	56.2 (10.7)	53.8 (12.6)	65.8 (6.1)	64.7 (9.0)	72.0 (2.8)
>= 65 Years Old – n (%)	478 (27.1)	162 (24.9)	135 (23.9)	12 (20.7)	3 (60.0)	10 (52.6)	2 (100.0)
Coronary artery disease (CAD) – n (%)	313 (17.8)	98 (15.1)	89 (15.7)	0	1 (20.0)	6 (31.6)	2 (100.0)
CVD or PAD – n (%)	112 (6.4)	32 (4.9)	26 (4.6)	2 (3.4)	1 (20.0)	3 (15.8)	0
Type II Diabetes Mellitus – n (%)	205 (11.6)	63 (9.7)	58 (10.2)	0	1 (20.0)	4 (21.1)	0
Triglycerides >= 150 mg/dL – n (%)	523 (29.7)	145 (22.3)	114 (20.1)	19 (32.8)	3 (60.0)	9 (47.4)	0
Low HDL-C – n (%)	552 (31.3)	194 (29.8)	166 (29.3)	14 (24.1)	3 (60.0)	10 (52.6)	1 (50.0)
Subjects with baseline metabolic syndrome (3 or more factors) and without diabetes mellitus – n (%)	640 (36.3)	216 (33.2)	183 (32.3)	21 (36.2)	3 (60.0)	8 (42.1)	1 (50.0)

Report Topic	All Combined (Phase 2 and 3)	Any Phase 3	S109	S114	S115	S116	S117
NCEP risk category – n (%)							
High risk	545 (30.9)	167 (25.7)	148 (26.1)	3 (5.2)	2 (40.0)	12 (63.2)	2 (100.0)
Moderately high risk	159 (9.0)	58 (8.9)	53 (9.4)	4 (6.9)	0	1 (5.3)	0
Moderate risk	551 (31.3)	213 (32.8)	191 (33.7)	16 (27.6)	2 (40.0)	4 (21.1)	0
Congestive Heart Failure – n (%)	41 (2.3)	10 (1.5)	10 (1.8)	0	0	0	0
Left ventricular systolic function known – n (%)	245 (13.9)	58 (8.9)	54 (9.5)	0	2 (40.0)	1 (5.3)	1 (50.0)
Normal systolic function (LVEF >= 50%) – n (%)	211 (12.0)	49 (7.5)	46 (8.1)	0	1 (20.0)	1 (5.3)	1 (50.0)
Mild dysfunction (LVEF 40-49%) – n (%)	30 (1.7)	9 (1.4)	8 (1.4)	0	1 (20.0)	0	0
Moderate dysfunction (LVEF 30-39%) – n (%)	4 (0.2)	0	0	0	0	0	0
Severe dysfunction (LVEF < 30%) – n (%)	0	0	0	0	0	0	0
Baseline Lipid medication – n (%)							
Statin	1251 (71.0)	508 (78.2)	497 (87.8)	0	5 (100.0)	4 (21.1)	2 (100.0)
Ezetimibe	259 (14.7)	124 (19.1)	122 (21.6)	0	0	0	2 (100.0)
Per ACC/AHA definition – n (% of statin subjects)							
High-intensity	494 (39.5)	259 (51.0)	256 (51.5)	0	2 (40.0)	0	1 (50.0)
Moderate-intensity	596 (47.6)	244 (48.0)	241 (48.5)	0	2 (40.0)	1 (25.0)	0
Low-intensity	161 (12.9)	5 (1.0)	0	0	1 (20.0)	3 (75.0)	1 (50.0)
Statin therapy at baseline per Amgen definition – n (%)							
Intensive	526 (29.9)	259 (39.8)	255 (45.1)	0	2 (40.0)	0	2 (100.0)
Non-Intensive	725 (41.2)	249 (38.3)	242 (42.8)	0	3 (60.0)	4 (21.1)	0
LDL-c (mg/dL) at baseline - mean (SD)	127.2 (39.2)	107.1 (30.9)	100.7 (22.3)	141.9 (19.9)	82.0 (16.7)	197.3 (58.7)	130.3 (26.5)
PCSK9 (ng/mL) at baseline - mean (SD)	439.6 (155.8)	456.9 (174.3)	478.6 (172.3)	285.2 (76.1)	391.8 (96.4)	296.1 (65.2)	504.5 (183.1)

Data cutoff date of 01 April 2014

27 July 2014 firm responds to IR of 5/07/14 re: bridging the phase 2 and phase 3 trials	"As the FDA has noted, drug substance for phase 1 and phase 2 clinical studies was manufactured using a different process (Process 1) than that employed in a majority of phase 3 studies (Process 2). Process 2 drug substance refers to the proposed commercial drug substance. To bridge the phase 2 and phase 3 programs for the evaluation of clinical safety, Amgen plans to provide the following in the proposed BLA: • A comprehensive analytic comparability assessment (Module 3 summary)

	• PK/PD dataset and analyses from 23 clinical studies (Module 5 & Module 2 summaries) • Individual and integrated clinical efficacy and safety data from 23 clinical studies (Module 5 & Module 2 summaries) These data will demonstrate similarities in drug substance, a consistent PK/PD profile, and consistency across all key safety and efficacy parameters across the studies."

2.6 Other Relevant Background Information

PCSK9 Inhibitors

Evolocumab is one of several drugs under development in a new lipid-altering class. It is a human monoclonal immunoglobulin G2 that binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and inhibits the binding of PCSK9 to the low-density lipoprotein receptor (LDLR). PCSK9 is a secretory protein produced predominantly in the liver, kidney and intestine. PCSK9 normally promotes downregulation of LDLR on the surface of hepatic cells; therefore, inhibition of PCSK9 leads to upregulation of LDLR, which increases the scavenging of LDL from the blood.

There are reports in the literature of individuals who have mutations in PCSK9 that decrease its activity. One article reports on a study in African Americans that have a single nonsense allele for PCSK9 and have a 28% lowering of circulating LDL-C levels and an 88% reduction in risk for CHD. The authors also report that white Americans carrying a different variant allele for PCSK9 had a 15% lowering of LDL-C levels and a 47% lower risk for CHD.[14] There are literature reports of individuals with loss-of-function alleles of PCSK9. One individual was a 21-year-old African woman homozygous for a PCSK9 loss-of-function allele with an LDL-C of 15.5 mg/dL and an HDL-C of 54 mg/dL.[15] Another individual was a 32-year-old African American woman who is compound heterozygous for loss-of-function alleles of PCSK9. She was reported to be an apparently healthy, normotensive, college-educated individual with normal liver and renal function tests who has given birth to two healthy children. Her reported LDL-C level was 14 mg/dL, HDL-C 65 mg/dL and TG of 119 mg/dL.[16] However, there are other cases where individuals did have health issues that may be related to their PCSK9 deficiency. One individual, a 49-year old French white man who was subsequently found to be heterozygous for two PCSK9 missense mutations, was hospitalized for the rapid-onset of insulin-requiring diabetes mellitus. He had low plasma LDLC levels (7 mg/dL) on admission and also at diabetes onset (16 mg/dL). Abdominal ultrasonography showed moderate liver steatosis. Hepatic enzymes levels and liver function tests were normal and there was no history of diarrhea, eye or neurological

14 Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. 2006. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med.. 354(12): 1264-72.
15 Hooper, AJ , Marais AD, Tanyanyiwa DM, Burnett JR. 2007. The C679X mutation in PCSK9 is present and lowers blood cholesterol in a Southern African population. Atherosclerosis.193(2): 445-8.
16 Zhao Z, Tuakli-Wosornu Y, Lagace TA, et al. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet 2006;79:514-23.

abnormalities related to vitamin deficiency. His mother was deceased at age 66 from dementia, whereas his father was healthy at age 79. His grandparents died at the ages of 79, 87, 91, and 94 years.[17]

Ttheoretical risks have been identified with the PCSK9 inhibitors as a class. The following issues of potential (theoretical) concern have been identified; please refer to Dr. Elmore's review for further information. Some of the theoretical concerns for evolocumab considered during the development of evolocumab include:

(1) Immunosuppression: Immune cells (such as lymphocytes, neutrophils, macrophages, NK cells, mast cells, and dendritic cells) are dependent on membrane cholesterol and cholesterol-containing lipid rafts for their function. There is a theoretical, mechanism-based concern to suggest that evolocumab-mediated lowering of LDL-C may be associated with immunosuppression. However, no significant effects of evolocumab on immune function, including immunophenotyping and T cell dependent antibody response, were observed in adult monkeys. No effects of evolocumab on immune function, including immunophenotyping, T cell dependent antibody response and NK cell function, were observed in monkeys administered a combination of 100 mg/kg evolocumab subcutaneously administered every other week with 5 mg/day oral rosuvastatin, which provides an 50, 10 and 8.8X safety margin to the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W, respectively, based on AUC. The 5 mg/day dose of rosuvastatin provides a 2X exposure multiple to the 40 mg QD recommended human dose, based on AUC.

(2) Increased risk of hepatocellular carcinoma secondary to increased risk for HCV infection: PCSK9 negatively regulates CD81, which is believed to play a role in lymphocyte development and activation and has been implicated in carcinogenesis. CD81-null mice have impaired B cell responses, and loss of CD81 expression has been associated with primary and metastatic liver adenocarcinomas. Based on these data, evolocumab could be hypothesized to have a protective effect against neoplasia via upregulation of CD81 expression. On the other hand, CD81 is thought to be a critical component of the receptor for the hepatitis C virus (HCV); therefore, evolocumab-mediated upregulation of CD81 may render subjects more susceptible to HCV infection and subsequent development of hepatocellular carcinoma.

(3) Increased risk of colorectal cancers secondary to increased intestinal bile acid load: Evolocumab lowers serum LDL-C by increasing the expression level of LDL-R in the liver, thereby increasing hepatic uptake of LDL-C. Given that the primary route of elimination of cholesterol by hepatocytes is conversion to bile acids, it can be anticipated that treatment with evolocumab may increase the load of bile acids delivered

17 Cariou B, Ouguerram K, Zaïr Y, Guerois R, Langhi C, Kourimate S, et. al., PCSK9 Dominant Negative Mutant Results in Increased LDL Catabolic Rate and Familial Hypobetalipoproteinemia. Arterioscler Thromb Vasc Biol. 2009;29:2191-2197.

to the intestine, especially in hypercholesterolemic patients. Given that secondary bile acids have been shown to be associated with genetic aberrations in colon cells and to be carcinogenic in the rodent colon, the risk of colorectal cancer could theoretically be increased by evolocumab. To address theoretical concerns for how evolocumab may increase the risk of cancer, the applicant conducted a two-year (i.e., lifetime) carcinogenicity bioassay in hamsters. No increase in colon tumors was observed in the hamster carcinogenicity study with evolocumab. Furthermore, no drug-related tumors were observed at exposure multiples of up to 38, 15 and 6.6 times the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W, respectively.

LDL as an Endpoint

Hypercholesterolemia, specifically an increase in LDL-C levels, is a major risk factor for the development of atherosclerosis and atherosclerotic cardiovascular disease. Many large-scale, randomized trials have shown that reducing LDL-C levels with statins reduces the risk of CHD, with a direct relationship between LDL-C levels and CHD events. One meta-analysis concluded that lowering LDL-C by 1 mmol/L (~40 mg/dL) for 4 to 5 years reduces the risk of major vascular events (non-fatal myocardial infarction, coronary death, ischemic stroke, or coronary revascularization) by 22%[18]. Several recent trials have shown that statin regimens using higher doses or more-potent agents, which both yield greater reductions in LDL-C, reduce the risk of vascular events more than less-intensive statin regimens in patients at very high cardiovascular risk.[19,20,21,22]

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease. Historically, reduction of LDL-C alone has been viewed favorably as a surrogate outcome if the reduction was sufficiently robust and if the investigational product did not have safety signals raising concern that risk exceeded benefit. Within the last few years, however, several controlled clinical trials have demonstrated that favorable changes in lipid parameters do not always translate into the expected cardiovascular benefit. One

18 Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet 2010;376:1670-1681.
19 Cannon CP, Braunwald E, McCabe CH, Rader D J, Rouleau JL, Belder R et al., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators*. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med 2004; 350(15): 1495-504.
20 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352:1425–35.
21 Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I et al., on behalf of the Incremental Decrease in End Points through Aggressive Lipid Lowering Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL study: a randomized controlled trial. JAMA 2005; 294:2437– 45. Erratum in: JAMA. 2005 Dec 28;294(24):3092.
22 Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.

example is the ILLUMINATE trial[23], which showed that treatment with torcetrapib decreased LDL-C by 25% and increased HDL-C levels by 72% but also increased the risk for death and CVD.

Additional examples include trials that have focused on lipid endpoints other than LDL-C, such as Action to Control Cardiovascular Risk in Diabetes – Lipid (ACCORD-Lipid),[24] Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial,[25] and Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)[26], which have failed to show cardiovascular benefits despite favorable lipid biomarker changes (predominantly changes in TG and HDL-C). Although the hypothesized reasons for these "failures" are varied, this experience should encourage us to remain vigilant and reassess previous assumptions about lipid-related surrogate endpoints in general.

The results from Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[27], which was presented by Dr. Christopher Cannon at the American Heart Association Scientific Sessions, Chicago, IL, November 17, 2014, has provided preliminary information regarding the association between non-statin-based LDL-C reduction and cardiovascular outcomes. IMPROVE-IT evaluated ezetimibe/simvastatin 10/40 mg combination compared to simvastatin 40 mg monotherapy in over 18,000 subjects with stabilized high-risk acute coronary syndrome with a composite primary outcome of cardiovascular death, myocardial infarction, nonfatal stroke, rehospitalization for acute coronary syndrome, or revascularization. The trial started in October 2005 and ended in November 2014. The incidence of the primary composite endpoint was reported to be lower in the ezetimibe/simvastatin group compared with the simvastatin group. Thus, at initial glance, the IMPROVE-IT results might provide evidence that in patients with stabilized high-risk acute coronary syndrome ezetimibe 10 mg/simvastatin 40 mg was modestly more effective than simvastatin 40 mg alone in reducing CV events. However, DMEP has not reviewed the IMPROVE-IT trial and it is possible that the Division will reach different conclusions than the trial's investigators.

23 Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109-2122.
24 Effects of combination lipid therapy in type 2 diabetes mellitus. NEJM 2010; 362:1563.
25 The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255-67.
26 The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203-12.
27 Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, Strony J, Musliner TA, McCabe CH, Veltri E, Braunwald E, Califf RM; IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008 Nov;156(5):826-32. Epub 2008 Sep 2.

In the absence of cardiovascular outcomes data, contemporary decisions to approve novel LDL-lowering therapies are influenced by the direction and magnitude of drug-induced changes in LDL-C as well as the effects of the drug on other lipid parameters, markers of cardiometabolic risk, and any evidence for off-target toxicity.

FOURIER, an ongoing cardiovascular outcome trial with evolocumab, is being conducted in the general hyperlipidemic (non-HoFH) population but results will not be known until late 2017/early 2018. As of 15 August 2014, approximately 15,000 subjects had been randomized to the trial and the mean and median investigational product treatment duration was 5.5 months and 4.9 months, respectively. As of 26 November 2014, 20,778 individuals (75.6% of 27,500 total) had been randomized, 330 subjects have had major adverse cardiac events (MACE) (20.2% of the 1630 planned events), 377 MACE had accrued of which 213 (57%) had been adjudicated and 186 (87% of 213) events had been positively adjudicated.

HoFH

HoFH is a rare genetic disorder in which both LDLR alleles are defective. The estimated US prevalence of HoFH has been often quoted to be approximately 1 in 1,000,000 persons according to the literature[28] which extrapolates to approximately 300 individuals in the US. Recent estimates, however, have suggested that HoFH may affect as many as 1 in 160,000 to 1 in 300,000 individuals[29]. Untreated individuals with HoFH have very high concentrations of LDL-C, often in the range of 650 to 1000 mg/dL, cutaneous and tendinous xanthomata, corneal arcus, and premature coronary artery disease and aortic stenosis[30]. HoFH patients who are LDLR-negative (<2% of LDL receptor function in cultured fibroblasts) tend to have higher levels of LDL-C and a worse prognosis than those who are LDLR-defective (2-25% residual LDLR activity). If untreated, LDLR-negative patients rarely survive beyond the second decade of life. Those who are LDLR-defective have a better prognosis, but still often develop clinically significant atherosclerotic vascular disease by the age of 30 years without treatment[31].

Treatment typically involves lipid-modifying medical therapy as well as mechanical removal of plasma LDL via LDL apheresis, typically once every 1-2 weeks. Lipid-lowering drugs such as statins, which act mainly by up-regulating hepatic LDL

28 Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial Hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipid 2011; 5:S9-S17.
29 Cuchel M, Bruckert E, Ginsberg HN, et al; for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. ePub ahead of print, 22 Jul 2014.
30 Goldstein AL, Brown MS. Molecular Medicine. The cholesterol quartet. Science. 2001;292(5520):1310-2.
31 Raal FJ, Santos RD, Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment, Atherosclerosis (2010), doi:10.1016/j.atherosclerosis.2012.02.019

receptors, are not particularly effective in reducing LDL-C levels in these individuals because their LDL receptors are dysfunctional. For example, in a study of HoFH individuals (n=40, 8-63 years) treated with rosuvastatin 20 to 40 mg[32] for 12 weeks, the mean LDL-C reduction from baseline (514 mg/dL) was 22%. In a study with atorvastatin (20 to 80 mg) without a concurrent control group[33], 29 patients (ages 6 to 37 years) achieved a mean LDL-C reduction of 18%. LDL-apheresis is an extracorporeal treatment that selectively removes LDL particles from plasma and achieves significant reductions of LDL-C during several weekly or biweekly sessions[34]. LDL apheresis is FDA approved and indicated if the LDL-C is: >500 mg/dl in patients with homozygous FH, >300 mg/dl in patients without CAD, or >200 mg/dl in patients with CAD despite 6 months of treatment with maximal drug and dietary therapy. While LDL apheresis significantly lowers LDL-C and is considered the standard of care for patients with HoFH, the limitations include limited availability, high cost, procedure duration, and the need to maintain adequate vascular access.[35]

The efficacy endpoints considered by the applicant for approval in the HoFH population, as well as approval in the general population, include reduction in LDL-C (primary) as well as changes in other lipid parameters such as total cholesterol (TC), apolipoprotein B (ApoB), and non-high-density lipoprotein cholesterol (non-HDL-C). Unlike hyperlipidemia and dyslipidemia in the general population, in which multiple genetic and environmental factors contribute to its pathophysiology, the HoFH phenotype is essentially a monogenic disorder of deranged LDL metabolism. Thus, lowering LDL-C is certainly a reasonable therapeutic goal in this orphan population, and this was supported in 2012 during meetings of the Endocrinologic and Metabolic Drugs Advisory Committee that preceded the approval of lomitapide and mipomersen for HoFH. It is unknown, however, whether the often-quoted quantitative relationship between cardiovascular risk and LDL-C reduction (i.e., ~22% reduction in major vascular events per 40 mg/dL reduction in LDL-C, based on clinical trials of statins) can be extrapolated to the extreme levels of LDL-C that characterize individuals with HoFH.

Statin Intolerance

There has been recent interest by companies in performing trials in “statin intolerant” populations. The Division’s working definition of statin intolerance for the purpose of exploring this concept in clinical trials of novel non-statin LDL-C lowering therapies follows:

> The inability to tolerate at least 2 statins: one statin at the lowest starting daily dose, defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg,

32 NDA 21366 Crestor PI, 9/25/2014
33 NDA 20702 Lipitor PI, 9/25/2014
34 Thompsen J, Thompson PD. A systematic review of LDL apheresis in the treatment of cardiovascular disease. Atherosclerosis. 2006: 189,31–38.
35 Thompson GR. Lipoprotein apheresis. Curr Opin Lipidol. 2010;21: 487–491.

> lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg, AND another statin at any dose, due to the prespecified intolerance symptoms (such as skeletal muscle, hepatic, psychiatric, or cognitive-related symptoms) that began or increased during statin therapy and stopped when statin therapy was discontinued.
>
> Patients receiving less than the lowest daily approved dose of a statin (e.g. 1 to 3 times weekly) will also be considered as not tolerating a daily dose and will be eligible for the study, if the other criteria above are met. To clarify, these patients cannot tolerate a cumulative weekly statin dose of seven times the lowest approved tablet size.

The Division's intent in developing such a definition was to encourage consistency among sponsors in exploring the concept of "statin intolerance" in clinical trials. Thus, equally important to the definition itself, the Division recommended trial design elements as well, including a blinded placebo run-in period and a statin rechallenge arm.

The recommendation to include a blinded placebo run-in period was intended to remove participants who experience recurrent symptoms on placebo and thus enrich the trial with those participants who would be more likely to have a true pharmacological intolerance to statins.

Another trial design element that has consistently been recommended is a blinded statin rechallenge arm. After the placebo run-in, the remaining participants should be randomized in a double-blinded manner to placebo (or a marketed non-statin LDL-lowering agent), a reasonably potent statin at low-mid dose (such as atorvastatin 10 or 20 mg), or the investigational product (and the highest to-be-marketed dose should be included). In this type of trial, one would expect that there would be more adverse events and a higher discontinuation rate for the adverse event of interest in the statin arm. It would not be ethical to rechallenge patients with a history of serious reactions such as rhabdomyolysis, but this makes up a small fraction of the purportedly statin intolerant population. Much more common is patients with tolerability issues such as muscle pain without concomitant CK elevations. With appropriate safety monitoring in place, these patients can be re-challenged.

We have seen trial data that included a blinded rechallenge and have discovered that a clinically reasonable definition of statin intolerance does not always ensure the identification of a population that is truly intolerant. Given that statins are the only lipid-lowering drugs with robust cardiovascular outcomes data, one must ensure a rigorous and trial tested definition of statin intolerance when a company is seeking such a claim. Our concern is that without these safeguards, patients with symptoms on statins that are not in fact due to the statin or are not decreased in a clinically meaningful manner could be inappropriately encouraged to switch over to a drug that likely has a much smaller safety database and lacks cardiovascular outcome data.

Another challenge of these types of trials is that it would be difficult to consider a marketing claim based on data demonstrating that a serious adverse event, especially a rare event such as rhabdomyolysis, did not occur during a 12- or 24-week trial testing a novel agent. The trial duration for efficacy depends on the specific pharmacokinetic properties of the investigational product to be tested but 12 weeks is a typical trial length for efficacy. However, the duration for safety and tolerability is longer and may be informed by time-to-event analysis of clinical trial data or other studies that estimate how long it may take for the adverse event of interest to occur.

When studying a statin-intolerant population, we are particularly interested in the incidence rate of and treatment withdrawal from the to-be-studied statin-induced adverse reaction as well as other adverse events that lead to treatment withdrawal. One possibility to consider is if a novel therapy has a lower incidence of discontinuations due to musculoskeletal adverse events than the control statin arm but a higher incidence of discontinuations due to some other adverse event, such that the overall discontinuation rate is similar or perhaps even greater in the novel therapy; this would call into question whether a real improvement in tolerability has been achieved.

Companies have been informed of our concerns regarding trial design issues with statin-intolerant trials and subsequent proposed claims based on the results of these trials. Companies have also been informed that it would be a review issue whether we would include data in the label from a statin-intolerant trial for a novel non-statin investigational product before the cardiovascular outcome trial was completed and provided a robust assessment of the long-term safety and efficacy profile of the investigational product.

One alternative interpretation of approving for a “statin-intolerant” population is to view this as a subset of the larger primary hyperlipidemia population and that such an indication would be restrictive and would limit the labeled use to patients at highest risk for CV events. One possible unintended consequence of including a statin-intolerant indication or claim in the label is that statin-intolerance as a clinical entity will likely be promoted and marketed. There may be widespread public health consequences if patients are encouraged to discontinue statins, which have CV outcome data and robust long-term safety data, and start a PCSK9 inhibitor as monotherapy, which does not have CV outcome data and has limited long-term controlled safety data. However, there are ways to craft an indication that would allow for the on-label use of PCSK9 inhibitor therapy in patients at CV risk who truly cannot tolerate a statin without resorting to a specific statin-intolerant indication.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The eCTD format of the submission was navigable and well organized. The submission quality and integrity was acceptable. The applicant was asked to provide additional information throughout the course of the review and did so in a timely fashion.

3.2 Compliance with Good Clinical Practices

The applicant asserts that the clinical trials were conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312. The applicant states that all clinical trials were conducted with the approval of Ethics Committees or Institutional Review Boards and that all subjects were asked to provide written informed consent before undergoing any study-related procedures. This information was included in each clinical study report located in Module 5 of this submission.

Three trials were selected for site inspection based on trial design and size of enrollment. Trial 20110109 (DESCARTES, n = 905), the only placebo-controlled, 52-week Phase 3 trial, was selected as one of the trials to be investigated. Trial 20110114(MENDEL-2, n=615), a 12-week, monotherapy, placebo- and ezetimibe-controlled phase 3 trial in hypercholesterolemic subjects with a 10-year Framingham Risk Score of ≤ 10%, and trial 20110115 (LAPLACE-2, n=1899), a 12-week combination therapy with atorvastatin, rosuvastatin or simvastatin, placebo- and ezetimibe-controlled phase 3 trial in subjects with primary hypercholesterolemia receiving background statin therapy were the other two trials selected.

The sites below were recommended for inspection primarily based on the number of subjects enrolled, total risk ranking, and efficacy results. In consultation with Dr. Cynthia Kleppinger (OSI, Good Clinical Practice Assessment Branch), the following sites were identified:

Trial 20110109

- Tomas Hala (Pardubice, Czechoslovakia): Site inspection completed: No Action Indicated (NAI)
- Ben Lasko (Toronto, Canada): Site inspection completed: NAI
- Annesofie Krogsaa (Ballerup, Denmark): Site inspection completed: NAI
- Michael Bolognese (Bethesda, MD, US): Site inspection completed: NAI

Trial 20110114

- Michael Bolognese (Bethesda, MD, US) : Site inspection completed: NAI
- Annesofie Krogsaa (Denmark): Site inspection completed: NAI

Trial 20110115

- Annesofie Krogsaa (Denmark): Site inspection pending
- Tomas Hala (Czechoslovakia): Site inspection completed: NAI
- Vivek Awasty (Marion, OH, US) (Listed as two separate sites): Received a 483 notice for minor issues (i.e., 12 of 13 subjects enrolled had only one BP value recorded at screening); Voluntary Action Indicated (VAI) for both sites

An establishment inspection was also conducted at Amgen, Inc. from November 12, 2014 to November 14, 2014, regarding Protocols 20110109, 20110114 and 20110115. From the review of the establishment inspection report and the documents submitted with that report, FDA/ CDR/ Office of Compliance/ Division of Good Clinical Practice Compliance concluded that Amgen adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

3.3 Financial Disclosures

The applicant submitted a completed Form FDA 3454 attesting to the absence of financial interests and arrangements for all investigators that submitted financial information, with the exception of one clinical investigator.

The applicant certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but was unable to do so for thirteen (13) sub-investigators who participated in covered clinical studies for evolocumab.

The covered clinical trials for this submission include the following protocols: 20110168, 20120133, 20101154, 20101155, 20090158, 20090159, 20110114, 20110115, 20110116, 20110117, 20110109, 20110110, 20120138, 20110233, 20110271, 20120348 and 20120356.

Table 2: Financial Disclosures of Covered Clinical Trials

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: _____		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 13		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. The 13 subinvestigators with a certification of due diligence because they either departed the site shortly after study initiation and are no longer affiliated with the facility or the facility has been closed do not raise questions about the integrity of the data. No investigators were also sponsor employees. Only one Primary Investigator had any financial interests or arrangements to disclose.

One clinical investigator (b) (6) had a significant equity interest, as defined in 21 CFR 54.2(b), which consisted of approximately 2000 shares purchased decades ago. Dr. (b) (6) enrolled a total of (b) (6) subjects: (b) (6) .

The applicant has employed the following steps to minimize bias of the clinical study results by any of the disclosed arrangements or interests:

- Use of multiple clinical sites
- Clinical site monitoring
- Clinical site audits
- Independent and centralized assessment of efficacy response data

The efficacy and safety studies used multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurements of endpoints by someone other than the investigator to minimize bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) directed against human PCSK9. Evolocumab has an approximate molecular weight (MW) of 144 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Evolucumab is a sterile, preservative-free, clear to opalescent; colorless to yellowish solution. For the to-be-marketed product, each 1 mL Single-Use PFS and Single-Use Prefilled Autoinjector for injection (for subcutaneous use) contains 140 mg evolocumab, 220 mM proline, 20 mM acetate, 0.01% polysorbate 80, Water for Injection and sodium hydroxide to a pH of 5.0.

Refer to the review by the Product Quality team (Drug Substance by Dr. Bazarragchaa Damdinsuren and Drug Product by Dr. Sang Bong Lee) for details on the CMC data. The conclusions from this review are that the data support the conclusion that the manufacture of Repatha™ (evolocumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Repatha™ (evolocumab) be approved for human use (under conditions specified in the package insert). Five post-marketing commitments were recommended and conveyed to the applicant and are listed in Section 1.4.

4.2 Clinical Microbiology

The microbiology product quality review contains an assessment of evolocumab bulk drug substance section of the BLA 3.2.S. from a microbiological quality perspective. The drug substance section of this application, as amended, is recommended for approval from a microbiology product quality perspective.

4.3 Preclinical Pharmacology/Toxicology

See Dr. Elmore's briefing document for an in-depth review of non-clinical data. The Pharmacology/Toxicology team recommends that evolocumab be approved for the treatment of hyperlipidemia/mixed dyslipidemia and homozygous familial hypercholesterolemia. Labeling changes were included in Dr Elmore's review.

Excerpts from Dr. Elmore's review:
"The Applicant identified the hamster and monkey as pharmacologically relevant species for toxicology testing with evolocumab; both species express PCSK9, to which evolocumab binds with high affinity. Evolocumab was subcutaneously administered to monkeys in a 6 month chronic toxicity study with once-weekly dosing. The tumorigenic potential of evolocumab was assessed in a lifetime hamster carcinogenicity assay with dosing once every other week. Fertility and early embryonic assessments were conducted in hamsters with dosing once every other week. Fertility assessments were also included in the 6 month monkey toxicity study. Evaluation of evolocumab administration during the periods of embryofetal and pre/postnatal development was conducted in monkeys with dosing once every other week. Overall, the toxicology program was appropriately designed to evaluate the clinical risks associated with chronic clinical administration of evolocumab per Agency guidance.

General toxicity:
Evolocumab was well tolerated by hamsters in a 3 month toxicology study with onceweekly subcutaneous dosing at up to 112-, 48- and 20-fold compared to the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W, respectively. Evolocumab was also well tolerated in monkeys in toxicology studies of up to 6 months duration with once weekly subcutaneous doses that provide exposure multiples up to 744-, 300- and 134-fold compared to the recommended human doses of 140 mg Q2W and 420 mg Q2W, respectively. The evolocumab injection site was identified as a potential target tissue (minimal to slight acute-chronic inflammation and slight fibrosis) in monkeys; the findings were low in incidence and of modest severity, which indicates that the toxicological significance of these lesions is limited. Local injection site reactions with administration of a human IgG in non-human primates are not unexpected, and are not necessarily predictive of a similar reaction in humans.

Combination with statins:
Evolocumab was coadministered to monkeys by the subcutaneous route once every other week for 3 months at up to 50-, 10- and 8.8-fold the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W, respectively, with once daily oral rosuvastatin at 2-fold the maximum recommended human dose of 40 mg/day, based on plasma exposure. No additive or synergistic toxicity was observed; rosuvastatin was not administered at a dose that caused any statin-related toxicity in monkeys.

Mutagenicity/carcinogenicity:

Evolocumab is not expected to interact directly with DNA and mutagenicity studies were not conducted, per ICH-S6. Evolocumab did not cause any drug-related tumors when administered to hamsters for up to 2 years in a lifetime carcinogenicity assay at doses administered once every other week that provide a 38-, 15- and 6.6-fold safety margin for evolocumab at the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W administered subcutaneously.

Reproductive toxicology:
Effects of evolocumab on fertility and mating were assessed in hamsters. No effects of evolocumab (subcutaneous dosing once every two weeks) on mating, fertility, estrous cycling, or male reproduction were observed at exposure multiples up to 30-, 12- and 5.3-fold the plasma exposures measured in humans at the 140 mg Q2W, 420 mg QM and 420 mg Q2W evolocumab doses. Effects on fertility were also assessed in the 6 month chronic monkey toxicity study at exposure multiples of up to 744-, 300- and 134-fold compared to the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W, respectively. No effects on fertility endpoints were observed.

Evolocumab was tested in pregnant monkeys during the period of embryofetal development to parturition with subcutaneous administration once every two weeks at doses that provide exposure multiples of 30-, 12- and 5.2-fold the recommended human doses of 140 mg Q2W, 420 mg QW and 420 mg Q2W. Offspring were followed to 6 months of infancy. No evaluation of the infant immune system was conducted. No clearly drug-related toxicity was observed in maternal or infant monkeys.

Summary:
Overall, evolocumab was well tolerated in hamsters and monkeys. The injection site was identified as a potential concern in monkeys, although local immune reactions to a human IgG2 monoclonal antibody in non-human primates are not necessarily indicative of a similar effect in humans."

4.4 Clinical Pharmacology

See the clinical pharmacology briefing document by Drs. Sista, Earp, Mehrotra and Vaidyanathan for an in-depth review of the clinical pharmacology data.

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 08/27/14 under BLA 125522 and recommend approval with the following comments.

- Primary Hyperlipidemia and Mixed Dyslipidemia: The sponsor's proposed dosing of either 140 mg every two weeks or 420 mg once monthly is acceptable.
- Homozygous Familial Hypercholesterolemia: The sponsor has proposed two regimens - 420 mg once monthly or 420 mg every two weeks. The 420 mg every two weeks dose appeared to offer little additional benefit (~6% additional reduction in LDL-C). Based on the exposure-response relationship in the

Heterozygous familial Hypercholesterolemia population, the exposures from the once monthly dose are already in the plateau of the response curve and dosing higher amounts will not likely provide additional benefit. Further, from a safety perspective, there may be an insufficient amount of data in patients who received 420 mg every two weeks.

4.4.1 Mechanism of Action

Evolocumab is a human monoclonal IgG2 directed against human PCSK9. Evolocumab binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein (LDL) receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-C.

4.4.2 Pharmacodynamics

Key pharmacodynamic properties of evolocumab are summarized below:

Primary Hyperlipidemia:

- LDL-C reduction of approximately 55% to 75% achieved as early as 1 week
- Maximal response generally achieved within 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly, respectively, and maintained during long-term therapy.

Homozygous Familial Hypercholesterolemia

- In patients with HoFH not on apheresis evolocumab, compared to placebo, evolocumab 420 mg QM significantly reduced LDL-C from baseline to Week 12 by 31%. The mean change from baseline to Week 12 within the evolocumab arm alone was -23% and within the placebo arm alone was +8%.
- Patients with HoFH who were being treated with apheresis had a reduced response to evolocumab (-20%) compared to the non-apheresis participants (-25%) at Week 24.
- Increasing the frequency of dosing from 420 mg QM to 420 mg Q2W in patients with HoFH resulted in approximately 6% greater reduction of LDL-C.

4.4.3 Pharmacokinetics

Key pharmacokinetic properties of evolocumab are summarized below:

Absorption

- Non-linear pharmacokinetics up to 140 mg, and linear pharmacokinetics between 140 mg and 420 mg

- Median single-dose Tmax: 3 – 4 days
- Estimated absolute bioavailability: 72%

Distribution

- Mean (SD) steady-state volume of distribution estimated to be 3.3 ±0.5 L, following a single 420 mg intravenous dose, suggesting evolocumab has limited tissue distribution.

Metabolism and Elimination

- Mean systemic clearance estimated to be 12 ± 2 mL/hr
- Accumulation: 2-3 fold following 140 mg dosed every 2 weeks or 420 mg dosed monthly
- Steady state by 12 weeks of dosing
- Estimated effective half-life: 11 to 17 days
- Evolocumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Intrinsic and Extrinsic Factors

- Statins increase clearance of evolocumab by approximately 20%.
- No dose adjustments based on age, race, and gender.
- Body weight influenced the pharmacokinetics of evolocumab without having any notable effect on LDL-C lowering.
- Less than 1% of evolocumab-treated subjects in the safety and efficacy studies were positive for the development of binding antibodies. Neutralizing antibodies have not been detected in any subject.

5 Sources of Clinical Data

Five short-term and one long-term Phase 2 trials and four short-term and two long-term Phase 3 trials support the indication in primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. The three long-term trials consist of one Phase 3 blinded, placebo-controlled trial of 52 weeks duration and 2 open-label extension trials. In addition, there were 2 trials (20120356 and 20120348) of 12 weeks and 8 weeks duration, respectively, to assess the user's ability to self-administer the product.

Two phase 2/3 studies conducted at durations of 12 weeks to ≥ 84 weeks support the indication in HoFH.

5.1 Tables of Studies/Clinical Trials

Table 3: Phase 2 and 3 Safety and Efficacy Clinical Trials for Evolocumab

Trial Name	Study Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	# Enrolled/ # Analyzed
PHASE 2: Primary Hyperlipidemia and Mixed Dyslipidemia						
20101154	Hypercholesterolemia LDL-C ≥ 100 and < 190 mg/dL, NCEP ATP III Framingham risk score of ≤ 10%, No lipid-lowering agents up to 3 months prior, Age 18 to 75 years	Phase 2, randomized, PBO and Eze controlled, dose-ranging, monotherapy	PBO SC Q2W or QM EvoMab 70, 105, or 140 mg SC Q2W; 280, 350, or 420 mg SC QM via vial and syringe Eze 10 mg PO QD; randomized with equal allocation into 1 of 9 trt groups	12 or 14 weeks	Primary efficacy endpoint: percent change from baseline in LDL-C at week 12.	411/406
20101155	Hypercholesterolemia LDL-C ≥ 85 mg/dL, Stable dose of statin with/without Eze, Age 18 to 80 years	Phase 2, double-blind, randomized, PBO-controlled, dose-ranging, combination therapy	PBO SC Q2W or QM EvoMab 70, 105, or 140 mg SC Q2W; 280, 350, or 420 mg SC QM Via vial/syringe; Randomized equally into 8 trt groups, EvoMab or placebo	12 or 14 weeks	Primary efficacy endpoint: percent change from baseline in LDL-C at week 12	631/629
20090158	HeFH , LDL-C ≥ 100 mg/dL, On stable dose of a statin with/without Eze for at least 4 weeks prior, Age 18 to 75 years	Phase 2, double-blind, randomized, PBO-controlled, combination therapy	PBO SC QM or EvoMab 350 or 420 mg SC QM Via vial and syringe Randomized equally into 3 trt groups, EvoMab or placebo	12 weeks	Primary efficacy endpoint: percent change from baseline in LDL-C at week 12	168/167
20090159	Hypercholesterolemia and documented statin intolerance LDL-C ≥ 100 mg/dL with diagnosed CHD or CHD risk equivalent , LDL-C ≥ 130 mg/dL without diagnosed CHD or risk equivalent and 2 or more risk factors, LDL-C ≥ 160 mg/dL without diagnosed CHD or risk equivalent and with 1 or no risk factors, Age 18 to 75 years	Phase 2, randomized, parallel group, double-blind, PBO and Eze-controlled, dose-ranging	EvoMab 280, 350, or 420 mg SC QM Eze 10 mg PO QD + EvoMab 420 mg SC QM Eze 10 mg PO QD + PBO SC QM Via vial and syringe Randomized equally into 5 trt groups, EvoMab or placebo	12 weeks	Primary efficacy endpoint: percent change from baseline in LDL-C at week 12	160/157
20110231	Japanese subjects with high risk for	Phase 2, double-blind, randomized,	PBO SC Q2W or QM EvoMab 70 or	12 or 14 weeks	Primary efficacy endpoint: percent	310/307

Trial Name	Study Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	# Enrolled/ # Analyzed
	CV events LDL-C ≥ 115 mg/dL Age 20 to 80 years	PBO- controlled, combination therapy	140 mg Q2W SC; 280 or 420 mg SC QM Via vial and syringe Randomized equally into 6 trt groups, EvoMab or placebo		change from baseline in LDL-C at week 12	
20110110	Completion of a qualifying EvoMab protocol without treatment related SAE that led to IP discontinuation	Phase 2 long-term Extension Year 1 controlled (vs SoC) Year 2+ open-label EvoMab[a]	**Year 1:** EvoMab 420 mg SC QM + SoC or SoC alone **Years 2 to 5:** EvoMab 420 mg SC QM + SoC Via vial and syringe or AI/pen Allocation 2:1 EvoMab: SoC	~ 5 years Ongoing; Interim submitted	subject incidence of adverse events	1324/1324
PHASE 3						
20110114	NCEP ATP III Framingham risk score of ≤ 10% LDL-C ≥ 100 and < 190 mg/dL No lipid-lowering agents 3 months prior Age 18 to 80 years	Phase 3, double-blind, randomized, parallel group, PBO and Eze-controlled, monotherapy	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via AI/pen Eze 10 mg PO QD; Allocation ratio of 2:2:1:1:1:1 into 6 treatment groups	12 or 14 weeks	Co-primary endpoints: • % change from BL in LDL-C at week 12 • mean % change from BL in LDL-C at weeks 10 and 12	615/614
20110115	primary hyper-cholesterolemia and mixed dyslipidemia, LDL-C ≥ 80 mg/dL if already on an intensive statin, LDL-C ≥ 100 mg/dL if on a non-intensive statin, LDL-C ≥ 150 mg/dL if not on a statin. No previous intolerance to rosuvastatin, atorvastatin, or simvastatin Age 18 to 80 years	Phase 3, double-blind, randomized, PBO and Eze-controlled, combination therapy	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via AI/pen Eze 10 mg PO QD Allocation 2:1 EvoMab:PBO	12 or 14 weeks	Co-primary endpoints: • % change from BL in LDL-C at week 12 • mean % change from BL in LDL-C at weeks 10 and 12	1899/1896[b]
20110116	Hyper-cholesterolemia and documented statin intolerance, LDL-C ≥ 100 mg/dL with CHD or CHD risk	Phase 3, double-blind, randomized, Eze-controlled	PBO SC Q2W or QM; EvoMab 140 mg SC Q2W or 420 mg SC QM Via AI/ pen Eze 10 mg PO QD Allocation 2:2:1:1	12 or 14 weeks	Co-primary endpoints: • % change from BL in LDL-C at week 12 • mean % change from BL in LDL-	307/307

Trial Name	Study Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	# Enrolled/ # Analyzed
	equivalent, LDL-C ≥ 130 mg/dL without diagnosed CHD or risk equivalent and ≥2 risk factors LDL-C ≥ 160 mg/dL without diagnosed CHD or risk equivalent and with 1 risk factor, LDL-C ≥ 190 mg/dL without diagnosed CHD or risk equivalent and with no risk factors Age 18 to 80 years		2:2:1:1 to EvoMab 140mg Q2W: EvoMab 420mg QM: eze 10mg: eze 10mg		C at weeks 10 and 12	
20110117	Subjects with HeFH LDL-C ≥ 100 mg/dL Age 18 to 80 years On stable dose of a statin with or without eze for 4 weeks	Phase 3, double-blind, randomized, PBO- controlled, combination therapy	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via AI/pen Allocation 2:1 EvoMab:PBO	12 or 14 weeks	Co-primary endpoints: • % change from BL in LDL-C at week 12 • mean % change from BL in LDL-C at weeks 10 and 12	331/329
20120356	Hypercholesterolemia or mixed dyslipidemia LDL-C ≥ 85 mg/dL Age 18 to 80 years	Phase 3, randomized, combination therapy, clinical home use	EvoMab 420 mg SC QM Via AMD or AI/pen Allocation 1:1 AMD:AI/pen	12 weeks	User ability to self-administer EvoMab	164/164
20120348	Subjects with primary hypercholesterolemia or mixed dyslipidemia LDL-C ≥ 85 mg/dL Age 18 to 80 years	Phase 3, randomized, combination therapy, clinical home use	EvoMab 140 mg SC Q2W Via PFS or AI/pen Allocation 1:1 PFS:AI/pen	8 weeks	User ability to self-administer EvoMab	149/149
20110109	Hypercholesterolemia, LDL-C ≥ 75 mg/dL at screening and then placed on background therapy based on NCEP ATP III risk Age 18 to 75 years	**Initiated as a phase 2 trial and was later reclassified by Amgen as a phase 3 trial while it was underway. Phase 2 drug product and method of drug administration was used. Double-blind,randomized PBO- controlled, long-term**	**PBO or EvoMab 420 mg SC QM Via vial and syringe (total volume per administration drawn from 6 sterile vials with a formulation of 70 mg/mL [not the to-be marketed device or formulation (140 mg/ml)]** Allocation 2:1 EvoMab:PBO	52 weeks	percent change from baseline in LDL-C at week 52	905/901
20120138	Completion of a	Phase 3, long-term	Year 1: EvoMab	~2 years	subject incidence	3121/2928[c]

Trial Name	Study Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	# Enrolled/ # Analyzed
	qualifying EvoMab protocol without discontinuation of IP for any reason	extension. Year 1 controlled (vs SoC) Year 2+ open-label EvoMab[a]	140 mg SC Q2W or 420 mg SC QM + SoC or SoC alone Year 2: EvoMab 140 mg SC Q2W or 420 mg SC QM + SoC Via AI/pen Allocation 2:1 EvoMab:SoC	Ongoing, interim submitted	of adverse events	
PHASE 2: HoFH						
20110233	HoFH , On a stable low-fat diet and pre-existing, lipid-lowering therapies at least 4 weeks prior with LDL-C ≥ 130 mg/dL Age 12 to 80 years	**Part A**: phase 2, open-label, single-arm, pilot **Part B**: phase 3, double-blind, randomized, PBO- controlled	**Part A:** EvoMab 420 mg SC QM **Part B:** PBO or EvoMab 420 mg SC QM Via vial and syringe or AI/pen Allocation 2:1 EvoMab:PBO	**Part A**: 12 weeks **Part B**: 12 weeks	percent change from baseline in LDL-C at week 12.	**Part A**: 8/8 **Part B:** 50/49
PHASE 2/3: HoFH and "Severe" HeFH[d]						
20110271	Completion of a qualifying EvoMab protocol without treatment related SAE that led to IP discontinuation and have a diagnosis of "severe" FH[d] If de-novo subject then must have "severe" FH and be on background lipid-lowering therapy for ≥ 4 weeks prior LDL-C ≥ 100 mg/dL (with CHD or CHD risk equivalent) or ≥ 130 mg/dL (no CHD or CHD risk equivalent) Age 12 to 80 years	Phase 2/3, open-label, long-term	EvoMab 420 mg SC QM or SC Q2W (if eligible) Via vial and syringe, AI/pen, or AMD; All on EvoMab	~ 5 years Ongoing; Interim submitted	subject incidence of treatment emergent adverse events	238/198 (of the 198 subjects, 96 were HoFH) Adolescent subgroup (N = 13): 10 non-apheresis and 3 apheresis subjects

[a] Year 1 of the study was standard of care (SoC)-controlled. The remainder of the study is open-label with all subjects receiving evolocumab. Interim data for these studies are included in the submission.
[b] Numbers reflect randomization to investigational product.
[c] Subject counts for Study 20120138 only include subjects from parent studies included in the integrated parent analysis set.

[d] "severe" FH: Amgen's definition: diagnosis of familial hypercholesterolemia and taking pre-existing lipid-lowering therapies. Non-apheresis subjects were required to have elevated LDL-C (≥ 100 mg/dL for subjects with diagnosed coronary heart disease or risk equivalent, and ≥ 130 mg/dL for subjects without diagnosed coronary heart disease or risk equivalent). There was No LDL-C entry requirement for apheresis subjects. (b) (4)

AI/pen = autoinjector/pen; AMD = auto mini-doser; PFS = prefilled syringe

It is important to note that trial 20110109 was initiated as a phase 2 trial and was later reclassified by Amgen as a phase 3 trial. This trial is the only trial with data available to date that is double-blind, randomized, placebo- controlled, and long-term (52 weeks). It is a concern that this trial used a vial and syringe, which is not the to-be-marketed device, and used a formulation of 70 mg/mL (total volume per administration drawn from 6 sterile vials with a formulation of 70 mg/mL) which is not the to-be marketed concentration (140 mg/mL) or formulation. These two formulations are described below:

1. Process 1: 70 mg/mL (b) (6)
2. Process 2 (to-be-marketed formulation): 140 mg/mL in 220 mM proline, 20 mM acetate, 0.01% polysorbate 80, pH 5.0.

The following table summarizes the device and formulation used in studies from Phase 1 through Phase 3. The shaded columns represent the to-be-marketed devices and formulations.

Table 4: Device and Formulation Used: Phase 1 through Phase 3

Phase	Protocol	Type of Study	Brief Descriptor	70 mg/mL Vial	140 mg/mL PFS	140 mg/mL AI/Pen	120 mg/mL AMD
1	20080397	Clinical pharmacology	Healthy subject PK/PD & initial tolerability	X			
1	20080398	Clinical pharmacology	Patient PK/PD & initial tolerability	X			
1	20110121	Clinical pharmacology	Healthy subject PK/PD & initial tolerability	X			
1	20110168	Clinical pharmacology	Healthy subject PK AI/Pen to AMD			X	X
1	20120133	Clinical pharmacology	Healthy subject PK AI/Pen to PFS		X	X	
1	20120136	Clinical pharmacology	Healthy subject PK/PD & initial tolerability	X			
1	20120341	Clinical pharmacology	Intrinsic factors			X	
2	20090158	LDL-C lowering	HeFH	X			
2	20090159	LDL-C lowering	Statin intolerant	X			
2	20101154	LDL-C lowering	Monotherapy	X			
2	20101155	LDL-C lowering	Combination therapy	X			
2	20110110	LDL-C lowering	Long-term efficacy and safety (OLE)	X		X	
2	20110231	LDL-C lowering	Japanese population	X			
2/3	20110233	LDL-C lowering	HoFH	X		X	
2/3	20110271	LDL-C lowering	Severe familial hypercholesterolemia	X		X	
3	20110109	LDL-C lowering	Long-term efficacy and safety	X			
3	20110114	LDL-C lowering	Monotherapy			X	
3	20110115	LDL-C lowering	Combination therapy			X	
3	20110116	LDL-C lowering	Statin intolerant			X	
3	20110117	LDL-C lowering	HeFH			X	
3	20120138	LDL-C lowering	Long-term efficacy and safety (OLE)			X	X
3	20120348	Device home use	PFS vs. AI/Pen			X	
3	20120356	Device home use	AMD vs. AI/Pen			X	X

PFS = prefilled syringe; AI/pen = autoinjector/pen; AMD = automated mini-doser; PK/PD = pharmacokinetics/pharmacodynamics; HeFH = heterozygous familial hypercholesterolemia; OLE = open-label extension; HoFH = homozygous familial hypercholesterolemia.

For Process 1, the mean and median exposures for evolocumab (all doses) were 5.5 months and 2.8 months, respectively. For Process 2, the mean and median exposures were 2.6 months and 2.8 months, respectively. A summary of the overall exposure to Process 1 vs Process 2 of evolocumab is presented below:

Table 5: Evolocumab Process 1 and Process 2 Overall Summary of Exposure (Integrated Parent, Extension SoC-Controlled Period, and Extension All-IP Period Analysis Sets)

	Any EvoMab Process 1	Any EvoMab Process 2
Total Number of Participants	2104	4065
Number of Participants		
≥ 3 months	2087	3246
≥ 6 months	1766	2014
≥ 12 months	1681	815
≥ 18 months	807	0
≥ 24 months	620	0

≥ 30 months	427	0
≥ 36 months	2	0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110110, 20110114, 20110115, 20110116, 20110117, 20110231, 20120138, 20120348, 20120356.
Patients can contribute data to more than one process. Time is based on device exposure. EvoMab = Evolocumab; patient years: where years are calculated as the sum of period process durations determined by the device exposure across subjects divided by 365.25. Months are calculated by multiplying the patient years by 12 and rounding to the nearest whole month.
Source: 120-day-appendix 05: Table 14-5.1.501

5.2 Review Strategy

I conducted a review of the efficacy and safety of evolocumab. The primary focus of this review is the Phase 3 trials (20110114, 20110115, 20110116 and 20110117), the 52-week trial 20110109, and the trials (20110233 and 20110271) that enrolled participants with HoFH. The 52-week trial 20110109 and trial 20110116 (statin intolerance) are discussed in greater detail in Section 5. The efficacy of the 4 phase 3 trials and the 52-week trial (20110109) that evaluated a primary hyperlipidemia population, as well as the two trials in the HoFH population, are discussed in Section 6. The safety review of the integrated phase 2 and phase 3 trials in the primary hyperlipidemia population, as well as the two trials in the HoFH population, are discussed in Section 7.

Dr. Shuxian Sinks, Office of Biometrics, conducted an independent review of the efficacy of evolocumab. Please refer to her review for the FDA's statistical analysis of efficacy. Dr. Sinks concludes that in all of the 6 reviewed phase 3 pivotal studies, both every 2 week (QM) and monthly (QM) administered evolocumab had large treatment effects in reducing LDL-C compared to control (ezetimibe or placebo). The reductions in LDL-C from baseline (the primary endpoint) were statistically significant at the prespecified alpha level in all studies. Estimated reductions on evolocumab were 37% to 47% greater compared to ezetimibe and 55% to 76% greater compared to placebo in studies in primary hyperlipidemia or mixed dyslipidemia, and 31% greater compared to placebo in the study in HoFH. The findings were consistent across different populations and background therapies. Dr. Sinks notes that the applicant's primary analysis relies on likely implausible assumptions about the missing data. FDA carried out additional analyses to more appropriately estimate the treatment effects on LDL-C. Treatment effect estimates were attenuated by around 1%–3% in FDA's analyses.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 20110109: DESCARTES

Study Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Long-term Tolerability and Durable Efficacy of AMG 145 on LDL-C in Hyperlipidemic Subjects (Trial 20110109; also referred to as DESCARTES)

Investigators: The coordinating investigator was Dr. Dirk Blom, Division of Lipidology, Department of Medicine, University of Cape Town, South Africa.

Study center(s): 88 study centers in the USA, Canada, South Africa, Czech Republic, Denmark, Hungary, Belgium, Australia, and Austria.

Study period: 05 January 2012 (first subject enrolled) to 07 November 2013 (last subject completed)

Phase of Development: 3

Publications Based on the Study: Blom DJ, Hala T, Bolognese M, et al. A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia. N Engl J Med 2014; 370:1809-1819.

Primary Objectives: Evaluate the effect of 52 weeks of subcutaneous (SC) evolocumab once monthly (QM), compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) when added to background lipid-lowering therapy.

Secondary Objectives:

- to evaluate the safety and tolerability of SC evolocumab, given for 52 weeks, compared with placebo, in subjects with hyperlipidemia on background lipid-lowering therapy
- to assess the effects of 52 weeks of SC evolocumab, compared with placebo, on change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, lipoprotein (a) [Lp(a)], triglycerides, total cholesterol, very low-density lipoprotein cholesterol (VLDL-C) and HDL-C in subjects with hyperlipidemia on background lipid-lowering therapy
- to evaluate the consistency of the long-term treatment effect of SC evolocumab, compared with placebo, in subjects with hyperlipidemia on background lipid-lowering therapy

Design: Multicenter, double-blind, double-dummy, randomized, placebo-controlled study designed to evaluate the effect of 52 weeks of subcutaneous (SC) evolocumab once monthly (QM), compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) when added to background lipid-lowering therapy. Eligible participants with screening central laboratory LDL-C values ≥ 75 mg/dL were instructed to follow National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP) Therapeutic Lifestyle Changes (TLC) diet and were assigned to 1 of the following 4 background lipid-lowering therapies for a 4-week stabilization

period based upon their screening LDL-C, NCEP ATP III risk category, and statin therapy:

1. No drug therapy required - diet alone
2. Low dose drug therapy required - diet plus atorvastatin 10 mg orally (PO) once daily (QD)
3. High dose drug therapy required - diet plus atorvastatin 80 mg PO QD
4. Maximal drug therapy required - diet plus atorvastatin 80 mg PO QD plus ezetimibe 10 mg PO QD

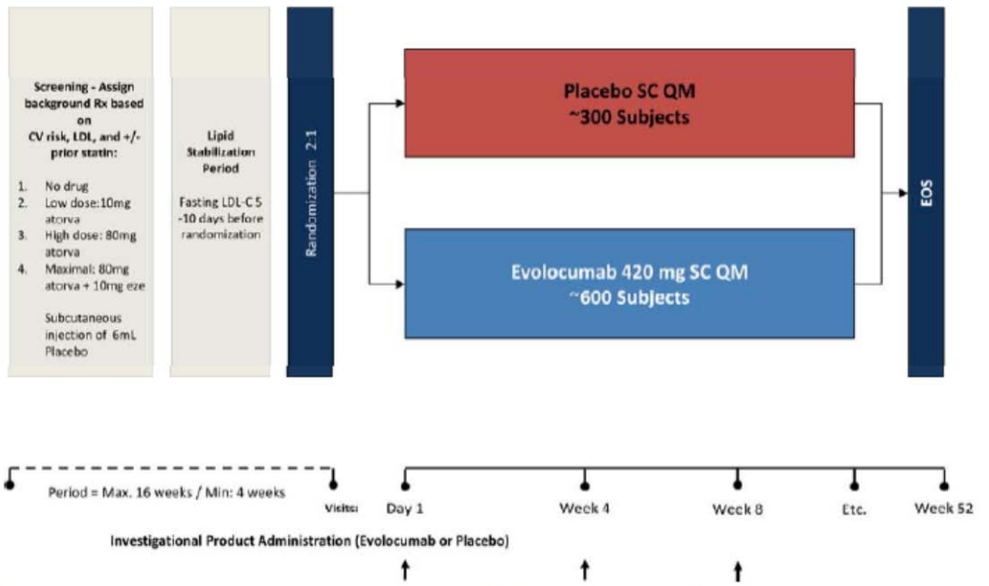
At the end of the 4-week stabilization period, participants who still exceeded the goal LDL-C value for their NCEP risk category (ie, ≥ 75 mg/dL and <100 mg/dL for those with coronary heart disease (CHD) or CHD risk equivalents, or ≥ 75 mg/dL and <130 mg/dL for those without CHD or CHD risk equivalents) underwent background therapy up-titration to the next therapy level and entered an additional 4-week stabilization period after which study eligibility based on LDL-C was reassessed. A maximum of 2 up-titrations were permitted. Participants with an initial LDL-C < 75 mg/dL were considered screen failures.

Participants on maximal drug therapy (ie, diet plus atorvastatin 80 mg PO QD plus ezetimibe 10 mg PO QD) were eligible if their LDL-C was ≥ 75 mg/dL at the end of the 4 week stabilization period. Participants on maximal background therapy whose LDL-C was < 75 mg/dL at the end of the 4-week stabilization period were allowed to down-titrate to diet plus atorvastatin 80 mg PO QD and enter an additional 4-week lipid stabilization period, after which study eligibility based on a final LDL-C blood draw was reassessed.

Once eligibility was confirmed, participants were randomized 2:1 to receive evolocumab 420 mg SC QM or placebo SC QM. Randomization was stratified by the protocol-determined background therapy. In addition to the randomized treatment groups, central laboratory results of the lipid panel, ApoA1, ApoB, high sensitivity C-reactive protein (hsCRP), and lipoprotein (a) Lp(a) were not provided to investigators, participants, and the study team after the lipid stabilization period until unblinding of the clinical database after end-of-study (EOS). Analyses of steroid hormone analytes (adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], cortisol, testosterone, and estradiol) and vitamin E testing were performed on all participants. Additionally, approximately 100 participants were enrolled in a vitamin E substudy where additional blood samples were collected at the day 1, week 12 and week 52 visits for a vitamin E analysis.

The EOS visit and the last estimation of lipids occurred at week 52, with the last dose of investigational product (IP) administration at week 48 for all participants.

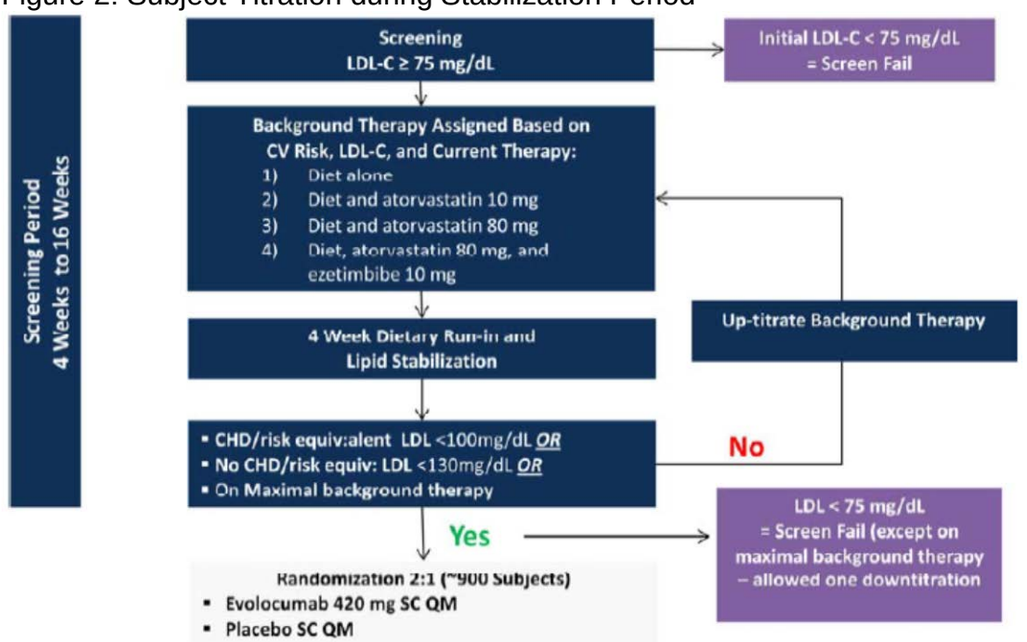
Figure 1: Study Design



CHD = coronary heart disease; CV = cardiovascular; EOS = end of study; LDL-C = low-density lipoprotein cholesterol; QM = once monthly; SC = subcutaneous

Source: Applicant's Figure 8-1 (CSR-20110109 Module 5.3.5.1)

Figure 2: Subject Titration during Stabilization Period



CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; QM = once monthly; SC = subcutaneous

Source: Applicant's Figure 8-1 (CSR-20110109 Module 5.3.5.1)

Patient Population: Approximately 900 subjects (600 evolocumab: 300 placebo)
Males and females, ≥ 18 to ≤ 75 years of age with fasting LDL-C ≥ 75 mg/dL at screening and fasting triglycerides ≤ 400 mg/dL at screening and end of lipid stabilization period were eligible. LDL-C values at end of lipid stabilization period had to be ≥ 75 mg/dL and <100 mg/dL for those with CHD or CHD risk equivalents, or ≥ 75 mg/dL and <130 mg/dL for those without CHD or CHD risk equivalents, or ≥ 75 mg/dL in those on maximal background therapy to be eligible for randomization, in alignment with NCEP ATP III risk categories.

Major exclusion criteria included, but were not limited to:

- diagnosed with coronary heart disease (CHD) or CHD risk equivalent and not receiving statin therapy with LDL-C at screening ≤ 99 mg/dL
- heart failure of New York Heart Association (NYHA) class II, III or IV, or last known left ventricular ejection fraction < 30%
- cardiac arrhythmia within 3 months prior to randomization that was not controlled by medication
- myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization
- planned cardiac surgery or revascularization
- type 1 diabetes; or newly diagnosed type 2 diabetes (within 6 months of randomization or new screening fasting plasma glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%) or poorly controlled type 2 diabetes (HbA1c > 8.5%)
- Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg, confirmed with repeat measurement
- Use in the last 6 weeks prior to LDL-C screening red yeast rice, > 200 mg/day niacin, or >1000 mg/day omega-3 fatty acids (eg, DHA and EPA) or prescription lipid-regulating drugs other than statins or ezetimibe, such as fibrates and derivatives, or bile-acid sequestering resins
- Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids (eg IV, intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane); (Note: vitamin A in a multivitamin preparation is permitted)
- Hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone TSH below the lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, at screening
- Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2 at screening, confirmed by a repeat measurement at least 1 week apart
- Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the ULN as

determined by central laboratory analysis at screening or at end of lipid stabilization period, confirmed by a repeat measurement at least 1 week apart
- CK > 3 times the ULN at screening or at end of lipid stabilization period, confirmed by a repeat measurement at least 1 week apart
- Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator
- Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to randomization
- Current therapeutic anticoagulation with vitamin K antagonist (eg, warfarin), heparin, low-molecular weight heparin, direct thrombin inhibitor, or Factor Xa inhibitor. (Note: anti-platelet agents [eg, aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole] are permitted).
- Female subject who is pregnant, breastfeeding or not willing to use at least 1 highly effective method of birth control during treatment and for an additional 15 weeks after the end of treatment unless subject is sterilized or postmenopausal
- History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma)

Investigational Product: Process 1 formulation via vial and syringe: 70 mg/mL evolocumab (b) (6) . Each vial was for single use only. Subjects received 420 mg evolocumab SC QM. Each 420 mg dose totaled 6 mL at 70 mg/mL and could be split into several injections (eg, 3 x 2 mL injections). All injections were to be completed within 30 minutes.

It is important to note that the drug substance for phase 1 and phase 2 clinical trials was manufactured using a different process (Process 1) than that used in most of the phase 3 trials (Process 2). Process 2 drug substance is the proposed commercial drug substance. Thus, this 52-week trial did not use the to-be-marketed device or formulation.

Treatment Groups:
Placebo and evolocumab were administered as follows:
- placebo QM: no evolocumab, 6 mL placebo
- evolocumab 420 mg QM: 6 mL evolocumab at 70 mg/mL, no placebo

Duration of Treatment: The lipid stabilization period lasted a minimum of 4 weeks and a maximum of 12 weeks (to allow for up to 2 up-titrations of background therapy) followed by 52 weeks of double-blind treatment with investigational product (evolocumab QM or placebo).

Endpoints:

Primary endpoint: percent change from baseline in ultracentrifugation (UC) LDL-C at week 52

Secondary endpoints (hypothesis testing):
Tier 1

- absolute change from baseline in LDL-C at week 52
- LDL-C response (percent of subjects with LDL-C < 70 mg/dL at week 52
- percent change from baseline in LDL-C at week 12
- percent change from baseline in total cholesterol at week 12
- percent change from baseline in total cholesterol at week 52
- percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C) at week 52
- percent change from baseline in apolipoprotein B (ApoB) at week 52
- percent change from baseline in the total cholesterol /high-density lipoprotein cholesterol (HDL-C) ratio at week 52
- percent change from baseline in the ApoB/apolipoprotein A-1 (ApoA1) ratio at week 52

Tier 2

- percent change from baseline in lipoprotein(a) (Lp(a)) at week 52
- percent change from baseline in triglycerides at week 52
- percent change from baseline in HDL-C at week 52
- percent change from baseline in very low-density lipoprotein cholesterol (VLDL-C) at week 52

Secondary endpoint (estimation): percent change from week 12 in LDL-C at week 52

Statistical Analyses:

- Efficacy and safety analyses were performed on the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of IP.
- All primary and secondary endpoint analyses of LDL-C used UC LDL-C. For the exploratory endpoint and longitudinal analyses of LDL-C over time, calculated LDL-C values were used.
- Reflexive testing used for sensitivity analyses was the method for selecting the appropriate LDL-C value to use. In the LDL-C reflexive approach, the calculated LDL-C values are used, unless the value is < 40 mg/dL or triglycerides are > 400 mg/dL, in which case, the calculated LDL-C value was replaced with the UC LDL-C value from the same blood sample, if available.
- The familywise error rate was preserved at 0.05 using a hierarchical testing procedure for the primary and secondary endpoints (tier 1 and tier 2 only).
- Unless specified otherwise, all other hypothesis testing was 2-sided with a significance level of 0.05.
- Deaths, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, cerebrovascular events (transient ischemic attack, stroke), and

noncoronary revascularization stroke were adjudicated by an independent Clinical Events Committee (CEC).

Analyses of Primary Endpoint: percent change in UC LDL-C from baseline at Week 52
A repeated measures linear effects model was used to compare the efficacy of evolocumab with placebo at week 52. The repeated measures linear effects model included terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Missing values were not imputed in the model.

Analyses of Secondary Efficacy Endpoints (Hypothesis Testing)
The secondary efficacy endpoint of LDL-C response at week 52 was analyzed using the Cochran-Mantel Haenszel test adjusted for the stratification factor.

Analyses of Secondary Efficacy Endpoints (Estimation)
The following estimation was performed to evaluate the consistency of the long term treatment effect of evolocumab.

- For consistency of treatment effects (evolocumab vs placebo) of week 12 and week 52, the 95% confidence interval (CI) of the difference of the treatment effect at week 52 and the treatment effect at week 12 were provided from the repeated measures linear effects model. The estimations were made using the FAS and the Effect Durability Analysis Set.
- For change in LDL-C from week 12 to week 52 adjusted for baseline, the treatment effect adjusted by baseline was estimated using an analysis of covariance (ANCOVA) model. The estimation of 95% CI was based on the Effect Durability Analysis Set.[36]

Safety Analyses

- Summary statistics of adverse events, laboratory parameters and background lipid-regulating therapy during the lipid stabilization period were presented.
- Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 16.1).
- Approximately 100 subjects (50 subjects per treatment arm) were selected to participate in the vitamin E substudy. Analytes for the vitamin E substudy (serum vitamin E, LDL-vitamin E, HDL-vitamin E, red blood cell (RBC)-vitamin E, and non-HDL-vitamin E) were summarized (both absolute values and normalized values) for each treatment group using descriptive statistics at each scheduled visit (Day 1, Week 12 and Week 52).
- Measurement of anti-evolocumab antibodies were collected from all subjects who received evolocumab at day 1, week 12, week 24, week 36, and week 52.

36 The effect durability analysis set included subjects in the FAS who adhered to the scheduled IP (ie, the treatment completion box is checked on the eCRF) and have nonmissing UC LDL-C values at baseline, week 12 and week 52.

Samples testing positive for binding antibodies were tested for neutralizing antibodies and could be further characterized for quantity/titer, isotype, affinity and presence of immune complexes.

- Missing data were not imputed for safety endpoints.
- The target IP exposure period in months was defined as follows: IP Exposure Period = [min (end of IP Date + 28 days, EOS Date) - First dose date of IP +1] / 365.25 * 12. The target IP exposure is equal to SC IP exposure.

Protocol Amendments:
The study protocol was amended 4 times during the conduct of the trial. The table below summarizes the changes to the protocol during the study.

Table 6: Summary of Protocol Amendments

Amendment	Major Changes
Original Protocol 09 September 2011 (16 subjects enrolled)	–
Amendment 1 09 February 2012 (351 subjects enrolled under this protocol amendment)	• added a vitamin E substudy • updated the study schema • added additional clarity on the definition of CHD risk equivalents • removed the term “absolute” from all endpoints • added information on drug dispensation and reconciliation • added information on retesting • added a rescreening cap • added steroid testing at day 1 and weeks 12, 24, and 52 • added a process for updating the DMC for consecutive LDL values below 25 mg/dl • better defined end of study (EOS) • updated blood pressure and waist circumference language to add additional clarity • clarified that doses should be split • updated the interim guidelines

Amendment 2 03 May 2012 (534 subjects enrolled under this protocol amendment)	• changed the sample size from 600 to 900 subjects in order to increase long-term safety and tolerability data • updated the evolocumab background section with the most currently available data • added information to the 420 mg dose selection with data from the most recent evolocumab interim analysis • changed "hypercholesterolemia" to "hyperlipidemia" to be consistent with Amgen's phase 3 protocols • updated the statistics section to align the hypothesis-testing secondary endpoints with Amgen's phase 3 protocols, adjusted for multiplicity • added language that allowed Amgen to limit the enrollment of patients in certain NCEP risk categories or background therapy arms in order to prevent overly skewed enrollment in these groups • allowed down titration for subjects randomized to maximal background therapy who overshoot the LDL entry cutoff • updated the vital sign and waist circumference sections to align the language with that used in Amgen's phase 3 protocols • changed the SAE reporting requirements from 1 business day to 24 hours • added additional information on pregnancy and lactation
Amendment 3 09 December 2012 (0 subjects enrolled)	• Amgen reclassified the study from a phase 2 study to a phase 3 study • changed the dosing terminology from Q4W to QM • updated the list of completed and ongoing studies
Amendment 4 21 February 2013 (0 subjects enrolled)	• updated three secondary endpoints • updated the study schema • added an alert threshold for elevated triglycerides • added new Amgen safety template AE & SAE language

AE = adverse event; CHD = coronary heart disease; DMC = data monitoring committee; EOS = end of study; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program; Q4W = every 4 weeks; QM = once monthly; SAE = serious adverse event

Summary of Statistical Amendments
The original SAP (dated 14 June 2012) was amended twice; amendment 1 (dated 02 May 2013) and amendment 2 (dated 08 October 2013) occurred prior to study unblinding.

Table 7: Changes in Statistical Analysis Plan

Amendment	Major Changes
Amendment 1 (version 2) 02 May 2013	• added total cholesterol as a secondary endpoint • upgraded VLDL-C from a tertiary to secondary endpoint • added exploratory endpoints to investigate pharmacokinetics of evolocumab , to estimate cardiovascular event rates in subjects treated with evolocumab and add HbA1c. • **changed text to refer to 20110109 as a phase 3 study** • clarified of study definitions, analysis sets and imputation rules for missing LDL-C data • added details of when UC and when calculated LDL-C will be used for each analysis • added Asian as a category for the baseline covariate of race • added reflexive approach as a sensitivity analysis for the primary endpoint • changed hsCRP summaries to a shift table • updated the AEs section to be in line with the other phase 3's, specifically changing 'treatment related' to be 'treatment emergent' and added 'Events of Interest'
Amendment 2 (version 3) 08 Oct 2013	• updated the ECG definition • added SCORE definition • added triglyceride cut off to the definition of the reflexive method. • added definitions for screening and end of lipid stabilization period (LSP) LDL-C, normalization formula for the vitamin E analytes and details of how to identify subjects receiving hormone replacement therapy (HRT) • defined screening value of LDL-C as the latest LDL-C value prior to entering their first LSP • defined end of lipid stabilization LDL-C value as the post screening values collected closest, but prior to day 1, or prior to or on their last screen failure date. • added normalization formula for vitamin E analytes • changed Kaplan Meier plots to cumulative percentage plots • clarified categories for geographic region • added the baseline covariate of 'glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither type 2 diabetes mellitus nor metabolic syndrome)', in replacement for "type 2 diabetes mellitus (yes, no)" and "metabolic syndrome per modified AHA /NHLBI criterion (yes, no)" • added clarification of the treatment effect of percent change of LDL-C from week 12 at week 52 [i.e. (week 52 – week 12) / baseline] • updated the events of interest [diabetes-related, muscle-related, liver-related, associated with injectable protein therapies (injection site reactions, hypersensitivity or allergic reactions) and potential hepatitis C infections were summarized by category and preferred

	term. • added 'normalized' analysis to the summary of the vitamin E substudy analytes • replaced the 'excluding subjects receiving testosterone sub-analysis with "subjects who also received at least one vitamin E supplement during the study." • added reflexive LDL-C algorithm to the appendix and description of reflexive approach for reflexive LDL-C

In addition to these changes in planned analyses, the following additional changes were made:

- Site (b) (6) was closed following an audit in which GCP violations were identified. An ad hoc sensitivity analysis was carried out excluding the FAS subjects (n = 5) from this site.
- Additional ad hoc analyses of treatment emergent adverse events for 3 subgroups of minimum postbaseline LDL-C concentrations (< 25 mg/dL, < 40 mg/dL, or ≥ 40 mg/dL) were carried out.
- Muscle events were included in the subject incidence of positively adjudicated events.
- The SAP specified that analytes, both original and normalized, for the vitamin E substudy would be summarized for each treatment group using descriptive statistics at each scheduled visit and repeated for those subjects who also received at least one Vitamin E supplement during the study. Additional ad hoc analyses were provided for those subjects in the vitamin E substudy who did not receive a vitamin E supplement.
- Additional ad hoc analyses for the steroid hormone analytes were carried out for FSH by women (FSH < 25 IU/L at baseline and < 50 years of age) and men (LH < 15 IU/L at baseline), LH by women (FSH < 25 IU/L at baseline and < 50 years of age) and men (LH < 15 IU/L at baseline), estradiol for women (FSH < 25 IU/L at baseline and < 50 years of age) only, and testosterone for men only. Analyses were performed in the FAS excluding subjects who received HRT.

Protocol Deviations:
Seventeen (2.8%) participants in the evolocumab group and 14 (4.6%) in the placebo group had at least one important protocol deviation (IPD). None of these participants were excluded from the FAS. The most common IPDs included receiving the wrong IP box (7 [1.2%] evolocumab, 5 [1.7%] placebo), receiving prohibited lipid-regulating medications (4 [0.7%] evolocumab, 4 [1.3%] placebo), and not meeting the LDL-C end of lipid stabilization criteria (4 [0.7%] evolocumab, 3 [1.0%] placebo).

Deviations to eligibility criteria occurred in 16 (1.8%) participants: 10 (1.7%) in the evolocumab arm and 6 (2.0%) in the placebo arm. The most common eligibility deviation was not meeting the LDL-C end of lipid stabilization criteria (6 [1.0%] evolocumab, 4 [1.3%] placebo) and diabetes (2 [0.3%] evolocumab, 2 [0.7%] placebo).

Results:

Patient Demographics
Sex: men (47.7%); women (52.3%)

Age: mean (SD) age of 56.2 (10.6) years; 22.8% of participants were ≥ 65 years old (235 placebo; 461 EvoMab).

Ethnicity: Hispanic/Latino (5.5%)

Race: white (80.4%); black/African American (8.4%); Asian (6.3%); other (4.3%); American Indian or Alaska native (0.2%); mixed race (0.2%); native Hawaiian or other Pacific Islander (0.1%)

Country: North America (57.8%), Europe (26.9%) and Asia Pacific (15.3% of participants)

When the demographics are examined by the 4 different background therapies, there were more women than men enrolled in the diet alone and diet plus atorvastatin 10 mg group (W: 55.0% and 56.1 % vs M: 45.0% and 43.9%, respectively); whereas more men than women were enrolled in the diet plus atorvastatin 80 mg plus ezetimibe 10 mg group (54.5% vs 45.5%, respectively). The diet alone group had the highest percentage of Hispanic/Latino subjects (12.6%) as well as the highest percentage of subjects who were either Asian (14.4%) or black/African American (16.2%) (see table below).

As participants were assigned to 1 of 4 background therapies based on NCEP risk categories (criteria summarized in Section 9.8 NCEP ATP III Risk Categories), and screening LDL-C, there were expected differences in baseline coronary heart disease demographics among the protocol-determined background therapy groups (see table below). Sixty-four percent of participants who required diet plus atorvastatin 80 mg plus ezetimibe 10 mg therapy were at high NCEP risk as opposed to only 5% of the diet only group. Those receiving diet plus atorvastatin 80 mg plus ezetimibe 10 mg therapy were more likely to have coronary artery disease, including angina and myocardial infarction, and cerebrovascular or peripheral arterial disease. They also had the highest current usage of cigarettes, the highest incidence of type 2 diabetes mellitus, the highest family history of premature CHD, and the highest incidence of 2 or more CV risk factors.

Overall, as classified by NCEP ATP III criteria, the majority of participants (64%) were at moderate or low CHD risk and only 26% were considered at high risk for coronary heart disease. Only 15% of participants had a medical history of coronary artery disease, with <8% having a history of prior myocardial infarction. Only 4% of participants had a medical history of cerebrovascular or peripheral arterial disease, with <1% having a history of prior stroke.

Reviewer comment: This long-term trial enrolled many participants at low or moderate CV risk; thus, the overall trial population does not represent a population at high CV risk with substantial CVD burden—arguably, the most appropriate patient population for add-on therapy to a statin.

Table 8: Summary of Baseline Demographics by Background Therapy and Investigational Product: Trial 20110109 (Full Analysis Set)

	Diet Only		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10mg**	
	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N=73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N = 63) n (%)	EvoMab QM (N=126) n (%)
Sex Female	22 (59.5)	39 (52.7)	70 (54.3)	145 (57.1)	40 (54.8)	69 (47.6)	30 (47.6)	56 (44.4)
Age (yrs) Mean	53.5	50.7	57.0	57.2	58.4	57.8	55.9	54.2
Age ≥ 65 years	8 (21.6)	10 (13.5)	32 (24.8)	69 (27.2)	19 (26.0)	34 (23.4)	8 (12.7)	25 (19.8)
White	25 (67.6)	50 (67.6)	112 (86.8)	217 (85.4)	65 (89.0)	123 (84.8)	46 (73.0)	86 (68.3)
Asian	5 (13.5)	11 (14.9)	6 (4.7)	15 (5.9)	1 (1.4)	5 (3.4)	4 (6.3)	10 (7.9)
Black	7 (18.9)	11 (14.9)	8 (6.2)	18 (7.1)	5 (6.8)	12 (8.3)	3 (4.8)	12 (9.5)
Europe	3 (8.1)	13 (17.6)	33 (25.6)	81 (31.9)	26 (35.6)	46 (31.7)	15 (23.8)	25 (19.8)
North America	28 (75.7)	53 (71.6)	87 (67.4)	156 (61.4)	43 (58.9)	91 (62.8)	19 (30.2)	44 (34.9)
Asia Pacific	6 (16.2)	8 (10.8)	9 (7.0)	17 (6.7)	4 (5.5)	8 (5.5)	29 (46.0)	57 (45.2)
Baseline Lipid Parameters, (mg/dL)								
LDL-C, UC (mean)	112.3	111.6	98.4	101.3	96.2	94.6	119.8	116.8
HDL-C, (mean)	54.4	49.2	55.8	55.7	52.6	50.1	49.3	51.3
TG, (median)	101.5	108.8	105.0	104.5	110.0	111.0	135.5	96.8
hsCRP, (median)	0.18	0.15	0.12	0.12	0.12	0.14	0.12	0.10
National cholesterol education program (NCEP) CHD risk categories								
	Diet Only		Atorvastatin 10 mg		Atorvastatin 80 mg		Atorva 80 mg + Ez 10	Total (N=901) n (%)
High	6 (5.4)		41 (10.7)		67 (30.7)		121 (64.0)	235 (26.1)
Mod-high	14 (12.6)		42 (11.0)		19 (8.7)		10 (5.3)	85 (9.4)
Moderate	41 (36.9)		138 (36.0)		86 (39.4)		35 (18.5)	300 (33.3)
Low	50 (45.0)		162 (42.3)		46 (21.1)		23 (12.2)	281 (31.2)
Coronary artery disease	2 (1.8)		10 (2.6)		34 (15.6)		90 (47.6)	136 (15.1)
Cerebrovascular or peripheral arterial disease	0 (0.0)		5 (1.3)		13 (6.0)		19 (10.1)	37 (4.1)
Current cigarette use	19 (17.1)		45 (11.7)		31 (14.2)		40 (21.2)	135 (15.0)
Type 2 diabetes	3 (2.7)		27 (7.0)		33 (15.1)		41 (21.7)	104 (11.5)

mellitus					
Hypertension	47 (42.3)	160 (41.8)	125 (57.3)	106 (56.1)	438 (48.6)

N = number of subjects randomized; CHD = coronary heart disease; EvoMab = Evolocumab (AMG 145); QM = monthly; CHD = coronary heart disease; UC=ultracentrifugation
Includes the following study: 20110109
Subjects from countries with an undefined risk are classed as low risk.
Source: Modified from CSR 20110109 Tables 14-2.2.1, 14-2.7.2 and 14-2.4.1 and confirmed with JMP analysis

Baseline overall mean lipid parameters, hsCRP, and PCSK9 are summarized for the evolocumab group and the placebo group in the following table.

Table 9: Baseline Lipid Parameters, High-Sensitivity C-Reactive Protein and PCSK9 in Trial 20110109 (Full Analysis Set)

Parameter Mean (SD)	**Placebo QM (N=302)**	**EvoMab 420 mg QM (N = 599)**
UC LDL-C mg/dL	104.0 (21.6)	104.2 (22.1)
reflexive LDL-C mg/dL	100.2 (21.5)	100.4 (22.2)
calculated LDL-C mg/dL	100.2 (21.6)	100.4 (22.3)
Total cholesterol mg/dL	179.1 (27.2)	176.8 (27.5)
HDL-C mg/dL	53.5 (16.1)	52.6 (15.5)
ApoA1 mg/dL	155.2 (28.0)	152.4 (27.3)
Triglycerides mg/dL	127.8 (65.8)	119.8 (63.2)
Triglycerides: Median (Q1, Q3) mg/dL	110.3 (85.0, 155.0)	105.0 (80.0, 140.0)
VLDL-C mg/dL	21.5 (13.4)	20.0 (11.4)
ApoB mg/dL	87.5 (16.3)	87.0 (16.3)
Non-HDL-C mg/dL	125.6 (26.9)	124.2 (25.6)

Parameter Mean (SD)	Placebo QM (N=302)	EvoMab 420 mg QM (N = 599)
Total cholesterol/ HDL-C ratio	3.6 (1.1)	3.6 (1.0)
ApoB/ApoA1 ratio	0.59 (0.2)	0.59 (0.2)
Lp(a)[a] nmol/L	89.3 (108.6)	84.0 (98.5)
Lp(a): Median (Q1, Q3) nmol/L	40.0 (12.0, 145.0)	38.0 (14.0, 137.0)
hsCRP∞ mg/L	2.9 (5.6)	2.7 (4.5)
hsCRP: Median (Q1, Q3) mg/L	1.2 (0.7, 3.1)	1.2 (0.6, 2.9)
PCSK9 ng/ml	481.7 (157.2)	477.6 (173.5)

ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B; EvoMab = Evolocumab (AMG 145);
HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein;
LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); N = number of subjects randomized and dosed in the full analysis set; PCSK9 = Proprotein convertase subtilisin/kexin type 9; QM = monthly ; UC=ultracentrifugation; VLDL-C = very low-density lipoprotein cholesterol
∞ According to the American Heart Association: Low risk of developing cardiovascular disease if hs-CRP level is < 1.0mg/L; average risk of developing cardiovascular disease if levels are between 1.0 and 3.0 mg/L; high risk for cardiovascular disease if hs-CRP level is > 3.0 mg/L.
Source: Modified from Table 14-2.4.1 and Table 14-2.4.3

Within the background therapy groups, the LDL-C (UC) and non-HDL-C was highest in the atorva 80+ezetimibe group (118 mg/dL and 141 mg/dL, respectively). Likewise, mean Lp(a) increased step-wise from the low risk (46 nmol/L) to high-risk group (120 nmol/L). However, mean hsCRP was highest in the low CHD risk group (3.4 mg/L) and lowest in the high CHD risk group (2.4 mg/L). At baseline, the mean LDL-C (UC: 104 mg/dL, calc 100 mg/dL), mean HDL-C (53 mg/dL) and median triglyceride (108 mg/dL) levels were well-controlled in the trial population. The median Lp(a) (39 nmol/L) and median hsCRP (1.2 mg/L) are supportive of a trial population that is at low to average risk of developing cardiovascular disease.

Approximately half (45.9%) of the participants reported the use of at least 1 lipid-regulating concomitant medication of interest at screening (before entry to lipid stabilization period). These medications included statins [42.6%: top 3 were simvastatin (16.6%), atorvastatin (15.1%), rosuvastatin (7.7%)], fenofibrate (0.2%), nicotinic acid and derivatives (0.1%), and other lipid-modifying agents [11.3%: ezetimibe (6.5%), fish

oil (3.1%), omega-3-fatty acids (2.1%)]. Less than 1% (0.4%) of participants reported use of lipid-regulating concomitant medications other than the protocol-assigned during the lipid stabilization period.

Patient Disposition

A total of 2120 participants were screened for the study at 88 centers in United States, Canada, South Africa, Czech Republic, Denmark, Hungary, Belgium, Australia, and Austria. Of the 2120 subjects screened, 1485 (70%) subjects met the requirements and entered the lipid stabilization period and 635 (30%) subjects did not. Of the 1485 subjects who entered the lipid stabilization period 905 (61%) subjects were randomized in the investigational product period and 580 (39%) subjects were not randomized into the investigational product period. Of the 580 subjects who were not randomized into the investigational product period following the lipid stabilization period, 539 (93%) were excluded because they did not meet one or more eligibility criteria. Four-hundred (69%) subjects were excluded because their fasting LDL-C at the end of lipid stabilization period was < 75 mg/dL (see additional details in Section 9.4 Screening Disposition in Trial 20110109). Overall, 905 participants were randomized to receive evolocumab (602 participants) or placebo (303 participants). A total of 901 received at least 1 dose of IP. The percentages of participants in the FAS by background therapy were:

- 12.3% were assigned to diet alone
- 42.5% to diet plus atorvastatin 10 mg
- 24.2% to diet plus atorvastatin 80 mg
- 21.0% to diet plus atorvastatin 80 mg plus ezetimibe 10 mg

Reviewer comment: A limitation of the trial design is having 12% of participants on no background drug therapy and 43% on low dose atorvastatin. Thus, at least 55% of the trial population represents a patient population who does not require an additional LDL lowering agent due to persistent CV risk or LDL-C elevation.

The table below describes the shift in background therapy after randomization. Approximately 4% of participants had a temporary change, of which the atorva 80 mg+ezetimibe group was the largest contributor, and 9% had an early termination of background therapy, of which the atorva 10 mg group was the largest contributor. Early termination of background therapy per treatment arm was as follows:

- Diet alone: 5/111= 4.5%
- Atorvastatin 10mg: 41/383= 10.7%
- Atorvastatin 80 mg: 22/218= 10.1%
- Atorvastatin 80 mg + ezetimibe 10 mg: 14/189= 7.4%

Table 10: Summary of Shift in Background Therapy after Randomization Study 20110109 (Full Analysis Set)

Background therapy at Randomization	**Post-randomization Background Therapy**						
	Diet Alone	Diet plus Atorvastatin 10 mg	Diet plus Atorvastatin 80 mg	Diet plus Atorvastatin 80 mg plus Ezetimibe 10 mg	Temporary Change of Background Therapy	Early Termination of Background Therapy	**Total**
Diet Alone	105 (11.7)	1 (0.1)	0	0	0	5 (0.6)	**111 (12.3)**
Diet plus Atorvastatin 10 mg	0	341 (37.8)	0	0	1 (0.1)	41 (4.6)	**383 (42.5)**
Diet plus Atorvastatin 80 mg	0	4 (0.4)	185 (20.5)	2 (0.2)	5 (0.6)	22 (2.4)	**218 (24.2)**
Diet plus Atorvastatin 80 mg plus Ezetimibe 10 mg	1 (0.1)	0	6 (0.7)	140 (15.5)	28 (3.1)[37]	14 (1.6)	**189 (21.0)**
Total	**106 (11.8)**	**346 (38.4)**	**191 (21.2)**	**142 (15.8)**	**34 (3.8)**	**82 (9.1)**	**901 (100.0)**

N = number of subjects randomized; Ezetimibe and Atorvastatin were administered orally once per day
Subjects are defined as having a change to background therapy if their last background therapy record is not their randomized background therapy regimen.
Subjects are defined as having a Temporary Change if they deviate from their randomized background regimen but return to it before the End of Study.
Subjects whose final background therapy record is not a protocol defined regimen, e.g. Ezetimibe 10mg (alone) are also included in the Temporary Change column.
Any records with no evidence of medication being taken (i.e. no return date, no number returned or number lost) are not considered.
Source: Applicant's Table 14-1.5.1 (CSR-20110109 Module 5.3.5.1)

37 28 (14.8%) of the 189 subjects randomized to the diet and atorvastatin 80 mg plus ezetimibe 10 mg background therapy group had temporary changes in background therapy after randomization. Further investigation showed that 5 of these subjects had an error in their eCRF and had actually remained on the assigned background regimen throughout the study. Therefore, a total of 23 subjects (12.2%) in the diet and atorvastatin 80 mg plus ezetimibe 10 mg background therapy group had a temporary change in background therapy during the study. Eighteen of the 23 subjects had 1 or more temporary changes from the background therapy assigned at randomization, but returned to the assigned background therapy before the end of the study. The most common changes in background therapy for these 18 subjects were to ezetimibe 10 mg alone or atorvastatin 80 mg alone (10 subjects each); a subject could have both types of changes during the study. The temporary changes were of ≤ 30 days duration for 16 of the 18 subjects. Two subjects had temporary changes in background therapy of > 30 days: 47 days for Subject 10966411003 and 37 and 76 days for Subject 10966439012. The other 5 subjects had background therapy regimens at the end of the study that were different than the 4 regimens specified in the protocol: One subject (10957205025) was receiving ezetimibe 10 mg alone at both randomization and the end of the study. This subject received the assigned diet and atorvastatin 80 mg plus ezetimibe 10 mg regimen during the rest of the study, except for a temporary change to atorvastatin 80 mg alone and a temporary gap in dispensation of all background therapy. Four subjects (10957205022, 10966411020, 10966452022, and 10966452043) were receiving ezetimibe 10 mg alone at the end of the study only. This was the only change in background therapy for each subject and occurred after at least 10 months of treatment with the assigned diet and atorvastatin 80 mg plus ezetimibe 10 mg regimen. Of the 23 subjects, 1 subject had a change in background therapy due to an adverse event. Subject 10957204018 discontinued dosing with atorvastatin 80 mg and then re-initiated dosing at 40 mg as a result of a non-serious adverse event of myalgia; evolocumab and ezetimibe doses were unchanged. The adverse event resolved within 54 days, and the atorvastatin dose was increased to 80 mg. None of the other 22 subjects had atorvastatin or ezetimibe dose changes due to an adverse event.

A similar percentage of participants completed the trial in both groups; a total of 855 participants completed the study including 568 (94.4%) participants in the evolocumab group and 287 (94.7%) in the placebo group. Eight hundred participants completed dosing of IP per protocol over the duration of the study (52 weeks) including 526 (87.4%) participants in the evolocumab group and 274 (90.4%) in the placebo group. A total of 101 participants discontinued IP, including 73 (12.1%) in the evolocumab group and 28 (9.2%) in the placebo group. The largest percentage of study discontinuations occurred in the Diet Only group (14.7%) and the smallest percentage was in the atorvastatin 80+ezetimibe group (9.5%). A similar percentage of participants completed the trial in both groups (EvoMab: 94%; Pbo 95%).

Slightly more participants in the placebo group (90%) completed IP than in the EvoMab group (87%). The most frequent reasons for discontinuation of IP in the evolocumab group included subject request (4.0%), “other” (2.3%), and adverse event (2.0%), while in the placebo group the two most frequent reasons for discontinuation of IP were subject request (2.6%) and full consent withdrawn (2.6%). The table below provides a summary of participant reporting for all randomized participants by background therapy and IP.

Table 11: Disposition with Discontinuation Reason by Background Therapy and Investigational Product Study 20110109

	Diet Only		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10mg**		**TOTAL**	
	Placebo QM (N =38) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =256) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=146) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 303) n (%)	EvoMab QM (N=602) n (%)
ASSESSMENT of STUDY COMPLETION by SUBJECTS										
Completed Study	33 (86.8)	66 (89.2)	123 (95.3)	244 (95.3)	71 (97.3)	137 (93.8)	60 (95.2)	121 (96.0)	287 (94.7)	568 (94.4)
Discontinued Study	5 (13.2)	8 (10.8)	6 (4.7)	12 (4.7)	2 (2.7)	9 (6.2)	3 (4.8)	5 (4.0)	16 (5.3)	34 (5.6)
Consent Withdrawn	3 (7.9)	1 (1.4)	3 (2.3)	6 (2.3)	1 (1.4)	2 (1.4)	2 (3.2)	2 (1.6)	9 (3.0)	11 (1.8)
Death	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)
Study Termination	0	0	0	0	0	0	0	0	0	0
Lost to Follow-up	1 (2.6)	5 (6.8)	1 (0.8)	2 (0.8)	0	2 (1.4)	0	2 (1.6)	2 (0.7)	11 (1.8)
Other	1 (2.6)	2 (2.7)	2 (1.6)	3 (1.2)	1 (1.4)	4 (2.7)	1 (1.6)	1 (0.8)	5 (1.7)	10 (1.7)
ASSESSMENT of INVESTIGATIONAL PRODUCT (IP) USE by SUBJECTS										
Received IP	37 (97.4)	74 (100.0)	129 (100.0)	254 (99.2)	73 (100.0)	145 (99.3)	63 (100.0)	126 (100.0)	302 (99.7)	599 (99.5)
Completed IP	32 (84.2)	62 (83.8)	117 (90.7)	225 (87.9)	67 (91.8)	127 (87.0)	58 (92.1)	112 (88.9)	274 (90.4)	526 (87.4)
Discontinued IP	5 (13.2)	12 (16.2)	12 (9.3)	29 (11.3)	6 (8.2)	18 (12.3)	5 (7.9)	14 (11.1)	28 (9.2)	73 (12.1)
Consent Withdrawn	2 (5.3)	1 (1.4)	3 (2.3)	4 (1.6)	1 (1.4)	2 (1.4)	2 (3.2)	1 (0.8)	8 (2.6)	8 (1.3)
Adverse Event	0	1 (1.4)	1 (0.8)	7 (2.7)	2 (2.7)	3 (2.1)	1 (1.6)	1 (0.8)	4 (1.3)	12 (2.0)
Pregnancy	0	0	0	0	0	0	0	0	0	0
Death	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)
Subject Request	0	4 (5.4)	4 (3.1)	9 (3.5)	2 (2.7)	9 (6.2)	2 (3.2)	2 (1.6)	8 (2.6)	24 (4.0)
Decision by Sponsor	0	1 (1.4)	0	1 (0.4)	1 (1.4)	1 (0.7)	0	1 (0.8)	1 (0.3)	4 (0.7)
Investigator decision	0	0	1 (0.8)	0	0	0	0	0	1 (0.3)	0
Lost to Follow-up	1 (2.6)	3 (4.1)	1 (0.8)	2 (0.8)	0	2 (1.4)	0	2 (1.6)	2 (0.7)	9 (1.5)
Other	2 (5.3)	2 (2.7)	2 (1.6)	5 (2.0)	0	0	0	7 (5.6)	4 (1.3)	14 (2.3)

N = number of subjects randomized; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); IP = investigational product. Number of subjects screened: 2120; First subject enrolled: 05JAN2012 Last subject completed study: 07NOV2013
Source: modified from Table 9-1 (CSR-20110109 Module 5.3.5.1) and confirmed with JMP analysis

Patient Exposure to Study Drug

The median duration of evolocumab exposure was 12 months and the mean duration of evolocumab exposure (SD) was 11.1 (2.6) months for the 599 participants who received at least one dose of evolocumab 420 mg and were included in the Full Analysis Set (FAS). The mean (SD) number of evolocumab doses administered was 11.8 (2.9). The number of participants exposed to evolocumab for at least 12, 24, 48, or 52 weeks was 579 (96.7%), 557 (93.0%), 529 (88.3%), and 404 (67.4%), respectively.

Concomitant Medications

Of the 901 trial participants, 68 (7.5%) reported using non-protocol assigned lipid-regulating concomitant medications. The concomitant medications of interest included the use of statins (14 [1.6%]), bile acid sequestrants (1 [0.1%]), nicotinic acid and derivatives (2 [0.2%]), or other lipid modifying agents (55 [6.1%]). Other lipid modifying agents was primarily use of fish oil (3.5%) or omega-3 fatty acids (2.2%).

By background therapy, the use of medications of interest was reported by 2.7% (n=3) of participants in the diet alone group, 7.6% (n=29) in the diet plus atorvastatin 10 mg group, 8.3% (n=18) in the diet plus atorvastatin 80 mg group, and 9.5% (n=18) in the diet plus atorvastatin plus ezetimibe group. The largest contributors were fish oil and omega-3 fatty acids. This reviewer does not believe that the limited use of non-protocol assigned lipid-regulating concomitant medications had a clinically relevant effect on the efficacy or safety results of this trial.

Primary Efficacy Outcomes

The primary efficacy endpoint was percent change from baseline in UC LDL-C at Week 52.The percent change (SE) in UC LDL-C from baseline to Week 52 for evolocumab (420 mg SC QM) compared with placebo QM was -57.0% (2.1%) (multiplicity adjusted $p < 0.001$) when added to background lipid-lowering therapy (see table below).

As shown in the table, compared with placebo, the treatment difference for the percent change from baseline at week 52 in UC LDL-C (SE) for the evolocumab QM group was -55.7% (4.2%) in the diet alone group, -61.6% (2.6%) in the diet plus atorvastatin 10 mg group, -56.8% (5.3%) in the diet plus atorvastatin 80 mg group, and -48.5% (5.2%) in the diet plus atorvastatin 80 mg plus ezetimibe 10 mg group.

Table 12: Analysis of Percent Change from Baseline in Ultracentrifugation LDL-C at Week 52 by Background Therapy in Trial 20110109 (Full Analysis Set)

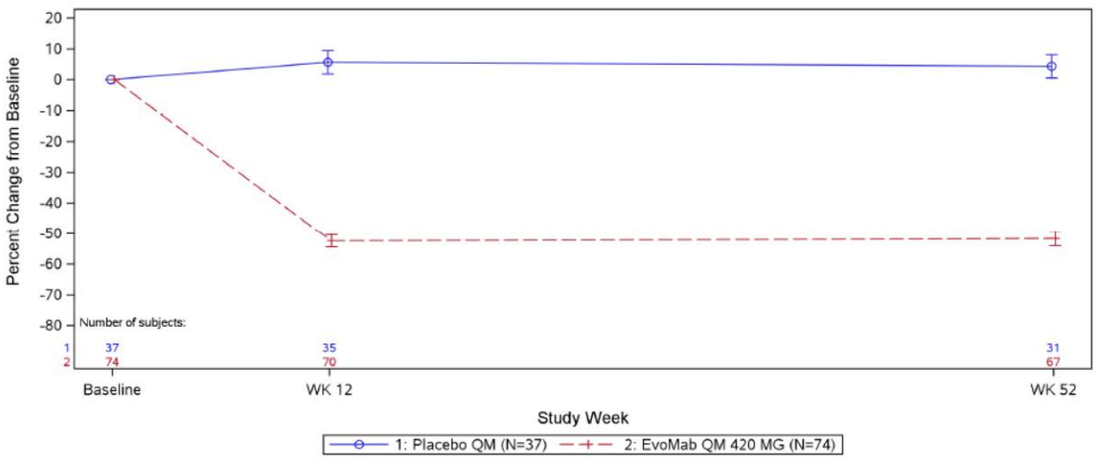
	Diet Only		Diet + Atorvastatin 10mg		Diet + Atorvastatin 80mg		Diet + Atorvastatin 80mg + Ezetimibe 10mg		Total	
	Placebo QM (N=37)	EvoMab 420 mg QM (N=74)	Placebo QM (N=129)	EvoMab 420 mg QM (N=254)	Placebo QM (N=73)	EvoMab 420 mg QM (N=145)	Placebo QM (N=63)	EvoMab 420 mg QM (N=126)	Placebo QM (N=302)	EvoMab 420 mg QM (N=599)
Summary Statistics										
n	31	67	113	233	66	130	54	112	264	542
Mean	4.36	-51.66	7.20	-55.79	9.26	-47.47	0.60	-46.92	6.03	-51.45
SE	3.72	2.36	2.15	1.47	4.04	3.13	4.31	2.97	1.69	1.20
Median	-1.53	-53.85	4.44	-60.98	0.99	-57.20	-0.57	-53.05	1.66	-57.63
Q1,Q3	(-5.58, 16.55)	(-63.79, -43.88)	(-8.00, 17.71)	(-70.91, -47.17)	(-10.07, 19.37)	(-68.42, -37.37)	(-16.67, 13.21)	(-68.48, -34.47)	(-9.60, 16.26)	(-68.63, -42.66)
Min,Max	(-32.5, 71.9)	(-82.6, 13.4)	(-33.7, 88.2)	(-95.1, 46.0)	(-32.6, 173.9)	(-88.8, 111.2)	(-91.7, 93.5)	(-87.0, 96.6)	(-91.7, 173.9)	(-95.1, 111.2)
LS Mean [a]										
Estimate	4.19	-51.51	6.88	-54.68	10.10	-46.68	1.71	-46.80	6.83	-50.14
SE	3.50	2.39	2.16	1.51	4.32	3.09	4.29	2.98	1.75	1.24
95% CI	(-2.76, 11.14)	(-56.26, -46.76)	(2.63, 11.13)	(-57.65, -51.71)	(1.58, 18.62)	(-52.77, -40.60)	(-6.75, 10.18)	(-52.69, -40.91)	(3.40, 10.27)	(-52.58, -47.69)
Treatment difference[b]										
Estimate	-	-55.70	-	-61.56	-	-56.78	-	-48.51	-	-56.97
SE	-	4.24	-	2.63	-	5.31	-	5.22	-	2.10
95% CI	(-, -)	(-64.12, -47.28)	(-, -)	(-66.75, -56.38)	(-, -)	(-67.25, -46.31)	(-, -)	(-58.82, -38.20)	(-, -)	(-61.08, -52.85)
p-value	-	<0.001	-	<0.001	-	<0.001	-	<0.001	-	<0.001

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
a Least squares mean is from the repeated measures model which includes treatment group, stratification factor(s) (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.
b Treatment difference are within each background therapy group using placebo in the same group as the reference.
Source: Applicant's Table 14-4.1.2 (CSR-20110109 Module 5.3.5.1)

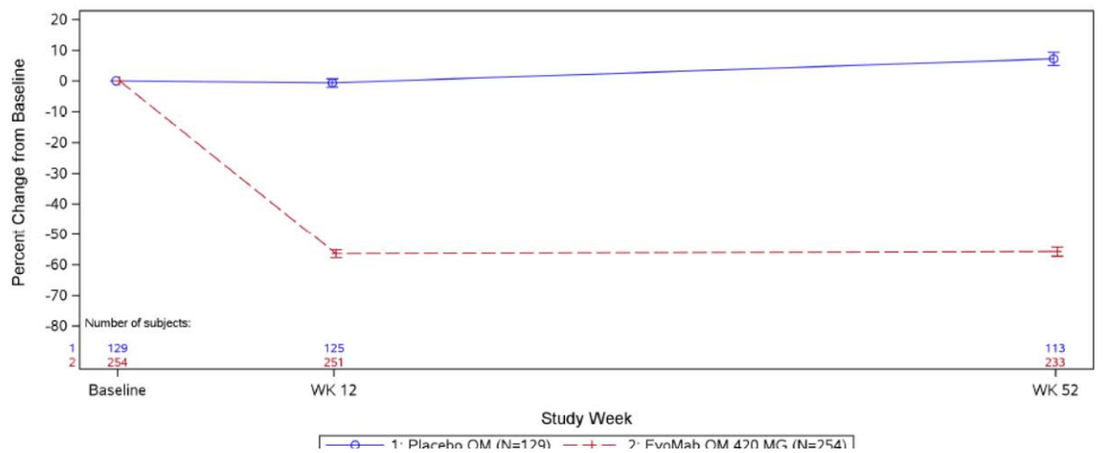
Consistency of Treatment Effect:
Statistically significant reductions in UC LDL-C from baseline (ie, end of lipid stabilization period) occurred during the first 12 weeks on study for participants treated with evolocumab; these reductions were maintained through Week 52 (EOS) for the 4 treatment groups although the atorvastatin 80 mg plus ezetimibe 10 mg group did exhibit a slight trend toward baseline at Week 52 (see figures below).

Figure 3: Plots of Mean Percent Change From Baseline in Ultracentrifugation LDL-C at Week 12 and Week 52 in Trial 20110109 (Full Analysis Set)

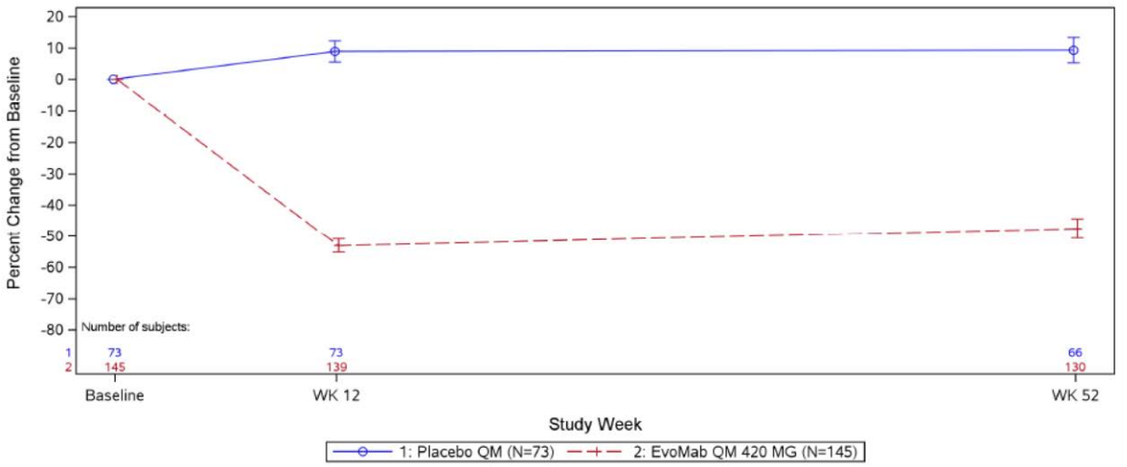
Background Therapy = Diet alone



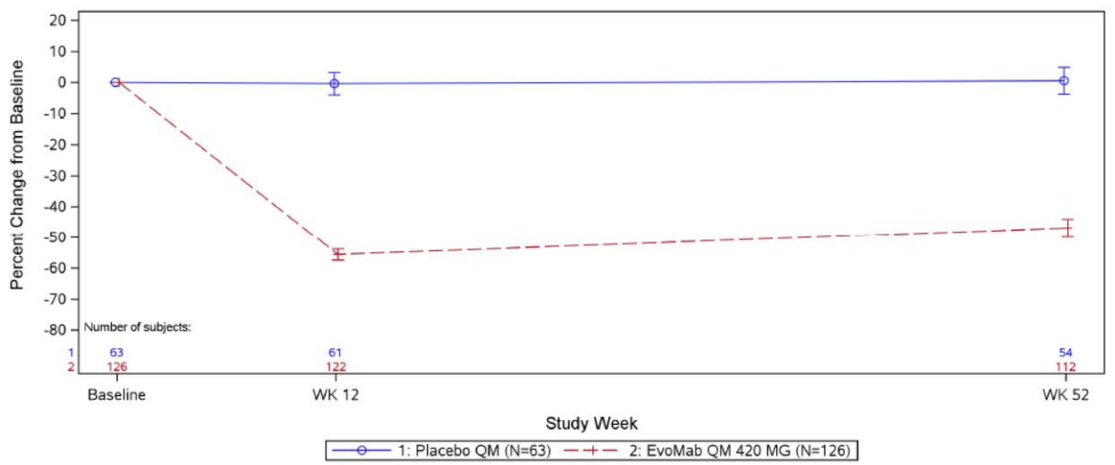
Background Therapy = Diet + Atorvastatin 10mg



Background Therapy = Diet + Atorvastatin 80mg



Background Therapy = Diet + Atorvastatin 80mg + Ezetimibe 10mg



EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.
Source: Applicant's Figures 14-4.27.4 (CSR-20110109 Module 5.3.5.1)

The table below shows the durability of treatment effects relative to baseline at Week 12 and Week 52 of evolocumab QM compared with placebo QM in the FAS.

Table 13: Treatment Effects (EvoMab vs Placebo) of Week 12 and Week 52 in Trial 20110109 (Full Analysis Set)

	Placebo QM		EvoMab 420 mg QM		EvoMab - Placebo
	n	LSM[a] (95% CI)	n	LSM[a] (95% CI)	Difference in LSM[a]

					(95% CI)
FAS	302		599		
% change from baseline					
Week 12	294	3.2 (0.6, 5.7)	582	-54.4 (-56.2, -52.5)	-57.5 (-60.6, -54.5)
Week 52	264	6.8 (3.4, 10.3)	542	-50.1 (-52.6, -47.7)	-57.0 (-61.1, -52.9)
Diff week 12 to week 52	262	3.7 (0.3, 7.0)	538	4.2 (1.9, 6.5)	0.5 (-3.5, 4.6)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
[a] Least squares mean is from the repeated measures model which includes treatment group, stratification factor(s) (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates. There will be no imputation for missing data.
Source: Applicant's Table 10-5 (CSR-20110109 Module 5.3.5.1)

Analyses of the percent change in LDL-C from baseline to Week 52 for evolocumab compared with placebo using reflexive LDL-C or calculated LDL-C values resulted in treatment differences of -58.0 (2.1%) and -59.3 (2.3%) ($p < 0.001$), respectively, when added to background lipid-lowering therapy (see table below).

Table 14: Treatment Differences in the Percent Change From Baseline at Week 52 Compared With Placebo Using UC LDL-C, Calculated LDL-C, or Reflexive LDL-C in Trial 20110109 (Full Analysis Set)

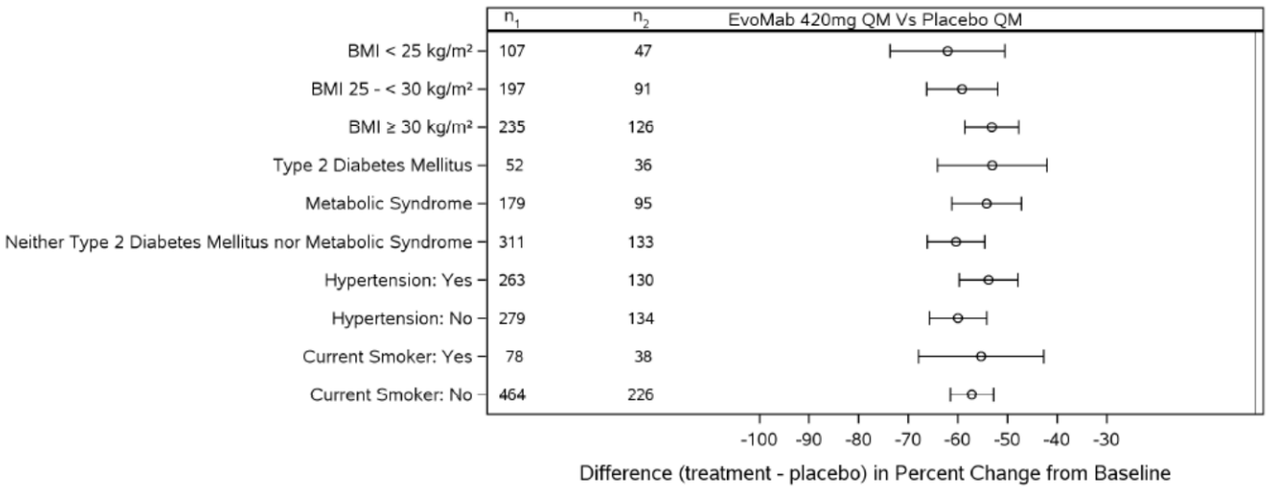
	Least Squares Mean (SE)[a]		Treatment difference (SE)[b]
LDL-C	Placebo QM (N=302)	EvoMab 420 mg QM (N=599)	EvoMab 420 mg QM vs Placebo QM
UC LDL-C	6.8 (1.8)	-50.1 (1.2)	-57.0 (2.1)
Reflexive[c]	8.1 (1.8)	-49.9 (1.3)	-58.0 (2.1)
Calculated	8.7 (1.9)	-50.6 (1.4)	-59.3 (2.3)

EvoMab = Evolocumab (AMG 145); LDL-C = low-density lipoprotein cholesterol; QM = monthly (subcutaneous); SE = standard error; UC = ultracentrifugation
a Least squares mean is from the repeated measures model which includes treatment group, stratification factor(s) (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.
b Treatment difference is within each background therapy group using placebo in the same group as the reference.
c When the calculated LDL-C is <40 mg/dL or triglycerides are > 400 mg/dL , calculated LDL-C will be replaced with UC LDL-C from the same blood sample, if available
Source: Modified from Table 14-4.1.1, Table 14-4.1.3, Table 14-4.3.1.

Subgroup analysis (ie, background therapy, age, sex, race, geographic region, UC LDL-C, body mass index [BMI], glucose tolerance status, hypertension, current smoker, CHD risk factors, family history of premature CHD, PCSK9, triglycerides, and NCEP high risk) of the placebo-adjusted mean percent change in UC LDL-C at Week 52 demonstrated

that evolocumab was effective across all subgroups with no significant differences. The forest plot below shows the results of some of the subgroup analyses; a trend toward greater LDL reduction with lower BMIs is noted.

Figure 4: Forest Plot of Treatment Differences in Percent Change From Baseline in Ultracentrifugation LDL-C at Week 52 - Subgroup Analyses in Trial 20110109 (Full Analysis Set)



n1 = number of subjects in the subgroup of interest included in the repeated measures model receiving EvoMab; n2 = number of subjects in the subgroup of interest included in the repeated measures model receiving placebo; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
Subgroup is data-derived.
Least squares mean differences and 95% CI are from the repeated measures model. No imputation is used for missing values.
Source: Applicant's Figure 10-2 (CSR-20110109 Module 5.3.5.1)

Secondary Efficacy Outcomes

Treatment with evolocumab resulted in statistically significant changes (multiplicity adjusted $p < 0.001$) in all tier 1 and tier 2 secondary efficacy endpoints compared with placebo, when added to background lipid-lowering therapy as summarized below.

Table 15: Secondary Efficacy Results in Trial 20110109 (Full Analysis Set)

	Treatment Difference EvoMab 420 mg QM vs Placebo QM
Tier 1 Secondary Endpoints	
Change from baseline in UC LDL-C at week 52	
Treatment difference (95% CI) - mg/dL	-57.8 (-62.3, -53.3)
Treatment difference (95% CI) - mmol/L	-1.496 (-1.612, -1.379)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent of subjects with UC LDL-C < 70 mg/dL (1.8 mmol/L) at week 52	
Treatment difference (95% CI)[a]	75.8 (70.8, 79.7)
p-value[b]	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in UC LDL-C at week 12	
Treatment difference (95% CI)	-57.51 (-60.57, -54.45)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in total cholesterol at week 12	
Treatment difference (95% CI)	-35.15 (-37.19, -33.11)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in total cholesterol at week 52	
Treatment difference (95% CI)	-33.45 (-36.21, -30.68)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in non-HDL-C at week 52	
Treatment difference (95% CI)	-50.27 (-54.25, -46.28)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in ApoB at week 52	
Treatment difference (95% CI)	-44.21 (-47.56, -40.85)
p-value	<0.001
Adjusted p-value	**<0.001**

	Treatment Difference EvoMab 420 mg QM vs Placebo QM
Percent change from baseline in the total cholesterol/HDL-C ratio at week 52	
Treatment difference (95% CI)	-37.14 (-40.41, -33.87)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in ApoB/ApoA1 ratio at week 52	
Treatment difference (95% CI)	-46.21 (-49.79, -42.63)
p-value	<0.001
Adjusted p-value	**<0.001**
Tier 2 Secondary Endpoints	
Percent change from baseline in Lp(a) at week 52	
Treatment difference (95% CI)	-22.35 (-26.15, -18.55)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in triglycerides at week 52	
Treatment difference (95% CI)	-11.54 (-17.21, -5.86)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in VLDL-C at week 52	
Treatment difference (95% CI)	-29.15 (-40.23, -18.08)
p-value	<0.001
Adjusted p-value	**<0.001**
Percent change from baseline in HDL-C at week 52	
Treatment difference (95% CI)	5.42 (3.28, 7.56)
p-value	<0.001
Adjusted p-value	**<0.001**

ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B; CI = confidence interval; EvoMab = Evolocumab (AMG 145); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); N = number of subjects randomized and dosed in the full analysis set; QM = once monthly (subcutaneous); UC = ultracentrifugation; VDL-C = very low-density lipoprotein cholesterol
Adjusted p-values are based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance
[a] 95% confidence interval is calculated using the Wilson Score method.
[b] Based on Cochran-Mantel Haenszel test stratified by the stratification factor. For testing, non-achievement was imputed for subjects with a missing value at week 52
Source: Applicant's Table 10-3 (CSR-20110109 Module 5.3.5.1)

Safety Data:

The following table presents an overall summary of the adverse events reported in the four different background therapy groups of evolocumab versus placebo.

Table 16: Summary of Subject Incidence of Adverse Events by Background Therapy in Trial 20110109 (Full Analysis Set) (n [%])

	Diet Only		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10mg**		**TOTAL**	
	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Adverse Events*	30 (81.1)	52 (70.3)	101 (78.3)	201 (79.1)	54 (74.0)	111 (76.6)	39 (61.9)	84 (66.7)	224 (74.2)	448 (74.8)
Grade ≥ 2	21 (56.8)	26 (35.1)	59 (45.7)	116 (45.7)	38 (52.1)	72 (49.7)	23 (36.5)	55 (43.7)	141 (46.7)	269 (44.9)
Grade ≥ 3	3 (8.1)	1 (1.4)	6 (4.7)	17 (6.7)	3 (4.1)	16 (11.0)	3 (4.8)	13 (10.3)	15 (5.0)	47 (7.8)
Grade ≥ 4	0	0	0	2 (0.8)	0	3 (2.1)	0	1 (0.8)	0	6 (1.0)
SAEs	3 (8.1)	1 (1.4)	1 (0.8)	13 (5.1)	3 (4.1)	11 (7.6)	6 (9.5)	8 (6.3)	13 (4.3)	33 (5.5)
AEs that led to D/C	0	1 (1.4)	1 (0.8)	8 (3.1)	1 (1.4)	3 (2.1)	1 (1.6)	1 (0.8)	3 (1.0)	13 (2.2)
Serious	0	0	0	2 (0.8)	0	1 (0.7)	0	1 (0.8)	0	4 (0.7)
Non-serious	0	1 (1.4)	1 (0.8)	6 (2.4)	1 (1.4)	2 (1.4)	1 (1.6)	0	3 (1.0)	9 (1.5)
Fatal AEs[a]	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); Coded using MedDRA version 16.1

*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.

Source: modified from Table 14-6.1.1 (CSR-20110109 Module 5.3.5.1) and confirmed with JMP analysis

[a] One additional death was reported after the subject's end of study visit.

The following table presents a summary of the adverse events and select laboratory results observed in the overall groups of evolocumab versus placebo. Common adverse events are presented for preferred terms reported for at least 1% of evolocumab participants where the incidence in the evolocumab group is greater than the placebo group. A review of MedDRA High Level Terms (HLT) that are not captured by a preferred term (PT) in this table include the HLTs of Skin neoplasms benign, Sensory abnormalities NEC, Non-site specific procedural complications and Nasal disorder NEC, all of which occurred in 7 participants (1.2%) in the evolocumab group vs 1 participant (0.3%) in the placebo group.

Table 17: Summary of Adverse Events and Notable Laboratory Results during Trial 20110109 (AE preferred terms reported for ≥ 1% of evolocumab group where incidence in evolocumab > placebo)

Event	Placebo (N = 302) n (%)	Evolocumab (N = 599) n (%)
Patients with adverse event		
Any	224 (74.2)	448 (74.8)
Serious	13 (4.3)	33 (5.5)
Leading to discontinuation of a study drug	3 (1.0)	13 (2.2)
Adjudicated atherosclerotic event	2 (0.7)	6 (1.0)
Death*	0	2 (0.3)
Common adverse events		
Nasopharyngitis	29 (9.6)	63 (10.5)
Upper respiratory tract infection	19 (6.3)	56 (9.3)
Influenza	19 (6.3)	45 (7.5)
Back pain	17 (5.6)	37 (6.2)
Urinary tract infection	11 (3.6)	27 (4.5)
Cough	11 (3.6)	27 (4.5)
Sinusitis	9 (3.0)	25 (4.2)
Headache	11 (3.6)	24 (4.0)
Myalgia	9 (3.0)	24 (4.0)
Dizziness	8 (2.6)	22 (3.7)
Musculoskeletal pain	9 (3.0)	20 (3.3)
Hypertension	7 (2.3)	19 (3.2)
Diarrhea	8 (2.6)	18 (3.0)
Gastroenteritis	6 (2.0)	18 (3.0)
Injection-site erythema	6 (2.0)	16 (2.7)
Oropharyngeal pain	4 (1.3)	15 (2.5)
Upper abdominal pain	2 (0.7)	13 (2.2)
Osteoarthritis	5 (1.7)	12 (2.0)
Vomiting	5 (1.7)	11 (1.8)
Viral upper respiratory tract infection	3 (1.0)	11 (1.8)
Dyspepsia	2 (0.7)	11 (1.8)
Rash	1 (0.3)	11 (1.8)
Cystitis	4 (1.3)	10 (1.7)
Tendonitis	3 (1.0)	10 (1.7)
Anxiety	2 (0.7)	10 (1.7)
Seasonal allergy	4 (1.3)	9 (1.5)
Neck pain	3 (1.0)	9 (1.5)
Insomnia	3 (1.0)	9 (1.5)
Pharyngitis	2 (0.7)	9 (1.5)
Arthropod bite	1 (0.3)	9 (1.5)
Noncardiac chest pain	0	8 (1.3)
Musculoskeletal chest pain	3 (1.0)	7 (1.2)
Abdominal pain	2 (0.7)	7 (1.2)
Palpitations	1 (0.3)	7 (1.2)
Anemia	0	7 (1.2)
Nephrolithiasis	0	7 (1.2)
Angina pectoris	2 (0.7)	6 (1.0)

Ventricular extrasystoles	2 (0.7)	6 (1.0)
Constipation	2 (0.7)	6 (1.0)
Injection-site swelling	2 (0.7)	6 (1.0)
Pyrexia	1 (0.3)	6 (1.0)
Procedural pain	1 (0.3)	6 (1.0)
ALT increased	0	6 (1.0)
Elevated ALT or AST at any postbaseline visit		
>3× ULN	3 (1.0)	5 (0.8)
>5× ULN	1 (0.3)	3 (0.5)
ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN or INR>1.5	0	0
Elevated creatine kinase at any postbaseline visit		
>5× ULN	1 (0.3)	7 (1.2)
>10× ULN	1 (0.3)	3 (0.5)
Injection-site reaction†	15 (5.0)	34 (5.7)

N = number of subjects randomized and dosed in the full analysis set
Coded using MedDRA version 16.1
Adverse events occurred between the first dose of Investigational Product and End of Study.
* The two deaths were from cardiac failure and myocardial infarction and are included as adjudicated atherosclerotic events. A third fatal event of sudden cardiac death occurred 21 days after the EOS (49 days after the last dose of evolocumab).
† Potential events were identified by means of a broad-search strategy, in which event categories were defined with the use of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) and either standard MedDRA queries or internal groupings. Injection site reactions included such terms as injection site erythema, pain, bruising, swelling, induration, pruritus, urticaria, and edema.

Deaths

Two fatal adverse events (cardiac failure, myocardial infarction) were reported during the trial, and 1 additional fatal adverse event (sudden cardiac death) was reported for a participant after the EOS visit. All three deaths occurred in the evolocumab 420 mg QM treatment group.

Table 18: Summary of Deaths in Trial 20110109

Subject ID	**Age (yrs) at Start/ Race/ Sex**	**Parent Study Day**	**Period Study Day**	**Days Since First Dose**	**Days Since Last Dose**	**Cause of Death** (Preferred Term)	**Relevant Other Medications** **Relevant Other Conditions/History**
10923201053	60 /W/ male	131	131	131	47	Cardiac failure	atorvastatin,dexamethasone, verapamil, zolpidem, oxycodone, betamethasone, levocetirizine, aminophylline, betahistine, combination of fenoterol and ipratropium, paracetamol and tramadol dyslipidemia, hypertension, current cigarette use, asthma, chronic bronchitis, peripheral edema, vertigo, varicose

Subject ID	Age (yrs) at Start/ Race/ Sex	Parent Study Day	Period Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
							ulceration in lower extremities. Nine days after the first dose of evolocumab 420 mg QM, the subject developed sideropenic anemia. An ultrasound revealed diffuse hepatopathy. Approximately 4 months and 1 week after the first dose of evolocumab, the subject died and was reported with an adverse event of fatal heart failure. The cause of death according to the autopsy was heart failure caused by chronic heart insufficiency. Underlying diseases included grade 3 central atherosclerosis, advanced coronary atherosclerosis with multiple stenosis (> 75%) and exacerbation of chronic atrophic bronchitis (acute purulent bronchitis). Complications reported included disperse myofibrosis corresponding to clinical diagnosis of chronic ischemic heart disease, vascular nephrosclerosis, chronic heart insufficiency (cyanotic induration of organs) and evidence of acute circulatory failure (pulmonary edema, brain edema and acute venostasis in organs). Reviewer note: class II-IV CHF was an exclusion criterion, and this patient does not appear to have been on any medications for CHF at baseline. Question if whether this patient's asthma/COPD may have been partly cardiogenic in nature. Not aware of any mechanism where EvoMab could precipate acute/chronic cardiac decompensation.
10923201092	67 /W/ male	13	13	13	13	Myocardial infarction	atorvastatin, tamsulosin hydrochloride hypercholesterolemia, obesity (weight of 101.5 kg and height of 176 cm), family history of premature coronary heart disease. Autopsy: cause of death as myocardial infarction complicated with cardiac tamponade. Direct cause of death as heart tamponade, with complications of generalized atherosclerosis of Grade 1-3, predominantly on coronary arteries, and acute myocardial infarction of left ventricular posterior wall, and thrombosis of the right coronary artery.
10957204007	51 /mixed race/ female	389	-	389	50	Sudden cardiac death	atorvastatin, ezetimibe, amlodipine, furosemide, acetylsalicylic acid, isosorbide mononitrate, fluoxetine, salbutamol, budesonide, theophylline, paracetamol, metformin, amitryptyline hyperlipidemia, peripheral vascular disorder, asthma, type 2 diabetes mellitus,

Subject ID	Age (yrs) at Start/ Race/ Sex	Parent Study Day	Period Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications / Relevant Other Conditions/History
							depression, myocardial ischemia, angina pectoris, coronary angioplasty. At the end of the study, the subject reported that she was still having angina pectoris, relatively frequently with effort, and using sublinguial nitrates regularly. Approximately 3 weeks after the last dose of the evolocumab, the subject suddenly collapsed and was found unarousable. The subject was taken to the hospital and was pronounced dead on arrival. No resuscitation was attempted; nor interventions were carried out neither treatment medications were administered. No relevant laboratory or diagnostic test results were reported. The investigator reported that the subject had been having increasing frequency of angina pectoris with effort, no rest pain, and that the family of the subject informed them of the subject's death. The family reported she had been having angina pectoris in her usual patterns in the days prior to death. The investigator reported the features of the event were strongly suggestive of sudden cardiac death due to suspected myocardial infarction.

Serious Adverse Events

A total of 33 (5.5%) participants in the evolocumab group and 13 (4.3%) participants in the placebo group reported SAEs. No SAE was reported by more than 2 (0.3%) participants. Serious adverse events that were reported by 2 participants each (0.3%) in the evolocumab group included angina pectoris, palpitation, ventricular extrasystoles, vertigo positional, back pain, and pulmonary embolism. Angina pectoris was reported by 2 participants (0.7%) in the placebo group; no other SAE was reported by more than 1 participant (0.3%) in the placebo group.

The number of overall SAEs is small, which limits the ability to detect differences or trends in AEs. While the percentage of cardiac disorders is balanced between the groups, only the evolocumab group reported cardiac failure, myocardial infarction and unstable angina events. The evolocumab group reported 3 infection-related SAEs compared to none in the placebo group. The infections were dispersed over different organ systems (appendicitis, pneumonia, skin). Similarly, the evolocumab group reported 4 neoplasm-related SAEs compared to none in the placebo group. The

neoplasms involved different organ systems but 3 of the 4 were female-specific in nature (breast, ovary, uterine and renal). Investigations related to laboratory abnormalities were balanced between the 2 groups. Musculoskeletal SAEs were slightly increased in the evolocumab group, primarily due to back pain and disc disease and not to myopathy-related events.

Table 19: Serious Adverse Events by System Organ Class and Preferred Term Where SAE Occurs in ≥ 2 (0.3%) Subjects in Total EvoMab Group, by Background Therapy and Investigational Product in Trial 20110109 (Full Analysis Set - Actual Treatment)

	Diet Only		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10mg**		**TOTAL**	
System Organ Class Preferred Term	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Serious Adverse Events*	**3 (8.1)**	**1 (1.4)**	**1 (0.8)**	**13 (5.1)**	**3 (4.1)**	**11 (7.6)**	**6 (9.5)**	**8 (6.3)**	**13 (4.3)**	**33 (5.5)**
Cardiac Disorders	0	0	0	3 (1.2)	0	1 (0.7)	3 (4.8)	2 (1.6)	3 (1.0)	6 (1.0)
Angina Pectoris	0	0	0	1 (0.4)	0	0	2 (3.2)	1 (0.8)	2 (0.7)	2 (0.3)
Palpitations	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)
Ventricular Extrasystoles	0	0	0	1 (0.4)	0	0	0	1 (0.8)	0	2 (0.3)
Ear & Labyrinth	0	0	0	2 (0.8)	0	1 (0.7)	0	0	0	3 (0.5)
Vertigo Positional	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)
Gastrointestinal	0	0	0	0	0	1 (0.7)	0	1 (0.8)	0	2 (0.3)
General Disorders	0	0	0	1 (0.4)	1 (1.4)	0	0	1 (0.8)	1 (0.3)	2 (0.3)
Hepatobiliary	0	1 (1.4)	0	0	0	1 (0.7)	0	0	0	2 (0.3)
Infections	0	0	0	3 (1.2)	0	0	0	0	0	3 (0.5)
Investigations	1 (2.7)	0	0	1 (0.4)	0	1 (0.7)	0	0	1 (0.3)	2 (0.3)
Musculoskeletal	0	0	0	2 (0.8)	1 (1.4)	1 (0.7)	0	1 (0.8)	1 (0.3)	4 (0.7)
Back Pain	0	0	0	0	0	1 (0.7)	0	1 (0.8)	0	2 (0.3)
Neoplasms, benign and malignant	0	0	0	1 (0.4)	0	0	0	2 (1.6)	0	4 (0.7)
Nervous System	0	0	0	0	0	1 (0.7)	2 (3.2)	1 (0.8)	2 (0.7)	2 (0.3)
Respiratory	0	0	1 (0.8)	2 (0.8)	1 (1.4)	2 (1.4)	0	0	2 (0.7)	4 (0.7)
Pulmonary Embolism	0	0	0	0	1 (1.4)	2 (1.4)	0	0	1 (0.3)	2 (0.3)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); Coded using MedDRA version 16.1
*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Source: modified from Table 14-6.3.1 (CSR-20110109 Module 5.3.5.1) and confirmed with JMP analysis

Adverse Events that Led to Discontinuation of Study Drug
Adverse events leading to discontinuation of IP were reported in 2.2% (n=13) of EvoMab and 1.0% (n=3) of placebo groups (see following table). Small but notable increases in discontinuations include

- Discontinuations from cardiac disorders (cardiac failure, myocardial infarction, supraventricular extrasystoles) was greater in the EvoMab group [3 (0.5%) vs 0].
- Discontinuations from general disorders (chills; injection site erythema/ pruritus/swelling/urticaria) was greater in the EvoMab group [2 (0.3%) vs 0].
- Discontinuations from investigations (CPK or hepatic enzyme increased) were greater in the EvoMab group [2 (0.3%) vs 0].
- Myalgia leading to drug discontinuation was reported by 2 participants (0.3%) in the evolocumab group and none in the placebo group.

Table 20: AEs Leading to Discontinuation of Investigational Product by SOC and Preferred Term Where AE Occurs in > 0 Subjects in Total EvoMab Group, by Background Therapy and Investigational Product in Trial 20110109 (Full Analysis Set - Actual Treatment)

	Diet Only		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10mg**		**TOTAL**	
System Organ Class Preferred Term	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Subjects reporting AEs that led to discontinuation*	**0**	**1 (1.4)**	**1 (0.8)**	**8 (3.1)**	**1 (1.4)**	**3 (2.1)**	**1 (1.6)**	**1 (0.8)**	**3 (1.0)**	**13 (2.2)**
Cardiac Disorders	**0**	**0**	**0**	**1 (0.4)**	**0**	**2 (1.4)**	**0**	**0**	**0**	**3 (0.5)**
Cardiac Failure	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Myocardial Infraction	0	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)
Supraventricular Extrasystoles	0	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)
Gastrointestinal	**0**	**0**	**0**	**1 (0.4)**	**1 (1.4)**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.2)**
Nausea	0	0	0	1 (0.4)	1 (1.4)	0	0	0	1 (0.3)	1 (0.2)
General Disorders	**0**	**1 (1.4)**	**0**	**1 (0.4)**	**0**	**0**	**0**	**0**	**0**	**2 (0.3)**
Chills	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Inj.site erythema	0	1 (1.4)	0	0	0	0	0	0	0	1 (0.2)
Inj.site pruritus	0	1 (1.4)	0	0	0	0	0	0	0	1 (0.2)
Inj.site swelling	0	1 (1.4)	0	0	0	0	0	0	0	1 (0.2)
Inj.site urticaria	0	1 (1.4)	0	0	0	0	0	0	0	1 (0.2)
Investigations	**0**	**0**	**0**	**1 (0.4)**	**0**	**1 (0.7)**	**0**	**0**	**0**	**2 (0.3)**
CK increased	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Hepatic enzyme inc.	0	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)
Musculoskeletal	**0**	**0**	**1 (0.8)**	**2 (0.8)**	**0**	**0**	**0**	**0**	**1 (0.3)**	**2 (0.3)**
Myalgia	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)
Muscle spasms	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Neoplasms, benign and malignant	**0**	**0**	**0**	**1 (0.4)**	**0**	**0**	**0**	**1 (0.8)**	**0**	**2 (0.3)**
Clear Cell Renal ca.	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Ovarian Ca. Mets.	0	0	0	0	0	0	0	1 (0.8)	0	1 (0.2)
Nervous System	**0**	**0**	**0**	**2 (0.8)**	**1 (1.4)**	**0**	**0**	**0**	**1 (0.3)**	**2 (0.3)**
Migraine	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
TIA	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Psychiatric Dis.	**0**	**0**	**0**	**1 (0.4)**	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Nervousness	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Respiratory Dis.	**0**	**0**	**0**	**1 (0.4)**	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Dyspnoea	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)
Skin Disorders	**0**	**0**	**0**	**1 (0.4)**	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Skin odour abnormal	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.2)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous). CK=creatine phosphokinase. TIA=transient ischemic attack. Coded using MedDRA version 16.1
*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Source: modified from Table 14-6.6.1 (CSR-20110109 Module 5.3.5.1) and confirmed with JMP analysis

Four adverse events that led to discontinuation of IP in the evolocumab group were reported as serious and included ovarian cancer metastasis (Subject 10931203003), creatine phosphokinase increased to 14.5 x ULN (Subject 10931202010), cardiac failure (Subject 10923201053; a fatal and positively adjudicated event previously discussed), and myocardial infarction (Subject 10923201092; a fatal and positively adjudicated event previously discussed in the section on fatal events/deaths).

I reviewed the 16 narratives from participants that experienced an adverse event that led to IP discontinuation (13 EvoMab, 3 placebo). The 3 cases of myalgia or muscle spasm that occurred on EvoMab are difficult to evaluate individually due to the participants' concomitant use of atorvastatin which may also cause musculoskeletal adverse reactions. There was one case of increased CPK (Subject 10931202010) that was confounded by the use of atorvastatin 10 mg and the onset of severe hypothyroidism.

Narratives of adverse events that the investigator considered related to evolocumab include:

- Subject 10916300019, a 56 year old male, received the first dose of 420mg QM EvoMab on 24 April 2012 and third (last) dose on 19 June 2012. On 19 June 2012, he developed injection site erythema, injection site pruritus, injection site swelling and injection site urticarial leading to withdrawal of EvoMab. Subject received cetirizine hydrochloride as treatment. The events resolved on the same day. The subject's medical history included thalassemia trait and insulin resistance. There was no relevant concomitant medication. This subject did not develop anti-evolocumab binding antibody.
- Subject 10925203034, a 61 year old female, received the first dose of 420mg EvoMab on 25 May 2012 (she had normal levels of ALT, AST, total bilirubin and alkaline phosphatase) and the last dose on 22 June 2012. The subject's medical history included myxoedema, thyroid surgery, appendicitis, tinnitus, and depression. Relevant concomitant medications included atorvastatin, levothyroxine and venlafaxine hydrochloride. On 25 June 2012 (31 days after the first dose of evolocumab and 3 days after the most recent dose on 22 June 2012), the subject experienced nonserious fatigue. The fatigue was assessed as possibly related to atorvastatin by the investigator, and evolocumab and atorvastatin were put on hold. On 13 July 2012 (49 days after the first dose of evolocumab and 21 days after the most recent dose on 22 June 2012), the subject had asymptomatic hepatic enzyme increased (results from this date not provided) and evolocumab and atorvastatin were permanently discontinued. The subject was evaluated by her personal physician for persistent fatigue, and laboratory testing performed on 17 July 2012 showed ALT 269 U/L (6x ULN; RR 10-45 U/L), TBL normal at 8 µmol/L (RR 5-25 µmol/L), and ALP 177 U/L (<2x ULN; RR 25-105 U/L); AST was not measured. On 20 July 2012, repeat laboratory testing done by the subject's personal physician showed ALT 198 U/L (4.4x ULN), TBL normal at 11 µmol/L, ALP 151 U/L (<2x ULN), and gamma glutamyltransferase 182 U/L (2.4x ULN; RR 10-75 U/L). Hepatitis A and B testing was negative. No imaging testing was performed. On 03 August 2012 at the week 12 visit, ALT, AST, TBL, and ALP were 64 U/L (2x ULN), 44 U/L (<2x ULN), 0.5 mg/dL (normal), and 95 U/L (normal), respectively, and on 10 August 2012 ALT, AST, TBL, and ALP were 41 U/L, 38 U/L, 0.5 mg/dL, and 84 U/L, respectively. There

was no treatment for the event, which was reported as resolved on 13 August 2012. On 17 August 2012, ALT, AST, TBL, and ALP were 47 U/L, 44 U/L, 0.6 mg/dL, and 76 U/L, respectively. On 25 September 2012, the fatigue resolved. The investigator reported the hepatic enzyme increased as related to evolocumab and unrelated to atorvastatin.

- Subject 10966403011, a 46 year old female, received the first dose of 420mg EvoMab on 19 April 2012 and fourth (last) dose on 09 August 2012. On 11 August 2012 (2 days after last dose of EvoMab), the subject experienced chills and nausea leading to withdrawal of EvoMab. The events resolved on 25 August 2012. The subject's medical history included migraine and seasonal allergy. Relevant concomitant medication included atorvastatin.

Adverse Events

Adverse events occurring between the first dose of Investigational Product and End of Study were reported in 74.8% of participants in the evolocumab group and 74.2% in the placebo group. The majority of adverse events were mild (CTCAE grade 1) to moderate (grade 2) in severity.[38] Although the number of AEs is small, there were more AEs of grades ≥3 in the evolocumab group, compared with placebo, in all background therapy groups except for diet only.Adverse events reported in ≥ 5% of participants in either group were nasopharyngitis (10.5% evolocumab, 9.6% placebo), upper respiratory tract infection (9.3% evolocumab, 6.3% placebo), influenza (7.5% evolocumab, 6.3% placebo), and back pain (6.2% evolocumab, 5.6% placebo). There were no events where the incidence was ≥ 5% and the incidence was greater in the placebo group.

Adverse events where there is a notable increase in the EvoMab group include the following system organ class terms (see table below for details):

- Blood and lymphatic system disorders (1.8% evolocumab, 0.3% placebo): primarily due to the preferred term anemia (1.2% evolocumab, 0% placebo)
- Cardiac disorders (4.8% evolocumab, 2.0% placebo): top 4 preferred terms for both groups are palpitations, angina pectoris, ventricular extrasystoles and atrial fibrillation
- Gastrointestinal disorders (4.8% evolocumab, 2.0% placebo): ≥ 1% increase in the preferred terms abdominal pain upper (2.2% evolocumab, 0.7% placebo) and dyspepsia (1.8% evolocumab, 0.7% placebo)

38 NCI Common Terminology Criteria for Adverse Events (CTCAE) was used as the grading scale for adverse events. This grading scale was designed to describe the severity of organ toxicity for patients receiving cancer therapy and has some limitations when used for non-oncology trials. As per protocol, when an AE could not be graded by CTCAE v4.0, the following severity grade could 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 patient was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
5 FATAL

- Infections and infestations (45.9% evolocumab, 43.7% placebo): ≥ 1% increase in the preferred terms upper respiratory tract (9.3% evolocumab, 6.3% placebo), influenza (7.5% evolocumab, 6.3% placebo) and sinusitis (4.2% evolocumab, 3.0% placebo)
- Investigations (5.0% evolocumab, 1.3% placebo): preferred terms of CK, ALT or AST increased account for the majority of cases for the EvoMab group
- Musculoskeletal and connective tissue disorders (26.5% evolocumab, 25.5% placebo): ≥ 1% increase in myalgia (4.0% evolocumab, 3.0% placebo).
- Nervous system disorders (12.0% evolocumab, 11.9% placebo): ≥ 1% increase in the preferred term dizziness (3.7% evolocumab, 2.6% placebo)
- Psychiatric disorders (5.0% evolocumab, 3.6% placebo): ≥ 1% increase in the preferred term anxiety (1.7% evolocumab, 0.7% placebo)
- Renal and urinary disorders (3.3% evolocumab, 1.7% placebo): top 2 preferred terms in the EvoMab group are nephrolithiasis and hematuria
- Respiratory, thoracic and mediastinal disorders (10.9% evolocumab, 11.6% placebo): ≥ 1% increase in the preferred term oropharyngeal pain (2.5% evolocumab, 1.3% placebo)
- Skin and subcutaneous tissue disorders (8.5% evolocumab, 8.9% placebo): ≥ 1% increase in the preferred term of rash (1.8% evolocumab, 0.3% placebo)

Of note, injection site reaction terms (such as erythema, pain, bruising, swelling) are balanced between the two groups (8.7% evolocumab, 8.3% placebo).

Table 21: AEs by SOC and PT by Background Therapy and Investigational Product: Selected from SOC and PT where Total EvoMab > Total Placebo and Occurs in ≥ 2 Subjects in Total EvoMab Group in Trial 20110109 (Full Analysis Set - Actual Treatment)

	Diet Only		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10mg**		**TOTAL**	
System Organ Class Preferred Term	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Subjects reporting AEs*	**30 (81.1)**	**52 (70.3)**	**101 (78.3)**	**201 (79.1)**	**54 (74.0)**	**111 (76.6)**	**39 (61.9)**	**84 (66.7)**	**224 (74.2)**	**448 (74.8)**
Blood/Lymphatic	**0**	**1 (1.4)**	**0**	**5 (2.0)**	**1 (1.4)**	**3 (2.1)**	**0**	**2 (1.6)**	**1 (0.3)**	**11 (1.8)**
Anemia	0	1 (1.4)	0	1 (0.4)	0	0	0	0	0	7 (1.2)
Lymphadenopathy	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)
Cardiac Disorders	**0**	**1 (1.4)**	**2 (1.6)**	**13 (5.1)**	**0**	**5 (3.4)**	**4 (6.3)**	**10 (7.9)**	**6 (2.0)**	**29 (4.8)**
Palpitations	0	0	1 (0.8)	7 (2.8)	0	0	0	0	1 (0.3)	7 (1.2)
Angina Pectoris	0	1 (1.4)	0	1 (0.4)	0	0	2 (3.2)	4 (3.2)	2 (0.7)	6 (1.0)
Ventricular Extrasystoles	0	0	1 (0.8)	2 (0.8)	0	1 (0.7)	1 (1.6)	3 (2.4)	2 (0.7)	6 (1.0)
Atrial Fibrillation	0	0	0	1 (0.4)	0	1 (0.7)	1 (1.6)	1 (0.8)	1 (0.3)	3 (0.5)
Cardiac failure	0	0	0	1 (0.4)	0	0	0	1 (0.8)	0	2 (0.3)
Sinus tachycardia	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)
Endocrine Dis.	**0**	**0**	**1 (0.8)**	**2 (0.8)**	**0**	**4 (2.8)**	**0**	**0**	**1 (0.3)**	**6 (1.0)**
Hypothyroidism	0	0	0	1 (0.4)	0	3 (2.1)	0	0	0	4 (0.7)
Eye Disorders	**0**	**3 (4.1)**	**6 (4.7)**	**10 (3.9)**	**2 (2.7)**	**3 (2.1)**	**1 (1.6)**	**3 (2.4)**	**9 (3.0)**	**19 (3.2)**
Conjunctivitis	0	1 (1.4)	1 (0.8)	3 (1.2)	0	0	0	0	1 (0.3)	4 (0.7)
Cataract	0	1 (1.4)	1 (0.8)	1 (0.4)	0	0	0	0	1 (0.3)	2 (0.3)
Eye haemorrhage	0	0	0	0	0	1 (0.7)	0	1 (0.8)	0	2 (0.3)
Vitreous floaters	0	0	0	0	0	0	0	1 (0.8)	0	2 (0.3)
Gastrointestinal	**2 (5.4)**	**13 (17.6)**	**23 (17.8)**	**48 (18.9)**	**16 (21.9)**	**28 (19.3)**	**7 (11.1)**	**15 (11.9)**	**48 (15.9)**	**104 (17.4)**
Diarrhea	1 (2.7)	2 (2.7)	3 (2.3)	11 (4.3)	0	4 (2.8)	4 (6.3)	1 (0.8)	8 (2.6)	18 (3.0)
Abd. pain upper	0	2 (2.7)	0	8 (3.1)	2 (2.7)	2 (1.4)	0	1 (0.8)	2 (0.7)	13 (2.2)
Dyspepsia	0	3 (4.1)	1 (0.8)	4 (1.6)	1 (1.4)	2 (1.4)	0	2 (1.6)	2 (0.7)	11 (1.8)
Vomiting	0	2 (2.7)	2 (1.6)	7 (2.8)	2 (2.7)	1 (0.7)	1 (1.6)	1 (0.8)	5 (1.7)	11 (1.8)

System Organ Class Preferred Term	Diet Only		Atorvastatin 10mg		Atorvastatin 80mg		Atorvastatin 80mg + Ezetimibe 10mg		TOTAL	
	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Abdominal pain	1 (2.7)	1 (1.4)	0	5 (2.0)	1 (1.4)	0	0	1 (0.8)	2 (0.7)	7 (1.2)
Constipation	0	4 (5.4)	1 (0.8)	1 (0.4)	1 (1.4)	1 (0.7)	0	0	2 (0.7)	6 (1.0)
Toothache	0	0	1 (0.8)	3 (1.2)	0	1 (0.7)	0	0	1 (0.3)	4 (0.7)
Abd. distension	0	0	1 (0.8)	1 (0.4)	0	2 (1.4)	0	0	1 (0.3)	3 (0.5)
Abd. Pain lower	0	0	0	2 (0.8)	0	0	0	1 (0.8)	1 (0.3)	3 (0.5)
Flatulence	0	0	0	1 (0.4)	1 (1.4)	1 (0.7)	0	1 (0.8)	1 (0.3)	3 (0.5)
Food poisoning	0	0	1 (0.8)	2 (0.8)	0	0	0	1 (0.8)	0	3 (0.5)
Haemorrhoids	0	0	0	1 (0.4)	0	1 (0.7)	0	1 (0.8)	0	3 (0.5)
Inguinal hernia	0	0	0	2 (0.8)	0	1 (0.7)	0	0	0	3 (0.5)
Irritable bowel syn.	0	0	0	2 (0.8)	0	0	0	1 (0.8)	0	3 (0.5)
General Disorders	**3 (8.1)**	**7 (9.5)**	**18 (14.0)**	**38 (15.0)**	**9 (12.3)**	**21 (14.5)**	**5 (7.9)**	**14 (11.1)**	**35 (11.6)**	**80 (13.4)**
Inj.site erythema	1 (2.7)	4 (5.4)	4 (3.1)	9 (3.5)	1 (1.4)	1 (0.7)	0	2 (1.6)	6 (2.0)	16 (2.7)
Non-cardiac chest pain	0	0	0	2 (0.8)	0	2 (1.4)	0	4 (3.2)	0	8 (1.3)
Inj.site swelling	0	1 (1.4)	2 (1.6)	5 (2.0)	0	0	0	0	2 (0.7)	6 (1.0)
Pyrexia	0	2 (2.7)	1 (0.8)	2 (0.8)	0	2 (1.4)	0	0	1 (0.3)	6 (1.0)
Inj. site induration	0	1 (1.4)	0	3 (1.2)	0	0	0	1 (0.8)	0	5 (0.8)
Chills	0	0	0	1 (0.4)	0	3 (2.1)	1 (1.6)	0	1 (0.3)	4 (0.7)
Influenza like illness	0	1 (1.4)	1 (0.8)	2 (0.8)	0	1 (0.7)	0	0	1 (0.3)	4 (0.7)
Malaise	0	0	1 (0.8)	2 (0.8)	0	1 (0.7)	0	0	1 (0.3)	3 (0.5)
Hepatobiliary	**1 (2.7)**	**1 (1.4)**	**0**	**3 (1.2)**	**0**	**2 (1.4)**	**0**	**1 (0.8)**	**1 (0.3)**	**7 (1.2)**
Infections/Infestat.	**19 (51.4)**	**38 (51.4)**	**57 (44.2)**	**129 (50.8)**	**30 (41.1)**	**59 (40.7)**	**26 (41.3)**	**49 (38.9)**	**132 (43.7)**	**275 (45.9)**
Nasopharyngitis	3 (8.1)	11 (14.9)	9 (7.0)	29 (11.4)	10 (13.7)	13 (9.0)	7 (11.1)	10 (7.9)	29 (9.6)	63 (10.5)
Upper Respir. Tract	4 (10.8)	6 (8.1)	7 (5.4)	22 (8.7)	2 (2.7)	15 (10.3)	6 (9.5)	13 (10.3)	19 (6.3)	56 (9.3)
Influenza	2 (5.4)	5 (6.8)	8 (6.2)	18 (7.1)	2 (2.7)	8 (5.5)	7 (11.1)	14 (11.1)	19 (6.3)	45 (7.5)
Urinary Tract Infection	4 (10.8)	5 (6.8)	2 (1.6)	9 (3.5)	3 (4.1)	5 (3.4)	2 (3.2)	8 (6.3)	11 (3.6)	27 (4.5)

System Organ Class Preferred Term	Diet Only		Atorvastatin 10mg		Atorvastatin 80mg		Atorvastatin 80mg + Ezetimibe 10mg		TOTAL	
	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Sinusitis	0	3 (4.1)	5 (3.9)	14 (5.5)	2 (2.7)	7 (4.8)	2 (3.2)	1 (0.8)	9 (3.0)	25 (4.2)
Gastroenteritis	2 (5.4)	4 (5.4)	2 (1.6)	8 (3.1)	1 (1.4)	3 (2.1)	1 (1.6)	3 (2.4)	6 (2.0)	18 (3.0)
Viral Upper Resp. tr	0	1 (1.4)	2 (1.6)	6 (2.4)	0	2 (1.4)	1 (1.6)	2 (1.6)	3 (1.0)	11 (1.8)
Cystitis	0	2 (2.7)	3 (2.3)	4 (1.6)	1 (1.4)	1 (0.7)	0	3 (2.4)	4 (1.3)	10 (1.7)
Pharyngitis	1 (2.7)	0	0	6 (2.4)	1 (1.4)	2 (1.4)	0	1 (0.8)	2 (0.7)	9 (1.5)
Gastroenteritis Viral	0	1 (1.4)	1 (0.8)	3 (1.2)	0	1 (0.7)	1 (1.6)	0	2 (0.7)	5 (0.8)
Pneumonia	0	0	1 (0.8)	4 (1.6)	0	1 (0.7)	0	0	1 (0.3)	5 (0.8)
Rhinitis	0	1 (1.4)	0	3 (1.2)	0	0	0	1 (0.8)	0	5 (0.8)
Ear Infection	0	1 (1.4)	1 (0.8)	2 (0.8)	0	1 (0.7)	0	0	1 (0.3)	4 (0.7)
Laryngitis	0	1 (1.4)	0	0	0	0	0	3 (2.4)	0	4 (0.7)
Respir. Tract Infect.	0	0	0	1 (0.4)	0	2 (1.4)	0	1 (0.8)	0	4 (0.7)
Tooth Infection	0	0	2 (1.6)	4 (1.6)	1 (1.4)	0	0	0	3 (1.0)	4 (0.7)
Acute Sinusitis	0	0	0	1 (0.4)	0	1 (0.7)	1 (1.6)	1 (0.8)	1 (0.3)	3 (0.5)
Folliculitis	0	0	0	3 (1.2)	0	0	0	0	0	3 (0.5)
Helicobacter Infect	0	2 (2.7)	0	0	1 (1.4)	0	0	1 (0.8)	1 (0.3)	3 (0.5)
Herpes Zoster	0	0	0	1 (0.4)	1 (1.4)	2 (1.4)	0	0	1 (0.3)	3 (0.5)
Oral Herpes	0	0	1 (0.8)	1 (0.4)	0	1 (0.7)	0	1 (0.8)	1 (0.3)	3 (0.5)
Skin Infection	0	1 (1.4)	0	2 (0.8)	0	0	0	0	0	3 (0.5)
Investigations	**2 (5.4)**	**3 (4.1)**	**1 (0.8)**	**12 (4.7)**	**1 (1.4)**	**7 (4.8)**	**0**	**8 (6.3)**	**4 (1.3)**	**30 (5.0)**
CK increased	0	1 (1.4)	1 (0.8)	4 (1.6)	0	1 (0.7)	0	3 (2.4)	1 (0.3)	9 (1.5)
ALT increased	0	1 (1.4)	0	1 (0.4)	0	2 (1.4)	0	2 (1.6)	0	6 (1.0)
AST increased	0	1 (1.4)	0	0	0	2 (1.4)	0	2 (1.6)	0	5 (0.8)
LFT abnl	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)

System Organ Class Preferred Term	Diet Only		Atorvastatin 10mg		Atorvastatin 80mg		Atorvastatin 80mg + Ezetimibe 10mg		TOTAL	
	Placebo QM (N =37) n (%)	EvoMab QM (N = 74) n (%)	Placebo QM (129) n (%)	EvoMab QM (N =254) n (%)	Placebo QM (N = 73) n (%)	EvoMab QM (N=145) n (%)	Placebo QM (N=63) n (%)	EvoMab QM (N=126) n (%)	Placebo QM (N = 302) n (%)	EvoMab QM (N=599) n (%)
Metabolism/Nutrit.	**2 (5.4)**	**6 (8.1)**	**8 (6.2)**	**6 (2.4)**	**1 (1.4)**	**8 (5.5)**	**1 (1.6)**	**8 (6.3)**	**12 (4.0)**	**28 (4.7)**
Gout	1 (2.7)	1 (1.4)	1 (0.8)	1 (0.4)	0	3 (2.1)	0	0	2 (0.7)	5 (0.8)
Diabetes Mellitus	0	0	0	0	0	2 (1.4)	1 (1.6)	2 (1.6)	1 (0.3)	4 (0.7)
Decreased Appetite	0	0	0	1 (0.4)	0	0	0	0	0	3 (0.5)
Dehydration	0	1 (1.4)	1 (0.8)	2 (0.8)	0	0	0	0	1 (0.3)	3 (0.5)
Hypocalcaemia	0	1 (1.4)	0	0	0	1 (0.7)	0	0	0	2 (0.3)
Hypomagnesaemia	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)
Musculoskeletal	**8 (21.6)**	**16 (21.6)**	**35 (27.1)**	**78 (30.7)**	**24 (32.9)**	**35 (24.1)**	**10 (15.9)**	**30 (23.8)**	**77 (25.5)**	**159 (26.5)**
Back Pain	2 (5.4)	2 (2.7)	8 (6.2)	17 (6.7)	5 (6.8)	7 (4.8)	2 (3.2)	11 (8.7)	17 (5.6)	37 (6.2)
Myalgia	1 (2.7)	1 (1.4)	3 (2.3)	14 (5.5)	5 (6.8)	3 (2.1)	0	6 (4.8)	9 (3.0)	24 (4.0)
Musculoskeletal Pain	1 (2.7)	3 (4.1)	3 (2.3)	5 (2.0)	1 (1.4)	5 (3.4)	4 (6.3)	7 (5.6)	9 (3.0)	20 (3.3)
Tendonitis	0	1 (1.4)	1 (0.8)	5 (2.0)	1 (1.4)	1 (0.7)	1 (1.6)	3 (2.4)	3 (1.0)	10 (1.7)
Neck Pain	0	0	2 (1.6)	4 (1.6)	0	3 (2.1)	1 (1.6)	2 (1.6)	3 (1.0)	9 (1.5)
Muscul. Chest Pain	0	2 (2.7)	1 (0.8)	2 (0.8)	1 (1.4)	1 (0.7)	1 (1.6)	2 (1.6)	3 (1.0)	7 (1.2)
Costochondritis	0	1 (1.4)	0	2 (0.8)	0	0	0	0	0	3 (0.5)
Groin Pain	0	0	0	3 (1.2)	0	0	0	0	0	3 (0.5)
Plantar Fasciitis	0	1 (1.4)	0	1 (0.4)	0	0	1 (1.6)	1 (0.8)	1 (0.3)	3 (0.5)
Synovial Cyst	0	2 (2.7)	0	0	0	1 (0.7)	0	0	0	3 (0.5)
Intervertebral Disc Protrusion	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)

Neoplasms, benign and malignant	**0**	**0**	**3 (2.3)**	**12 (4.7)**	**0**	**3 (2.1)**	**0**	**6 (4.8)**	**3 (1.0)**	**21 (3.5)**
Skin papilloma	0	0	0	3 (1.2)	0	0	0	2 (1.6)	0	5 (0.8)
Benign breast neopl.	0	0	0	4 (1.6)	0	0	0	0	0	4 (0.7)
Nervous System	**2 (5.4)**	**7 (9.5)**	**13 (10.1)**	**31 (12.2)**	**13 (17.8)**	**17 (11.7)**	**8 (12.7)**	**17 (13.5)**	**36 (11.9)**	**72 (12.0)**
Headache	1 (2.7)	3 (4.1)	3 (2.3)	8 (3.1)	4 (5.5)	6 (4.1)	3 (4.8)	7 (5.6)	11 (3.6)	24 (4.0)
Dizziness	0	1 (1.4)	6 (4.7)	11 (4.3)	2 (2.7)	4 (2.8)	0	6 (4.8)	8 (2.6)	22 (3.7)
Hypoaesthesia	0	0	0	2 (0.8)	0	0	1 (1.6)	1 (0.8)	1 (0.3)	4 (0.7)
Paraesthesia	0	0	0	2 (0.8)	0	1 (0.7)	0	1 (0.8)	0	4 (0.7)
Syncope	0	0	0	2 (0.8)	1 (1.4)	1 (0.7)	0	0	1 (0.3)	3 (0.5)
Sinus headache	0	1 (1.4)	0	0	0	0	0	1 (0.8)	0	2 (0.3)
TIA	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)
Psychiatric Dis.	**3 (8.1)**	**4 (5.4)**	**4 (3.1)**	**17 (6.7)**	**0**	**4 (2.8)**	**4 (6.3)**	**5 (4.0)**	**11 (3.6)**	**30 (5.0)**
Anxiety	0	0	0	5 (2.0)	0	2 (1.4)	2 (3.2)	3 (2.4)	2 (0.7)	10 (1.7)
Insomnia	1 (2.7)	2 (2.7)	2 (1.6)	6 (2.4)	0	0	0	1 (0.8)	3 (1.0)	9 (1.5)
Depression	0	1 (1.4)	1 (0.8)	2 (0.8)	0	1 (0.7)	1 (1.6)	1 (0.8)	2 (0.7)	5 (0.8)
Anxiety Disorder	0	0	0	0	0	1 (0.7)	0	1 (0.8)	0	2 (0.3)
Restlessness	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)
Renal/Urinary	**0**	**0**	**4 (3.1)**	**11 (4.3)**	**0**	**5 (3.4)**	**1 (1.6)**	**4 (3.2)**	**5 (1.7)**	**20 (3.3)**
Nephrolithiasis	0	0	0	4 (1.6)	0	2 (1.4)	0	1 (0.8)	0	7 (1.2)
Haematuria	0	0	0	3 (1.2)	0	0	0	1 (0.8)	0	4 (0.7)
Pyuria	0	0	0	2 (0.8)	0	0	0	0	0	2 (0.3)
Reproductive System/Breast Dis.	**1 (2.7)**	**3 (4.1)**	**3 (2.3)**	**9 (3.5)**	**1 (1.4)**	**5 (3.4)**	**1 (1.6)**	**2 (1.6)**	**6 (2.0)**	**19 (3.2)**
Ben. Prostatic Hyper	0	0	0	1 (0.4)	0	1 (0.7)	0	1 (0.8)	0	3 (0.5)
Erectile Dysfunction	0	0	0	3 (1.2)	0	0	1 (1.6)	0	1 (0.3)	3 (0.5)
Ovarian cyst	0	0	0	0	0	2 (1.4)	0	0	0	2 (0.3)
Testicular pain	0	0	0	0	0	2 (1.4)	0	0	0	2 (0.3)
Respiratory Dis.	**4 (10.8)**	**6 (8.1)**	**14 (10.9)**	**33 (13.0)**	**13 (17.8)**	**20 (13.8)**	**4 (6.3)**	**6 (4.8)**	**35 (11.6)**	**65 (10.9)**
Cough	3 (8.1)	4 (5.4)	4 (3.1)	12 (4.7)	2 (2.7)	9 (6.2)	2 (3.2)	2 (1.6)	11 (3.6)	27 (4.5)
Oropharyngeal Pain	0	0	2 (1.6)	9 (3.5)	2 (2.7)	3 (2.1)	0	3 (2.4)	4 (1.3)	15 (2.5)
Skin Disorders	**2 (5.4)**	**9 (12.2)**	**12 (9.3)**	**25 (9.8)**	**7 (9.6)**	**14 (9.7)**	**6 (9.5)**	**3 (2.4)**	**27 (8.9)**	**51 (8.5)**
Rash	1 (2.7)	3 (4.1)	0	4 (1.6)	0	3 (2.1)	0	1 (0.8)	1 (0.3)	11 (1.8)
Dermatitis Contact	0	1 (1.4)	1 (0.8)	1 (0.4)	0	3 (2.1)	0	0	1 (0.3)	3 (0.5)
Erythema	0	0	0	3 (1.2)	1 (1.4)	0	0	1 (0.8)	1 (0.3)	3 (0.5)
Vascular Disorders		**3 (4.1)**	**7 (5.4)**	**13 (5.1)**	**4 (5.5)**	**10 (6.9)**	**3 (4.8)**	**4 (3.2)**	**14 (4.6)**	**30 (5.0)**
Hypertension		3 (4.1)	5 (3.9)	7 (2.8)	1 (1.4)	7 (4.8)	1 (1.6)	2 (1.6)	7 (2.3)	19 (3.2)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous). CK=creatine phosphokinase. TIA=transient ischemic attack. Coded using MedDRA version 16.1
*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Source: modified from Table 14-6.6.1 (CSR-20110109 Module 5.3.5.1) and confirmed with JMP analysis

These findings, in general, were observed in the demographic groups of male, female and age < or ≥ 65 years. In the age ≥ 65 years subgroup (N=138 EvoMab; N=67 Placebo), exceptions included sinusitis (5.8% evolocumab, 9.0% placebo), dizziness (2.9% evolocumab, 3.0% placebo), and depression (2.2% evolocumab, 0% placebo).

The analysis of adverse events that occurred during the target IP exposure period[39] (end of study+28 days) is similar to the findings when adverse events were defined as occurring between the first dose of Investigational Product and End of Study.

Adverse Events in LDL-C Subgroups
Adverse events for 3 subgroups defined by minimum postbaseline LDL-C concentrations (< 25 mg/dL, < 40 mg/dL, or ≥ 40 mg/dL) are provided in the table below. The overall incidence of adverse events in participants in the evolocumab group who achieved postbaseline LDL-C concentrations of < 25 mg/dL (n = 299/398; 75.1%), < 40 mg/dL (n = 391/522; 74.9%) or ≥ 40 mg/dL (n = 53/65; 81.5%) were similar. The number of placebo participants achieving postbaseline LDL-C concentrations of either or < 25 mg/dL or < 40 mg/dL was small (3 and 6 participants, respectively) which does not allow for meaningful comparisons due to the very small sample size. The number of EvoMab-treated patients with a minimum postbaseline LDL-C ≥ 40 mg/dL (N=65) is also small, which affects the ability to make direct comparisons. Note that these comparisons do not preserve randomization, since the groups are defined based on post-randomization assessments. Three of the 6 subgroups have larger sample sizes (EvoMab <25, EvoMab <40 and placebo ≥ 40 mg/dL) which make some descriptive comparisons possible. Some observations include:

- The incidence of cardiac events is similar across the 3 EvoMab groups defined by minimum postbaseline LDL-C level
- The incidence of ALT and AST increases is higher among EvoMab-treated patients with a minimum postbaseline LDL-C≥ 40 mg/dL as compared to the EvoMab-treated patients who achieved LDL-C levels of < 25 or < 40 mg/dL
- Although the number of cases are small, there were more cases of diarrhea, nausea, GERD, injection site pain/erythema, upper respiratory tract infection, bronchitis, viral upper respiratory tract infection, contusion, osteoarthritis, tendonitis, cough, oropharyngeal pain and hypertension among EvoMab-treated patients with minimum postbaseline LDL-C <25 and LDL-C < 40 mg/dL as compared to the EvoMab-treated patients with all LDL-C≥ 40 mg/dL. The remainder of AEs in the table below are either similar across all 3 EvoMab groups or are increased in the EvoMab-treated patients who had all LDL-C≥ 40 mg/dL.

39 Target IP Exposure Period in Months
IP Exposure Period = [min (EOIP Date + 28 days, EOS Date) - First SCIPD +1] / 365.25 * 12
EOIP=End of Investigational Product; EOS= End of study; SCIPD=Dose Date of Investigational Product

- There does not appear to be an increase in reported AEs of diabetes mellitus, musculoskeletal pain, and myalgia among EvoMab-treated patients with lower LDL levels as compared to those with all LDL-C≥ 40 mg/dL.
- There does not appear to be an increase in nervous system disorders in participants achieving low LDL-C levels on EvoMab as compared to participants on placebo or on EvoMab with higher LDL-C levels

Table 22: Subgroup Analysis of Adverse Events That Occurred in ≥ 2 % of Participants (in Any Treatment Group) in Those With Minimum Postbaseline LDL-C Concentrations < 25 mg/dL, < 40 mg/dL or ≥ 40 mg/dL in Trial 20110109 (Full Analysis Set - Actual Treatment)

	LDL-C < 25 mg/dL		LDL-C < 40 mg/dL		LDL-C ≥ 40 mg/dL	
System Organ Class Preferred Term	Placebo QM (N = 3) n (%)	EvoMab 420 mg QM (N = 398) n (%)	Placebo QM (N = 6) n (%)	EvoMab 420 mg QM (N = 522) n (%)	Placebo QM (N = 291) n (%)	EvoMab 420 mg QM (N = 65) n (%)
Any Adverse Event	3 (100.0)	299 (75.1)	4 (66.7)	391 (74.9)	220 (75.6)	53 (81.5)
CARDIAC DISORDERS	1 (33.3)	20 (5.0)	1 (16.7)	25 (4.8)	5 (1.7)	3 (4.6)
Angina Pectoris	1 (33.3)	4 (1.0)	1 (16.7)	4 (0.8)	1 (0.3)	2 (3.1)
EAR AND LABYRINTH DISORDERS	0 (0.0)	11 (2.8)	0 (0.0)	14 (2.7)	14 (4.8)	3 (4.6)
Vertigo	0 (0.0)	2 (0.5)	0 (0.0)	3 (0.6)	5 (1.7)	2 (3.1)
GASTROINTESTINAL DISORDERS	1 (33.3)	70 (17.6)	1 (16.7)	92 (17.6)	47 (16.2)	12 (18.5)
Constipation	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.6)	2 (0.7)	3 (4.6)
Abdominal Pain Upper	0 (0.0)	8 (2.0)	0 (0.0)	11 (2.1)	2 (0.7)	2 (3.1)
Dyspepsia	1 (33.3)	5 (1.3)	1 (16.7)	9 (1.7)	1 (0.3)	2 (3.1)
Diarrhoea	0 (0.0)	13 (3.3)	0 (0.0)	17 (3.3)	8 (2.7)	1 (1.5)
Vomiting	0 (0.0)	8 (2.0)	0 (0.0)	10 (1.9)	5 (1.7)	1 (1.5)
Nausea	0 (0.0)	16 (4.0)	0 (0.0)	20 (3.8)	10 (3.4)	0 (0.0)
Gastroesophageal Reflux Disease	0 (0.0)	7 (1.8)	0 (0.0)	8 (1.5)	8 (2.7)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (33.3)	55 (13.8)	1 (16.7)	73 (14.0)	34 (11.7)	7 (10.8)
Fatigue	0 (0.0)	10 (2.5)	0 (0.0)	11 (2.1)	9 (3.1)	2 (3.1)
Injection Site Bruising	0 (0.0)	4 (1.0)	0 (0.0)	5 (1.0)	6 (2.1)	2 (3.1)
Injection Site Erythema	1 (33.3)	11 (2.8)	1 (16.7)	15 (2.9)	5 (1.7)	1 (1.5)
Injection Site Pain	1 (33.3)	6 (1.5)	1 (16.7)	8 (1.5)	3 (1.0)	0 (0.0)
INFECTIONS AND INFESTATIONS	2 (66.7)	182 (45.7)	3 (50.0)	239 (45.8)	129 (44.3)	36 (55.4)
Nasopharyngitis	1 (33.3)	43 (10.8)	1 (16.7)	53 (10.2)	28 (9.6)	10 (15.4)
Influenza	0 (0.0)	28 (7.0)	0 (0.0)	36 (6.9)	19 (6.5)	9 (13.8)
Upper Respiratory Tract Infection	0 (0.0)	46 (11.6)	0 (0.0)	51 (9.8)	19 (6.5)	5 (7.7)
Urinary Tract Infection	0 (0.0)	14 (3.5)	0 (0.0)	22 (4.2)	11 (3.8)	5 (7.7)
Sinusitis	1 (33.3)	15 (3.8)	1 (16.7)	22 (4.2)	8 (2.7)	3 (4.6)
Gastroenteritis	0 (0.0)	9 (2.3)	1 (16.7)	15 (2.9)	5 (1.7)	3 (4.6)
Bronchitis	0 (0.0)	20 (5.0)	0 (0.0)	25 (4.8)	14 (4.8)	2 (3.1)
Fungal Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	2 (3.1)
Vaginal Infection	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.7)	2 (3.1)
Viral Upper Respiratory Tract Infection	0 (0.0)	9 (2.3)	0 (0.0)	11 (2.1)	3 (1.0)	0 (0.0)

System Organ Class Preferred Term	LDL-C < 25 mg/dL Placebo QM (N = 3) n (%)	LDL-C < 25 mg/dL EvoMab 420 mg QM (N = 398) n (%)	LDL-C < 40 mg/dL Placebo QM (N = 6) n (%)	LDL-C < 40 mg/dL EvoMab 420 mg QM (N = 522) n (%)	LDL-C ≥ 40 mg/dL Placebo QM (N = 291) n (%)	LDL-C ≥ 40 mg/dL EvoMab 420 mg QM (N = 65) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (33.3)	54 (13.6)	1 (16.7)	69 (13.2)	42 (14.4)	7 (10.8)
Muscle Strain	1 (33.3)	9 (2.3)	1 (16.7)	11 (2.1)	9 (3.1)	3 (4.6)
Ligament Sprain	0 (0.0)	2 (0.5)	0 (0.0)	3 (0.6)	3 (1.0)	2 (3.1)
Contusion	0 (0.0)	8 (2.0)	0 (0.0)	8 (1.5)	5 (1.7)	0 (0.0)
Fall	1 (33.3)	3 (0.8)	1 (16.7)	3 (0.6)	4 (1.4)	0 (0.0)
INVESTIGATIONS	0 (0.0)	20 (5.0)	1 (16.7)	24 (4.6)	3 (1.0)	6 (9.2)
Alanine Aminotransferase Increased	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.6)	0 (0.0)	3 (4.6)
Aspartate Aminotransferase Increased	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)	3 (4.6)
Hepatic Enzyme Increased	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (0.3)	1 (1.5)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	21 (5.3)	0 (0.0)	25 (4.8)	12 (4.1)	3 (4.6)
Diabetes Mellitus	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.4)	1 (0.3)	2 (3.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0)	110 (27.6)	0 (0.0)	140 (26.8)	77 (26.5)	19 (29.2)
Musculoskeletal Pain	0 (0.0)	12 (3.0)	0 (0.0)	15 (2.9)	9 (3.1)	5 (7.7)
Back Pain	0 (0.0)	26 (6.5)	0 (0.0)	34 (6.5)	17 (5.8)	3 (4.6)
Myalgia	0 (0.0)	19 (4.8)	0 (0.0)	21 (4.0)	9 (3.1)	3 (4.6)

System Organ Class Preferred Term	LDL-C < 25 mg/dL Placebo QM (N = 3) n (%)	LDL-C < 25 mg/dL EvoMab 420 mg QM (N = 398) n (%)	LDL-C < 40 mg/dL Placebo QM (N = 6) n (%)	LDL-C < 40 mg/dL EvoMab 420 mg QM (N = 522) n (%)	LDL-C ≥ 40 mg/dL Placebo QM (N = 291) n (%)	LDL-C ≥ 40 mg/dL EvoMab 420 mg QM (N = 65) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (CONTINUED)						
Arthralgia	0 (0.0)	18 (4.5)	0 (0.0)	23 (4.4)	14 (4.8)	2 (3.1)
Pain In Extremity	0 (0.0)	10 (2.5)	0 (0.0)	11 (2.1)	13 (4.5)	2 (3.1)
Muscle Spasms	0 (0.0)	10 (2.5)	0 (0.0)	12 (2.3)	8 (2.7)	2 (3.1)
Neck Pain	0 (0.0)	7 (1.8)	0 (0.0)	7 (1.3)	3 (1.0)	2 (3.1)
Osteoarthritis	0 (0.0)	7 (1.8)	0 (0.0)	12 (2.3)	5 (1.7)	0 (0.0)
Tendonitis	0 (0.0)	9 (2.3)	0 (0.0)	10 (1.9)	3 (1.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS	0 (0.0)	47 (11.8)	0 (0.0)	61 (11.7)	36 (12.4)	10 (15.4)
Headache	0 (0.0)	15 (3.8)	0 (0.0)	21 (4.0)	11 (3.8)	3 (4.6)
Dizziness	0 (0.0)	14 (3.5)	0 (0.0)	18 (3.4)	8 (2.7)	3 (4.6)
Migraine	0 (0.0)	4 (1.0)	0 (0.0)	4 (0.8)	3 (1.0)	2 (3.1)
Hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.3)	2 (3.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	46 (11.6)	0 (0.0)	59 (11.3)	35 (12.0)	5 (7.7)
Cough	0 (0.0)	17 (4.3)	0 (0.0)	23 (4.4)	11 (3.8)	4 (6.2)
Nasal Congestion	0 (0.0)	7 (1.8)	0 (0.0)	9 (1.7)	7 (2.4)	1 (1.5)
Oropharyngeal Pain	0 (0.0)	11 (2.8)	0 (0.0)	15 (2.9)	4 (1.4)	0 (0.0)

System Organ Class Preferred Term	LDL-C < 25 mg/dL Placebo QM (N = 3) n (%)	LDL-C < 25 mg/dL EvoMab 420 mg QM (N = 398) n (%)	LDL-C < 40 mg/dL Placebo QM (N = 6) n (%)	LDL-C < 40 mg/dL EvoMab 420 mg QM (N = 522) n (%)	LDL-C ≥ 40 mg/dL Placebo QM (N = 291) n (%)	LDL-C ≥ 40 mg/dL EvoMab 420 mg QM (N = 65) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	33 (8.3)	0 (0.0)	41 (7.9)	27 (9.3)	10 (15.4)
Rash	0 (0.0)	9 (2.3)	0 (0.0)	9 (1.7)	1 (0.3)	2 (3.1)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	2 (3.1)
VASCULAR DISORDERS	0 (0.0)	19 (4.8)	0 (0.0)	26 (5.0)	14 (4.8)	3 (4.6)
Hypertension	0 (0.0)	11 (2.8)	0 (0.0)	17 (3.3)	7 (2.4)	1 (1.5)

N = number of subjects randomized and dosed in the full analysis set and had a minimum postbaseline LDL-C value < 25 mg/dL, < 40 mg/dL or ≥ 40mg/dL; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
Coded using MedDRA version 16.1
Adverse events are adverse events occurring between the first dose of Investigational Product and End of Study.

Low LDL-C group is identified by the minimum postbaseline LDL-C value, whether calculated or UC, in a study period.
Source: Modified from Applicant's Table 14-6-2-401, Table 14-6-2-402, and Table 14-6-2-403 and Table 12-5 (CSR-20110109 Module 5.3.5.1)

This reviewer compared adverse event preferred terms in the four different CV risk groups and four different background therapy groups in this 52-week trial to see if there were any notable differences in adverse event profiles. The number of subjects experiencing a particular AE was small across the treatment arms. There did not appear to be any notable differences in the AE profiles in the four different CV risk/background therapy groups. There were some AE preferred terms that occur more often in the EvoMab group across several of the different CV risk/background therapy groups, examples include abdominal pain or distension, dyspepsia, hypertension, injection site related terms, rash, anxiety, AST increased, ALT increased, diabetes mellitus, nephrolithiasis, cystitis, vertigo, musculoskeletal pain or strain and skin papilloma.

Severity of Adverse Events
The majority of adverse events were mild or moderate in severity; National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 3 adverse events were reported by 7.8% (n=47) and 5.0% (n=15) of subjects in the evolocumab and placebo groups, respectively; and ≥ grade 4 adverse events were reported by 1.0% (n=6) of subjects in the evolocumab group and no subjects in the placebo group. Adverse events ≥ grade 4 in the EvoMab group included the following:

- Cardiac failure-fatal event, Subject 10923201053, diet plus atorvastatin 10 mg
- Myocardial infarction-fatal event, Subject 10923201092, diet plus atorvastatin 80 mg
- Alanine aminotransferase (ALT) increased (ALT > 20 x ULN, asymptomatic, resolved when atorvastatin/EvoMab withheld, EvoMab restarted without recurrence of ALT elevation), Subject 10966415011, diet plus atorvastatin 80 mg, IP dose altered or withheld
- Blood creatine phosphokinase increased (peak CK=14.5, developed severe hypothyroidism with CK and creatinine elevation), Subject 10931202010, diet plus atorvastatin 10 mg, IP withdrawn
- Blood creatine phosphokinase increased (peak CK=10.2, CK < 5xULN on repeat assessment), Subject 10966452044, diet plus atorvastatin 80 mg, IP dose altered or withheld
- Blood creatine phosphokinase increased (peak CK=17.7, CK < 5xULN on repeat assessment), Subject 10957206030, diet plus atorvastatin 80 mg plus ezetimibe 10 mg, IP dose not changed

Additional information for the 4 participants with ALT or CK elevations is provided in the sections discussing ALT and CK laboratory abnormalities.

Adverse Events of Special Interest

Adverse events associated with other lipid lowering therapies (ie, diabetes, liver, and muscle events), other injectable protein therapies (ie, hypersensitivity events, injection site reactions), and those theoretically associated with PCSK9 inhibition (ie, hepatitis C events) were evaluated using Standardized MedDRA Queries (SMQs) (broad and narrow search terms) or Amgen search strategies (see Table below).

- Diabetes events[40]: increase in the EvoMab group, especially in the two groups using atorvastatin 80 mg (8/271, 3.0% EvoMab vs 2/136, 1.5% placebo).
- Hepatitis C: There was no signal for hepatitis C events.
- Hypersensitivity events: numerically greater in the EvoMab group, particularly for the MedDRA high level term of Dermatitis and Eczema (3.0% EvoMab vs 2.0% placebo) and Rashes, Eruptions & Exanthems (1.8% EvoMab vs 0.7% placebo).
- Injection site reactions (ISRs): slight increase in the EvoMab group, (5.7% EvoMab vs 5.0% placebo). Terms include erythema, pain, bruising and swelling
- Rhabdomyolysis/Myopathy: There was no signal on the narrow MedDRA search but the broad MedDRA search was increased (9.2% EvoMab vs 6.6% placebo) based on terms such as muscle pains/myalgia (4.0% EvoMab vs 3.0% placebo).
- Transaminase elevation/hepatic disorder: Increase in the EvoMab group (2.2% EvoMab vs 0.7% placebo) driven primarily by increases in reported adverse events[41] of increased liver transaminases.

Table 23: Summary of Adverse Events Using Narrow Search Strategy for Potential Hepatitis C Infections and Those Potentially Associated with Lipid Lowering Therapies or Injectable Protein Therapies in Trial 20110109 (Full Analysis Set - Actual Treatment)

Adverse Event of Interest	**Diet Only**		**Atorvastatin 10mg**		**Atorvastatin 80mg**		**Atorvastatin 80mg + Ezetimibe 10 mg**		**Total**	
High Level Term	Pbo N=37 n (%)	EvoMab N=74 n (%)	Pbo N=129 n (%)	EvoMab N=254 n (%)	Pbo N=73 n (%)	EvoMab N=145 n (%)	Pbo N=63 n (%)	EvoMab N=126 n (%)	Pbo N=302 n (%)	EvoMab N=599 n (%)
# subjects reporting AE of interest	4 (10.8)	13 (17.6)	17 (13.2)	38 (15.0)	7 (9.6)	17 (11.7)	7 (11.1)	12 (9.5)	35 (11.6)	80 (13.4)
Diabetes Events	0	1 (1.4)	1 (0.8)	0	1 (1.4)	4 (2.8)	1 (1.6)	4 (3.2)	3 (1.0)	9 (1.5)

40 Diabetes events encompass the hyperglycaemia-new onset diabetes mellitus SMQ from MedDRA 16.1. Preferred terms that occurred include diabetes mellitus, type 2 diabetes mellitus, glycosylated haemoglobin increased, and impaired fasting glucose.
41 This reflects adverse events of abnormal transaminases but does not capture all elevations in transaminases based on laboratory criteria alone.

Adverse Event of Interest High Level Term	Diet Only		Atorvastatin 10mg		Atorvastatin 80mg		Atorvastatin 80mg + Ezetimibe 10 mg		Total	
	Pbo N=37 n (%)	EvoMab N=74 n (%)	Pbo N=129 n (%)	EvoMab N=254 n (%)	Pbo N=73 n (%)	EvoMab N=145 n (%)	Pbo N=63 n (%)	EvoMab N=126 n (%)	Pbo N=302 n (%)	EvoMab N=599 n (%)
Hepatitis C	0	0	0	0	0	0	0	0	0	0
Hypersensitivity SMQ	1 (2.7)	10 (13.5)	7 (5.4)	16 (6.3)	3 (4.1)	8 (5.5)	5 (7.9)	1 (0.8)	16 (5.3)	35 (5.8)
Dermatitis and Eczema	1 (2.7)	4 (5.4)	3 (2.3)	9 (3.5)	1 (1.4)	5 (3.4)	1 (1.6)	0	6 (2.0)	18 (3.0)
Rashes/Eruptions/ Exanthems	1 (2.7)	3 (4.1)	0	4 (1.6)	0	3 (2.1)	1 (1.6)	1 (0.8)	2 (0.7)	11 (1.8)
Urticarias	0	1 (1.4)	1 (0.8)	1 (0.4)	0	1 (0.7)	0	0	1 (0.3)	3 (0.5)
Dermatitis to a specific agent	0	1 (1.4)	0	0	0	0	0	0	0	1 (0.2)
Edema NEC	0	0	0	0	1 (0.4)	0	0	0	0	1 (0.2)
Angioedema	0	0	0	0	1 (0.4)	0	0	0	1 (0.3)	0
ISRs	2 (5.4)	4 (5.4)	9 (7.0)	20 (7.9)	3 (4.1)	5 (3.4)	1 (1.6)	5 (4.0)	15 (5.0)	34 (5.7)
IS Erythema	1 (2.7)	4 (5.4)	4 (3.1)	9 (3.5)	1 (1.4)	1 (0.7)	0	2 (1.6)	6 (2.0)	16 (2.7)
IS Pain	1 (2.7)	0	2 (1.6)	5 (2.0)	1 (1.4)	2 (1.4)	0	1 (0.8)	4 (1.3)	8 (1.3)
IS Bruising	0	0	5 (3.9)	3 (1.2)	1 (1.4)	2 (1.4)	0	2 (1.6)	6 (2.0)	7 (1.2)
IS Swelling	0	1 (1.4)	2 (1.6)	5 (2.0)	0	0	0	0	2 (0.7)	6 (1.0)
Rhabdomyolysis-myopathy narrow SMQ	0	0	0	0	0	0	0	0	0	0
Rhabdomyolysis-myopathy broad SMQ	2 (5.4)	6 (8.1)	8 (6.2)	23 (9.1)	6 (8.2)	10 (6.9)	4 (6.3)	16 (12.7)	20 (6.6)	55 (9.2)
Muscle Pains/ Myalgia	1 (2.7)	1 (1.4)	3 (2.3)	14 (5.5)	5 (6.8)	3 (2.1)	0	6 (4.8)	9 (3.0)	24 (4.0)
Transaminase elevation/hepatic disorder	1 (2.7)	2 (2.7)	0	5 (2.0)	1 (1.4)	3 (2.1)	0	3 (2.4)	2 (0.7)	13 (2.2)
Liver Function Analyses	1 (2.7)	1 (1.4)	1 (1.4)	3 (1.2)	1 (1.4)	3 (2.1)	1 (1.4)	2 (1.6)	2 (0.7)	9 (1.5)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab; Pbo=Placebo; ISRs= injection site reactions and includes such terms as injection site erythema, pain, bruising, swelling, induration, pruritus, urticaria, and edema.

Event categories are defined using preferred terms (PT) from MedDRA and either Standard MedDRA Queries (SMQ) or internal groupings. Each event category is defined by a unique set of PT while one PT can be categorized into more than one event category.
Coded using MedDRA version 16.1
Adverse events occurred between the first dose of Investigational Product and End of Study.
Source: Modified from Table 14-2.8.1 and 14-6.8.2 (CSR-20110109 Module 5.3.5.1)

In the table above, a Hypersensitivity SMQ was used to identify cases possibly related to hypersensitivity/allergic reactions. The number of events identified using this approach was slightly higher in the EvoMab group than the placebo group (5.8% vs. 5.3%). To further explore this issue, adverse events were identified using the Anaphylactic Reaction algorithmic SMQ. Listed below are the participants who reported at least one of these adverse events during the treatment period and contained some of the preferred terms from the anaphylactic reaction SMQ (asthma, cough, erythema, eyelid edema, face edema, hypotension, pruritus, pruritus generalized, and rash). There were no deaths or hospitalizations associated with these adverse events. There were no serious events and the AE severity grade was 1 or 2 only. While there were more subjects in the EvoMab group that experienced potential hypersensitivity/allergic reactions, the individual events were often temporally distinct (for example, rash and cough did not occur at the same time). There was no clear signal for anaphylaxis in the EvoMab group.

Placebo

1. Subject ID 20110109-10925202092: pruritus (Study days 111-125 and 228-255), cough (Study days 176-209); drug withdrawn due to pruritus; background therapy: atorvastatin 80mg +Ezetimibe
2. Subject ID 20110109-10966425008: pruritus (Study days 115-117), cough (Study days 51-EOS); dose not changed; background therapy: atorvastatin 80+Ezetimibe

Evolocumab

1. Subject ID 20110109-10914206003[42]: hypotension (Study day 64); erythema,

42 This 69-year-old white female had a medical history that included hypertension, chronic sinusitis, suspected chronic obstructive pulmonary disease, lumbar facet osteoarthritis, diaphragmatic hernia, focal nodular dysplasia, smoking, and hysterectomy. Concomitant medications included hydrochlorothiazide, losartan, salbutamol, omeprazole, ibuprofen, and estradiol/ norgestrel. 143 days after start of evolocumab and 2 days after the most recent dose, the subject experienced facial erythema, eyelid edema, periauricular itching and edema, and headache. All events were grade 1. Blood pressure was not reported. The facial erythema, eyelid edema, and headache were assessed by the investigator as related to evolocumab; the periauricular itching and edema were considered unrelated. Three days later, the subject reported an event of eyelid itching (grade 1, assessed by the investigator as unrelated to evolocumab). All of these events reportedly resolved on this day; no treatment was reported. 199 days after start of evolocumab, 2 days after the most recent dose, and 1 day after receiving triamcinolone injection, the subject experienced grade 1 generalized itching which was assessed by the investigator as related to evolocumab. Blood pressure was not reported. The generalized itching resolved after 1 week; no treatment was reported. No action was taken with evolocumab in response to the events. The subject was subsequently dosed with evolocumab monthly for 5 months and did not report any recurrence of erythema, itching, edema, or hypotension, or any other event potentially related to hypersensitivity.

eyelid edema, pruritus (Study days 143-146); pruritus generalized (Study days 199-206); dose not changed; dose group: EvoMab 420 +atorvastatin 10mg

2. Subject ID 20110109-10931202010[43]: face edema (Study days 152-154), cough (Study days 357-362); dose not changed; dose group: EvoMab 420 + atorvastatin 10mg
3. Subject ID 20110109-10957207007: skin rash on face and chest (Study day 79-ongoing/EOS), cough (Study day 164-185, 258-269, 337-349); dose not changed; dose group: EvoMab 420 + diet
4. Subject ID 20110109-10966425001: rash [Study day 143-155; subject had a concomitant AE of Poison ivy rash, torso (coded Dermatitis contact)], asthma (Study day 27-50); dose not changed; dose group: EvoMab 420 +atorvastatin 80mg
5. Subject ID 20110109-10966426001: erythema (verbatim terms suggestive of ISR)(Study day 309), cough (Study day 359-367); dose not changed; dose group: EvoMab 420 +atorvastatin 80mg+Ezetimibe
6. Subject ID 20110109-10966426023: cough (Study day -14-24, 162-200), erythema (verbatim term “Dime-sized erythema on left side” suggestive of ISR)((Study day 1); dose not changed; dose group: EvoMab 420 + atorvastatin 10mg
7. Subject ID 20110109-10966430022: rash (ongoing-EOS, onset was ~3 months before receiving evolocumab), cough (Study day 322-327); dose not changed;

43 Subject 10931202010 was a 55-year-old woman who developed creatine phosphokinase (CPK) increase, face edema, and cough. Medical history included hypercholesterolemia, hypertension, subclinical hypothyroidism, deep vein thrombosis, chronic pancreatitis, gastroesophageal reflux disease, hyperuricemia, sleep apnea, anxiety, and depression. Concurrent medications included valsartan, rilmenidine, carvedilol, indapamide, rabeprazole, pancreatin, calcium dobesilate, clonazepam, venlafaxine, carbamazepine, allopurinol, alverine citrate/DL methionine, pinaverium bromide, and furosemide. The subject received the first dose of atorvastatin in April 2012 and the first dose of evolocumab in May 2012. Approximately 5 months later, on 14 October 2012, the subject developed face edema. On (b) (6), she developed an increased CPK of 2138 U/L and was referred to the emergency department. Baseline CPK in May 2012 was 134. The subject reported 2 days of dizziness, atypical chest pain, ankle and facial edema but no muscular or skeletal complaints or signs. The subject had bumped against the wall due to dizziness but there were no visible signs of injury or significant tenderness. Serum creatinine was normal at 102 µmol/L (1.15 mg/dL) on presentation to the emergency department. Diuretic therapy was intensified with furosemide, and on 16 October 2012, the facial and ankle edema resolved. Atorvastatin was discontinued on 23 October 2013, and evolocumab was temporarily withheld. Consultation with an immunologist and nephrologist was obtained and CPK and creatinine levels were monitored. Immune serology testing for myositis was negative. On 24 October 2012, CPK was 2549 U/L and creatinine was 143 µmol/L (1.62 mg/dL). CPK and creatinine peaked at 5344 U/L and 177 µmol/L (2.00 mg/dL), respectively, on 27 December 2012 and thyroid stimulating hormone (TSH) was found to be elevated at 191.2 mU/L. TSH values during screening were 2.79 and 6.95 mU/L in March 2012 and May 2012, respectively. Subsequently, severe hypothyroidism was diagnosed and thyroxine replacement was started. Further treatment included indapamide (Apadex), valsartan (Valsacor), rilmenidine (Tenaxum), potassium, spironolactone, esomeprazole, and tolperisone. On 31 January 2013, CPK and creatinine levels decreased to 170 U/L and 124 µmol/L (1.40 mg/dL), respectively, and TSH decreased to 37.210 mU/L. The subject’s last dose of evolocumab prior to the event was 03 October 2012 and the last dose of atorvastatin prior to the event was 14 October 2012; both were discontinued due to increased CPK. On 07 May 2013, approximately 1 year after the first dose of evolocumab and approximately 7 months after the last dose, the subject developed grade 1 nonserious cough. The subject had reported fever on 01 May 2013. The subject was treated with a 1-week course of amoxicillin/clavulanate for cough. The cough was reported as resolved on 12 May 2013.

dose group: EvoMab 420 +atorvastatin 80mg

Positively Adjudicated Events (deaths, myocardial infarction, hospitalization for unstable angina, stroke, and hospitalization for heart failure):

Seven (1.2%) participants in the evolocumab group and 2 (0.7%) participants in the placebo group had positively adjudicated events. Six out of seven cases in the evolocumab group occurred while participants were on-treatment and the remaining case (sudden cardiac death) occurred during the 30-day followup. This participant was in the evolocumab group and had completed the trial 3 weeks before death.

Positively adjudicated events included

- cardiovascular death (evolocumab: 3 [0.5%]; placebo: 0 [0%])
- non-fatal myocardial infarction (evolocumab: 1 [0.2%]; placebo: 0 [0%])
- PCI (evolocumab: 1 [0.2%]; placebo: 1 [0.3%])
- CABG (evolocumab: 0 subjects [0%]; placebo: 1 [0.3%])
- transient ischemic attack (evolocumab: 1 [0.2%]; placebo: 0 [0%])
- myalgia with creatine kinase (CK) elevation (evolocumab: 1 [0.2%]; placebo: 0 [0%])

Of note, while the number of adjudicated CV-related events is too small to make any reliable conclusions regarding CV risk reduction, there are a numerically greater subject incidence of positively adjudicated events, including deaths, in the evolocumab group as compared to placebo (1.2% vs 0.7%).

Laboratory Parameters

Examination of summary statistics for chemistry, hematology and urine values did not reveal any notable trends in laboratory abnormalities. Examination of shift tables for laboratory values revealed the following lab shifts:

- increased creatinine (1 in the placebo group),
- increased glucose (1 in the placebo group, 3 in the evolocumab group)
- decreased potassium (1 in the placebo group)
- increased sodium (1 in the placebo group)
- decreased sodium (1 in the evolocumab group)
- increased INR (1 in the evolocumab group)
- decreased neutrophils (3 in the placebo group, 1 in the evolocumab group)
- decreased white blood cells (1 in the evolocumab group)

Laboratory shifts from baseline for CK, AST and ALT are discussed in the specific sections for these tests.

Creatine Kinase (CK):

The incidence of any postbaseline incidence of CK > 5 x upper limit of normal (ULN) was 7 (1.2%) in the evolocumab group and 1 (0.3%) in the placebo group, respectively. The subject incidence of any postbaseline incidence of CK > 10 x ULN was 3 (0.5%) in the evolocumab group and 1 (0.3%) in the placebo group, respectively (see table). As previously noted, myalgia was reported by 24 participants (4.0%) in the EvoMab group and 9 (3.0%) in the placebo group. As the case report forms did not prespecify to ask participants about myalgias at every visit, it is likely that this spontaneous reporting may be an underestimate of the true incidence of myalgias.

Table 24: Incidence of Creatine Kinase > 5 x ULN or > 10 x ULN by Background Therapy and Investigational Product in Trial 20110109 (Full Analysis Set - Actual Treatment)

	Diet Only		Diet + Atorvastatin 10mg		Diet + Atorvastatin 80mg		Diet + Atorvastatin 80mg + Ezetimibe 10mg		Total	
	Pbo (N = 37) n (%)	EvoMab 420 mg (N = 74) n (%)	Pbo (N = 129) n (%)	EvoMab 420 mg (N = 254) n (%)	Pbo (N = 73) n (%)	EvoMab 420 mg (N = 145) n (%)	Pbo (N = 63) n (%)	EvoMab 420 mg (N =126) n (%)	Pbo (N=302) n (%)	EvoMab 420 mg (N = 599) n (%)
Baseline										
CK > 5 x ULN	0	0	0	0	1 (1.4)	0	0	0	1 (0.3)	0
CK > 10 x ULN	0	0	0	0	1 (1.4)	0	0	0	1 (0.3)*	0
Any Postbaseline Visit										
CK > 5 x ULN	0	0	0	2 (0.8)	1 (1.4)	1 (0.7)	0	4 (3.2)	1 (0.3)	7 (1.2)
CK > 10 x ULN	0	0	0	1 (0.4)	1 (1.4)	1 (0.7)	0	1 (0.8)	1 (0.3)	3 (0.5)
Week 12 visit										
CK > 5 x ULN	0	0	0	0	0	0	0	3 (2.4)	0	3 (0.5)
CK > 10 x ULN	0	0	0	0	0	0	0	0	0	0
Week 24 visit										
CK > 5 x ULN	0	0	0	0	0	0	0	0	0	1 (0.2)
CK > 10 x ULN	0	0	0	0	0	0	0	0	0	1 (0.2)
Week 36 visit										
CK > 5 x ULN	0	0	0	0	1 (1.4)	1 (0.7)	0	1 (0.8)	1 (0.3)	2 (0.3)
CK > 10 x ULN	0	0	0	0	1 (1.4)	1 (0.7)	0	1 (0.8)	1 (0.3)	2 (0.3)
Week 52 visit										
CK > 5 x ULN	0	0	0	1 (0.4)	0	1 (0.7)	0	0	0	2 (0.3)
CK > 10 x ULN	0	0	0	0	0	0	0	0	0	0

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab ; Pbo=placebo;
ULN = upper limit of normal
*This subject did not contribute to any of the post-baseline elevations reported.
Summary is based on observed data and no imputation is used for missing values.
Source: modified from Table 12-7 (CSR-20110109 Module 5.3.5.1)

As summarized in the table below, 5 of the 8 participants had physical activity associated with their CK elevations. Seven of 8 participants completed IP. For 6 participants, CK returned to < 5 x ULN by the next assessment; for 1 participant, CK remained elevated at the EOS visit (Subject 10925201014), and for another participant, CK remained elevated for several subsequent assessments. CK was < 5 x ULN at the EOS visit, which was approximately 7 months after her last dose of study drug (Subject 10931202010).

Subject 10931202010 was a 55-year-old woman with a history of subclinical hypothyroidism with normal thyroid stimulating hormone at screening as well as hypercholesterolemia and hypertension. Concurrent medications included valsartan, rilmenidine, carvedilol, indapamide, rabeprazole, pancreatin, calcium dobesilate, clonazepam, venlafaxine, carbamazepine, allopurinol, alverine citrate/DL methionine, pinaverium bromide, and furosemide. During the study, this participant developed severe hypothyroidism with CK elevation and renal failure as described below:

> Approximately 5 months after starting evolocumab, she developed an increased CPK of 2138 U/L and was referred to the emergency department. Baseline CPK was 134. She reported 2 days of dizziness, atypical chest pain, ankle and facial edema but no muscular or skeletal complaints or signs. Serum creatinine was normal at 102 µmol/L (1.15 mg/dL) on presentation to the emergency department. Diuretic therapy was intensified with furosemide. Atorvastatin and evolocumab were permanently discontinued. Consultation with an immunologist and nephrologist was obtained and CPK and creatinine levels were monitored. Immune serology testing for myositis was negative. CPK and creatinine peaked at 5344 U/L and 177 micromol/L (2.00 mg/dL), respectively, approximately 2 months after presenting to the emergency room and thyroid stimulating hormone (TSH) was found to be elevated at 191.2 mU/L. TSH values during screening were 2.79 and 6.95 mU/L approximately one month later but prior to starting atorvastatin or evolocumab. Subsequently, severe hypothyroidism was diagnosed and thyroxine replacement was started. Further treatment included indapamide (Apadex), valsartan (Valsacor), rilmenidine (Tenaxum), potassium, spironolactone, esomeprazole, and tolperisone. Approximately one month later, CPK and creatinine levels decreased to 170 U/L and 124 micromol/L (1.40 mg/dL), respectively and TSH decreased to 37.2 mU/L. The event was adjudicated as "myalgia with CK elevation".

Table 25: Summaries from Participants with Postbaseline Creatine Kinase Concentrations > 5 Times the Upper Limit of Normal in Trial 20110109

Subject Number (age/sex; race) Group	Peak CK (U/L)	Peak CK (x ULN[a])	Associated Exertion	CK < 5 x ULN on Repeat Assessment	CK AE[b] Yes/No	CK AE[b] Severity	Continued IP
10966424001 (57/M; White) Placebo +	3848	19.4	Yes	Yes	No	–	Yes

atorvastatin 80 mg							
10925201014 (65/M; White) EvoMab + atorvastatin 10 mg	1012	5.1	Yes	No (end of study)	Yes	Grade 3	Yes
10931202010 (55/F; White) EvoMab + atorva 10 mg (see narrative above)	2453	14.5	No[c]	No (resolved by end of study)	Yes	Grade 4	No
10957203009 (50/M; Asian) EvoMab + atorvastatin 80 mg + ezetimibe 10 mg	1050	5.3	Yes[d]	Yes	No	_	Yes
10957206030 (51/M; White) EvoMab + atorvastatin 80 mg + ezetimibe 10 mg (see narrative below)	3496	17.7	Yes	Yes	Yes	Grade 4	Yes
10957208038 (62/M; White) EvoMab + atorvastatin 80 mg + ezetimibe 10 mg	1409	7.1	Yes	Yes	Yes	Grade 3	Yes
10966430029 (57/F; Black) EvoMab + atorva 80 mg + ezetimibe 10 mg	1442	8.5	No	Yes	Yes	Grade 3	Yes
10966452044 (63/F; White) EvoMab + atorva 80 mg (see narrative below)	1730	10.2	No	Yes	Yes	Grade 4	Yes

CK = creatine kinase, ULN = upper limit of normal, IP = investigational product;
[a] CK ULN for males = 198 U/L; CK ULN for females = 169 U/L
[b] CTCAE grade of reported treatment emergent adverse event with a preferred term of "blood creatine phosphokinase increased"
[C] Subject had a history of subclinical hypothyroidism with normal TSH at screening. The subject was assigned to the diet + atorvastatin 10 mg evolocumab group. During the study, the subject developed severe hypothyroidism with CK elevation and renal failure. Treatment with Levothyroxine was initiated. The event was adjudicated as "myalgia with CK elevation". CK< 5 x ULN by end of study assessment
[d] Subject had mechanical backstrain plus intramuscular injection of diclofenac one day prior to the blood draw
Source: Modified from Table 12-8 (CSR-20110109 Module 5.3.5.1)

10957206030 10957206030: 51-year-old male, enrolled in the parent study 20110109, IP evolocumab QM 420 mg (rolled over to Year 1 SoC-controlled study 20120138, IP evolocumab QM 420 mg). The baseline CK in the parent study was 181 U/L (WNL). CK levels were elevated twice during screening in the parent study [241U/L (1.2xULN), 6 weeks prior and 317 U/L (1.6xULN), 1 week prior to the first dose). Approximately 9 months after the first dose in parent study, and 4 weeks after the last dose of evolocumab QM 420 mg, the

subject's CK increased to 3496 U/L (17.7xULN), and this was reported as the adverse event blood creatine phosphokinase increased. Creatinine was WNL (0.9 mg/dL). AST was 2xULN (72 U/L). One week later, the CK levels decreased to 590 U/L (3xULN). The adverse event was considered resolved when the CK decreased to 329 U/L (1.7xULN). Twenty-two weeks after the last dose in the parent study, the subject was administered the first dose of evolocumab QM 420 mg in the year 1 SoC-controlled study. The baseline CK level on this date was 2504 U/L (12.7x ULN), AST was 79 U/L (2.2xULN), ALT was 60 U/L (1.4xULN), and creatinine was 0.98 mg/dL (WNL). Seven days later, CK had fallen to 235 U/L (1.2xULN). Nine weeks after the elevated baseline CK level, CK was 161 U/L (WNL), AST was 56 U/L (1.6xULN), ALT was 79 U/L (1.8xULN), and creatinine was 0.96 (WNL). Pertinent medical history included increased CK levels and arthralgia. Pertinent concomitant medications included atorvastatin 80 mg, ezetimibe and acetylsalicylic acid. The subject continued treatment with evolocumab. The investigator assessed the event as unrelated to IP. This reviewer believes the atorvastatin, and potentially the evolocumab, contributed to this CK increase.

10966452044: 63-year-old female enrolled in the parent study 20110109, evolocumab QM 420 mg with atorvastatin 80mg background therapy (rolled over into Year 1 SoC-controlled study 20120138, assigned to SoC only). Baseline CK was 95 U/L (WNL) on the date of the first dose. At Week 36, approximately 9 months after the first dose and 4 weeks after the last dose of evolocumab QM 420 mg, the subject's CK increased to 1730 U/L. AST was 66 U/L (1.9xULN), ALT was 87 U/L (2.6xULN), and creatinine was 0.9 mg/dL (WNL). The peak at week 36 was preceded by an elevated CK of 588 U/L (3.5xULN) at week 24. After the peak, CK continued to be elevated 9 days later (1205 U/L, 7xULN), 1 month later (797 U/L, 4.7xULN), and 2 months later (853 U/L, 5xULN). The subject had IP withheld at week 36, restarted at week 44, and completed the rest of the dosing ending at week 52. At the end of the parent study (in week 52) the CK was 314 U/L (1.9xULN), although the adverse event was judged to be resolved at this time. At the beginning of the Year 1 SoC-controlled study, in which the patient was assigned to SoC, the atorvastatin dose was reduced to 20 mg. On this dose, and approximately 25 weeks after the last dose of evolocumab, the subject's CK increased to 1243 U/L (7.4xULN). The investigator assessed the blood creatine phosphokinase increased adverse event as not related to IP. This reviewer believes the atorvastatin, and potentially the evolocumab, contributed to the CK increase at Week 36. Evolocumab was not likely to be related to the CK increase in the Year 1 study.

Liver Transaminases (ALT/AST):
At baseline, 1 (0.2%) participant in the evolocumab group and 3 (1.0%) in the placebo group had ALT or AST > 3 x ULN; none in the evolocumab group and 1 (0.3%) in the placebo group had ALT or AST > 5 x ULN at baseline; and none in the evolocumab group and 1 (0.3%) in the placebo group had Total Bilirubin > 2 x ULN at baseline.

The participant incidence of any postbaseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN was 5 (0.8%) in the evolocumab group and 3 (1.0%) in the placebo group. The participant incidence of any postbaseline ALT or AST > 5 x ULN was 3 (0.5%) in the evolocumab group and 1 (0.3%) in the placebo group. The participant incidence of any postbaseline total bilirubin > 2 x ULN was 5 (0.8%) in the evolocumab group and 1 (0.3%) in the placebo group. No participant

had an ALT or AST >3 x ULN and a total bilirubin > 2 x ULN at any postbaseline visit (Hy's Law).

Table 26: Incidence of Liver Test Abnormality in Participants in Trial 20110109 (Full Analysis Set - Actual Treatment)

	Diet Only		Atorvastatin 10mg		Atorvastatin 80mg		Atorvastatin 80mg + Ezetimibe 10 mg		Total	
	Pbo N=37 n (%)	EvoMab N=74 n (%)	Pbo N=129 n (%)	EvoMab N=254 n (%)	Pbo N=73 n (%)	EvoMab N=145 n (%)	Pbo N=63 n (%)	EvoMab N=126 n (%)	Pbo N=302 n (%)	EvoMab N=599 n (%)
Baseline										
ALT or AST > 3 x ULN	0	1 (1.4)	1 (0.8)	0	2 (2.7)	0	0	0	3 (1.0)	1 (0.2)
ALT or AST > 5 x ULN	0	0	0	0	1 (1.4)	0	0	0	1 (0.3)	0
Total bilirubin > 2 x ULN	0	0	1 (0.8)	0	0	0	0	0	1 (0.3)	0
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR>1.5)	0	0	0	0	0	0	0	0	0	0
Any Post-Baseline visit										
ALT or AST > 3 x ULN	1 (2.7)	0	0	1 (0.4)	2 (2.7)	1 (0.7)	0	3 (2.4)	3 (1.0)	5 (0.8)
ALT or AST > 5 x ULN	1 (2.7)	0	0	0	0	1 (0.7)	0	2 (1.6)	1 (0.3)	3 (0.5)
Total bilirubin > 2 x ULN	0	0	1 (0.8)	0	0	1 (0.7)	0	4 (3.2)	1 (0.3)	5 (0.8)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR>1.5)	0	0	0	0	0	0	0	0	0	0

N = number of subjects randomized and dosed in the full analysis set with normal baseline ALT and AST; EvoMab = Evolocumab; Pbo = placebo; ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = International Normalized Ratio.
ALT ULN for males = 43 U/L; ALT ULN for females = 34 U/L; AST ULN for males = 36 U/L; AST ULN for females = 34 U/L.
Summary is based on observed data and no imputation is used for missing values.
Source: modified from Table 14-7.50.1 (CSR-20110109 Module 5.3.5.1) and FDA JMPSTART liver labs analysis

*Additional information on the participant who experienced ALT > 20 times the upper limit of normal is provided below:

Subject # 10966415011: 57-year-old white woman who developed increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT).

The subject's medical history included hypercholesterolemia, hot flushes, menopause, headache, and diarrhea. Concomitant medications while on study included ibuprofen, multivitamins, and Lactobacillus acidophilus. The subject was not receiving a statin before entering in the study.

The subject received the first dose of atorvastatin 80mg on 14 March 2012 and the first dose of evolocumab on 18 April 2012. On 07 March 2012 and 11 April 2012, prior to the baseline, laboratory test values for AST, ALT, and alkaline phosphatase (AP) were below the laboratory upper limit of normal (ULN). Baseline laboratory tests on 18 April 2012 obtained prior to the first dose of evolocumab revealed ALT of 50 U/L (1.5xULN; ULN was 34 U/L), AST of 33 U/L (ULN 34 U/L), and AP of 145 U/L (1.2xULN; ULN 123 U/L).

Approximately 3 months after the first dose of evolocumab, laboratory tests showed ALT of 695 U/L (20.4xULN) and AST of 539 U/L (15.6xULN). Additional results included AP of 319 U/L, lactate dehydrogenase of 237 U/L (ULN 234 U/L), total bilirubin of 0.5 mg/dL, direct bilirubin of 0.3 mg/dL, and fasting glucose of 113 mg/dL. On this same date (10 July 2012), the investigator advised the subject to discontinue atorvastatin. Evolocumab had already been administered that day, but was withheld subsequently. Laboratory results of samples collected on 16 July 2012 were negative for hepatitis B core antibody, hepatitis C virus, and hepatitis A virus immunoglobulin M. Additional results included AP of 275 U/L, ALT of 631 U/L (18.6xULN), AST of 414 U/L (12.2xULN), lactate dehydrogenase of 237 U/L, prothrombin time of 10.4 sec, international normalized ratio (INR) of 0.9, total bilirubin 0.6 mg/dL, direct bilirubin 0.3 mg/dL, hemoglobin 12.2 g/dL, hematocrit of 38%, and white blood cell (WBC) count 5.11 x 10^3/µL. On this date (16 July 2012), the subject stated that she had no symptoms, had no change in her concomitant medications, and denied pain or any other side effects due to medication or any additional alcohol consumption. On 18 July 2012, at her scheduled week 13 visit, the subject reported feeling well without any nausea, itching, anorexia or fever. The subject's blood pressure was 128/79 mmHg, pulse rate was 79 per minute, and physical examination was normal. Analysis of urine collected on 19 July 2012 revealed specific gravity of 1.026, pH of 5.5, normal glucose, RBC count of 1/high power field (HPF), and WBC count of 1/HPF and the sample was negative for protein, bilirubin, and blood. The investigator noted that the event was "probable atorvastatin-hepatitis". No treatment was given for the events.

On 08 August 2012, the subject's liver tests returned to baseline (AST 25 U/L, ALT 26 U/L, AP 100 U/L, total bilirubin of 0.3 mg/dL, direct bilirubin 0.1 mg/dL, and lactate dehydrogenase 161 U/L), and the end date for the events of increased AST and increased ALT was reported as 08 August 2012. Laboratory results of a blood sample collected on 17 October 2012 included total bilirubin 0.4 mg/dL, direct bilirubin 0.1 mg/dL, AP 86 U/L, AST 25 U/L, and ALT 14 U/L. Evolocumab was restarted on 17 October 2012, but atorvastatin was not. Laboratory test results obtained on 14 November 2012 revealed AP of 70 U/L, ALT of 13 U/L, and AST of 18 U/L. On 12 December 2012, results were total AP of 68 U/L, ALT of 15 U/L, and AST of 21 U/L. The subject's last dose of evolocumab was on 10 January 2013, as the subject requested to discontinue treatment on 20 February 2013 "due to not being provided a statin to finish study with." Laboratory tests performed on 16 January 2013 had shown

AP of 71 U/L, ALT of 15 U/L, and AST of 20 U/L. Repeated laboratory tests performed at an end-of-study visit on 16 April 2013 showed AP of 72 U/L, ALT of 13 U/L, and AST of 20 U/L.

The investigator reported that there was a reasonable possibility that the events of increased AST and increased ALT were related to evolocumab. Atorvastatin was reported as a co-suspect. This reviewer concurs with this assessment. As the hepatic enzyme tests started to increase with atorvastatin prior to the addition of evolocumab and did not increase with the re-challenge of evolocumab as monotherapy (atorvastatin 80 mg was not re-started), the statin appears to be the primary suspect.

This reviewer also looked at participants who had normal AST/ALT levels at baseline. The incidence of postbaseline ALT, AST or total bilirubin elevations was equal between the two treatment groups.

Steroid Hormones:
One of the theoretical concerns with PCSK9 inhibitors was that the marked plasma LDL-C lowering (with or without a statin) could secondarily impact other cholesterol-related processes. The adrenal glands are heavily dependent on cholesterol for hormone production, and evolocumab might be expected to affect adrenal function. No effects on the adrenal were noted in hamsters administered evolocumab for 28 days, at doses which represents 112, 48 and 20X the maximum recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W doses, respectively, based on AUC. Evolocumab, administered for up to 6 months, did not cause any effects on the adrenal of monkeys at doses which represent 744, 300 and 134X the recommended human doses of 140 mg Q2W, 420 mg QM and 420 mg Q2W, respectively. Adrenal-derived hormones were not directly measured in any animal study.

In the clinical trials, samples for steroid hormone analyses (ACTH, FSH, LH, cortisol, testosterone, estradiol) were collected at baseline, Week 24, and Week 52. Analysis was done for each treatment group (FAS) as well as the FAS excluding those participants who took hormone replacement therapy (HRT). Following treatment with evolocumab, no notable trends were seen for changes from baseline in the steroid hormones of ACTH, FSH, LH and testosterone. For cortisol, there was an increase in cortisol seen in the EvoMab group at Week 52 that was not observed in the placebo group.

Change from Baseline to Week 52:
ACTH:

- FAS: (data available for 48 placebo and 110 EvoMab participants):
  - Mean change: -0.2 pmol/L for both groups.
  - Median change: EvoMab 0.3 pmol/L; Pbo 0 pmol/L.
  - No notable difference was seen when subjects on HRT were excluded.

FSH:

- FAS: (data available for 251 placebo and 481 EvoMab participants):
  - Mean change: EvoMab 0.7 IU/L; Pbo 0.9 IU/L.
  - Median change: EvoMab -0.2 IU/L; Pbo 0 IU/L.
  - No notable difference was seen when subjects on HRT were excluded.

LH:

- FAS: (data available for 251 placebo and 481 EvoMab participants):
  - Mean change: EvoMab 0 IU/L; Pbo -0.2 IU/L.
  - Median change: -0.2 IU/L for both groups.
- FAS without HRT group: results are the same

Cortisol:

- FAS at Week 52: (data available for 252 placebo and 481 EvoMab participants):
  - Mean change: EvoMab 24.1 nmol/L; Pbo 1.4 nmol/L.
  - Median change: EvoMab 24.4 nmol/L; Pbo 5.5 nmol/L.
  - No notable difference was seen when subjects on HRT were excluded.

Testosterone:

- FAS: (data available for 251 placebo and 481 EvoMab participants):
  - Mean change: EvoMab -0.2 nmol/L; Pbo 0.03 nmol/L.
  - Median change: EvoMab 0 nmol/L; Pbo 0 nmol/L.
- FAS without HRT group: (data available for 242 placebo and 468 EvoMab participants):
  - Mean change: EvoMab -1.3 nmol/L ; Pbo 0.09 nmol/L.
  - Median change: EvoMab 0 nmol/L; Pbo 0 nmol/L.

Estradiol

- FAS: (data available for 252 placebo and 481 EvoMab participants):
  - Mean change: EvoMab: 0.5 pmol/L; Pbo -15.6 pmol/L
  - Median change: EvoMab 3.7 pmol/L; Pbo 0 pmol/L.
  - No notable difference was seen when subjects on HRT were excluded.

Ad hoc analyses for the FAS excluding subjects who received HRT were examined for the following steroid hormone analyses and subgroups:

- FSH for women with baseline FSH < 25 IU/L and < 50 years of age and for men with baseline LH < 15 IU/L
- LH for women baseline FSH < 25 IU/L and < 50 years of age and for men with baseline LH < 15 IU/L
- estradiol for women with baseline FSH < 25 IU/L and < 50 years of age
- testosterone for men

FSH and LH were relatively stable in both men and women throughout the study. Testosterone levels in men were relatively constant throughout the trial. Estradiol levels for women with baseline FSH < 25 IU/L and < 50 years of age (data available for 14 placebo and 38 EvoMab participants) decreased at Week 24 in the EvoMab group compared to the placebo group:

- Mean change from baseline to Week 24: EvoMab -109 IU/L; Pbo 68 IU/L.
- Median change: EvoMab -28 IU/L; Pbo 6 IU/L.

This decrease was not seen at Week 52:

- Mean change from baseline to Week 52: EvoMab 22 IU/L; Pbo 32 IU/L.
- Median change: EvoMab 7 IU/L; Pbo 20 IU/L.

Vitamin E:
Lipoproteins are the major carriers of plasma lipid-soluble antioxidants, including vitamin E. Plasma α-tocopherol levels are well correlated with plasma lipid levels.[44] In humans, relative lipoprotein distribution analysis indicates that tocopherols are mostly transported in LDL and HDL at similar proportions with less than 20% carried in VLDL and other lipoproteins[45]. Thus, plasma vitamin E homeostasis is intimately connected to mechanisms underlying normal lipoprotein metabolism in vivo.[44] Patients given PCSK9 inhibitors may develop very low LDL-C levels but the HDL-C levels do not decrease with PCSK9 inhibitor therapy. This is important because HDL is also a major carrier of plasma α-tocopherol as well as an efficient source of vitamin E for cellular uptake.

The mean and median concentration of normalized serum vitamin E at Week 52 was similar to baseline concentrations for both the evolocumab and placebo groups. The mean and median concentration of total serum vitamin E at all postbaseline timepoints is decreased in the evolocumab group as compared to placebo and baseline values. This was expected as vitamin E is a fat-soluble vitamin and plasma concentrations decrease as the concentration of lipoproteins (such as chylomicrons, VLDL-C and LDL-C) transporting vitamin E decrease.

Table 27: Serum Vitamin E in µmol/L and Normalized Serum Vitamin E in µmol/L in Trial 20110109 (Full Analysis Set - Actual Treatment)

	Vitamin E		Normalized Vitamin E	
	Placebo QM (N=302)	EvoMab 420 mg QM (N=599)	Placebo QM	EvoMab 420 mg QM (N=599)
Baseline				

44 Rigotti A. Absorption, transport, and tissue delivery of vitamin E. Molecular Aspects of Medicine 28 (2007) 423–436.
45 Perugini, C., Bagnati, M., Cau, C., Bordone, R., Paffoni, P., Re, R., Zoppis, E., Albano, E., Bellomo, G., 2000. Distribution of lipid-soluble antioxidants in lipoproteins from healthy subjects. Effects of in vivo supplementation with a-tocopherol. Pharmacol. Res.2000. 41, 65–72.

n	295	591	295	591
Mean	33.8	32.8	7.3	7.2
SE	0.5	0.4	0.1	0.1
Median	32.3	31.3	7.1	7.0
Q1,Q3	28.3, 37.8	26.7, 37.2	6.3, 8.1	6.2, 8.0
Week 12				
n	289	556	289	555
Mean	33.5	24.1	7.1	7.9
SE	0.6	0.3	0.1	0.1
Median	32.0	23.5	6.7	7.8
Q1,Q3	27.2, 38.1	19.3, 27.7	6.0, 7.9	6.9, 9.0
Week 24				
n	283	556	281	550
Mean	34.1	25.4	7.3	8.3
SE	0.5	0.3	0.1	0.1
Median	32.5	24.6	7.0	8.1
Q1,Q3	28.3, 38.3	20.0, 29.3	6.3, 8.1	7.1, 9.2
Change from baseline to Week 24				
n	278	549	276	544
Mean	0.4	-7.5	0.0	1.1
Median	0.0	-7.2	-0.1	1.0
Week 36				
n	276	539	265	522
Mean	32.4	24.0	6.9	7.8
SE	0.5	0.3	0.1	0.1
Median	31.5	23.0	6.9	7.5
Q1,Q3	26.5, 37.0	18.8, 28.3	5.9, 7.8	6.6, 8.7
Week 52				
n	273	534	258	509
Mean	34.5	26.5	7.2	8.2
SE	0.5	0.4	0.1	0.1
Median	33.7	25.1	7.0	8.0
Q1,Q3	28.8, 38.3	20.9, 30.2	6.2, 7.9	7.0, 9.2
Change from baseline to week 52				
n	268	528	253	503
Mean	0.6	-6.7	-0.1	1.0
Median	0.2	-6.7	-0.1	0.9

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous).
Normalized Serum Vitamin E = Serum Vitamin E (µmol/L) / Total Cholesterol (mmol/L)
Summary is based on observed data and no imputation is used for missing values.
Source: Modified from Table 14-7.52.1, Table 14-7.52.4 and Table 12-11 (CSR-20110109 Module 5.3.5.1)

Vitamin E Substudy

To evaluate the potential impact of evolocumab dosing on vitamin E levels, 100 participants (55 in the evolocumab group and 45 in the placebo group) were enrolled in the vitamin E substudy. The goal of the substudy was to provide additional data

exploring whether evolocumab affected vitamin E concentrations in specific lipid components[46,47] (serum vitamin E, LDL-C vitamin E, HDL-C vitamin E, red blood cell (RBC) vitamin E, and non-HDL-C vitamin E). The concentration of vitamin E in RBCs was measured to evaluate the tissue levels of vitamin E.[48] The RBC vitamin E assay was selected as the most appropriate method for tissue measurements by the applicant because it does not require a tissue biopsy and had previously been used in a study of a microsomal triglyceride transfer protein (MTP) inhibitor. These components were summarized (both absolute values and values normalized against the cholesterol concentration in the relevant component [eg, normalized HDL-C vitamin E was normalized by dividing the vitamin E concentration by the HDL-C concentration]) for each treatment group at each scheduled visit. These analyses were also repeated with exclusion of participants who had received any vitamin E supplementation[49] during the study. There were 36 placebo and 44 evolocumab participants in the substudy that did not receive vitamin E supplements or multivitamins containg vitamin E.

The baseline demographics and baseline lipid parameters for the Vitamin E substudy group was consistent with the FAS.

The table below provides the changes in serum and normalized serum vitamin E in the lipid components in the vitamin E substudy. The mean and median total vitamin E (µmol/L) in the placebo group was stable from baseline to Week 12 and decreased slightly from Week 12 to Week 52. As expected, the total vitamin E declined in the evolocumab group over 52 weeks. However, total vitamin E normalized by total cholesterol remained stable in both groups. This is likely the same reasoning as was given for the FAS results; namely, the decrease in total vitamin E resulted from a reduction in total cholesterol while the concentration of vitamin E in cholesterol containing lipoproteins, represented by the normalized vitamin E values, was not changed.

Similarly, mean LDL vitamin E (µmol/L) in the placebo group was stable from baseline to Week 12 and decreased slightly from Week 12 to 52, while LDL vitamin E declined over time in the evolocumab group. LDL vitamin E normalized by LDL-C remained largely stable in both groups at baseline, Week 12, and Week 52.

46 Ford L, Farr J, Morris P, Berg J. The value of measuring serum cholesterol-adjusted vitamin E in routine practice. Ann Clin Biochem. 2006; 43 (Pt 2):130–134
47 Horwitt MK, Harvey CC, Dahm CH Jr, et al. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. Ann NY Acad Sci. 1972;203:223-236.
48 Saito M, Nakatsugawa K, Ohhashi A, Nishimuta M, Kodama N. Comparison of vitamin-E levels in human plasma, red-blood-cells, and platelets following varying intakes of vitamin-E. J Clin Biochem Nutr. 1992;12:59-68.
49 In the analysis of the Study 20110109 vitamin E substudy, a medication containing vitamin E, including a multivitamin, would have resulted in excluding a subject from the analysis.

Mean HDL vitamin E (µmol/L) concentrations and HDL vitamin E normalized by HDL-C in both the placebo and evolocumab groups were fairly stable from baseline to Week 12 and Week 52. The ~5% increase in HDL-C seen with evolocumab treatment did not significantly impact vitamin E carried in HDL-C or its concentration.

The concentration of vitamin E in red blood cells (RBCs) was evaluated to assess for tissue levels of vitamin E. This substudy was substantially limited by a very small sample size at the onset (14 placebo, 17 EvoMab) and by ~40% missing data by Week 12, with only 9 placebo and 6 EvoMab contributing to the Week 52 assessment.[50] At least for those with data, for the most part, mean and median RBC vitamin E (µmol/L) values in both the placebo and evolocumab groups were stable from baseline to Week 12 and Week 52. RBC vitamin E normalized by hematocrit also remained stable in both groups.

Table 28: Summary of Vitamin E Lipid parameters in Trial 20110109 (Vitamin E Substudy Analysis Set - Actual Treatment)

	Serum Vitamin E		Normalized Vitamin E	
	Placebo (N=45)	EvoMab 420 mg (N=55)	Placebo (N=45)	EvoMab 420 mg (N=55)
Serum Vitamin E (µmol/L) Baseline				
n	45	55	45	55
Mean	33.1	36.0	7.1	8.0
Median	33.0	32.7	7.2	7.5
Week 12				
n	44	54	44	54
Mean	34.1	27.4	7.2	8.8
Median	33.6	26.6	6.7	8.6
Week 52				
n	41	52	37	49
Mean	30.4	26.4	6.7	8.4
Median	31.1	24.6	6.4	8.1
Change from baseline to week 52				
Mean	-3.2	-10.1	-0.4	0.2
Median	-3.3	-8.8	-0.7	0.4
LDL-C Vitamin E (µmol/L) Baseline				
n	41	48	41	48
Mean	14.	14.6	5.6	5.9
Median	13.	14.5	5.4	5.6

50 Total vitamin E is composed of both an alpha and a gamma fraction. According to the applicant, for RBC-vitamin E measurements, the central lab did not calculate the total vitamin E unless both the alpha and gamma components were present. Gamma vitamin E was often below the quantifiable limit (BQL), which led to a number of samples being excluded from the analysis of RBC-vitamin E. In addition, out of 300 possile samples (100 subjects collected at baseline, Weeks 12 and 52) only 194 (65%) were received by the central lab for testing.

	Serum Vitamin E		Normalized Vitamin E	
	Placebo (N=45)	EvoMab 420 mg (N=55)	Placebo (N=45)	EvoMab 420 mg (N=55)
Week 12				
n	40	51	40	51
Mean	13.	6.5	5.0	5.9
Median	12.	5.6	4.9	5.4
Week 52				
n	36	44	33	40
Mean	11.5	5.5	4.3	6.1
Median	10.1	4.5	4.0	3.9
Change from baseline to week 52				
Mean	-3.1	-9.1	-1.2	0.2
Median	-2.1	-10.0	-1.3	-1.7
HDL-C Vitamin E (µmol/L)				
Baseline				
n	42	48	42	48
Mean	9.9	11.8	7.5	8.5
Median	9.5	11.0	7.5	8.3
Week 12				
n	40	51	40	51
Mean	11.4	12.9	9.0	9.1
Median	10.7	12.1	8.6	9.2
Week 52				
n	40	48	36	45
Mean	12.5	13.8	9.3	9.8
Median	12.5	13.5	9.6	9.9
Change from baseline to week 52				
Mean	2.2	2.0	1.9	1.0
Median	2.3	2.6	2.3	1.1
Non-HDL-C Vitamin E				
Baseline				
n	42	48	42	48
Mean	23.6	25.0	7.1	7.9
Median	22.3	21.6	6.6	7.5
Week 12				
n	40	51	40	51
Mean	22.3	14.5	6.5	8.6
Median	21.5	13.2	6.1	8.4
Week 52				
n	39	47	35	44
Mean	17.8	13.2	5.5	7.4
Median	17.0	11.1	5.2	7.0
Change from baseline to week 52				
Mean	-5.7	-12.0	-1.5	-0.5
Median	-4.1	-10.9	-1.5	-0.4
RBC Vitamin E (µmol/L)				
Baseline				
n	14	17	14	17
Mean	3.0	3.0	7.1	7.5

	Serum Vitamin E		Normalized Vitamin E	
	Placebo (N=45)	EvoMab 420 mg (N=55)	Placebo (N=45)	EvoMab 420 mg (N=55)
Median	2.9	3.0	6.7	7.4
Week 12				
n	11	7	11	6
Mean	3.0	3.2	7.1	8.1
Median	3.0	2.8	7.0	7.9
Week 52				
n	9	6	9	6
Mean	3.2	2.9	7.9	6.7
Median	3.3	2.9	7.6	6.9
Change from baseline to week 52				
Mean	0.2	0.4	0.4	0.6
Median	0.3	0.3	0.5	0.7

N = number of subjects randomized and dosed in the Vitamin E substudy analysis set; EvoMab = Evolocumab
Summary is based on observed data and no imputation is used for missing values.
Normalized HDL Vitamin E = HDL-Vitamin E (µmol/L) / HDL-C (mmol/L)
Normalized RBC Vitamin E = RBC Vitamin E (µmol/L) / Hematocrit (fraction of 1)
*normal: 3.9–12.5 µmol/L or 1.7–5.4 µg/mL
Source: Modified from Applicant's Table 14-7.52.2, Table 14-7.52.5, Table 14-7.53.1, Table 14-7.53.3, Table 14-7.54.1,Table 14-7.54.3, Table 14-7.56.1, Table 14-7.56.3, Table 14-7.55.1, Table 14-7.55.3 (CSR-20110109 Module 5.3.5.1)

Excluding the 20 participants who received at least 1 vitamin E supplement/multivitamin containing vitamin E during the course of the trial did not result in notable changes in any of the vitamin E substudy parameters.

Anti-evolocumab binding antibodies:
A total of 900 participants (598 in the evolocumab group; 302 in the placebo group) had available samples for antibody analysis. A total of 894 participants (301 from placebo groups and 593 from evolocumab groups) had pre-dose results and 882 participants (297 from placebo groups and 585 from evolocumab groups) had post-baseline results. Two participants randomized to evolocumab tested positive for pre-existing anti-evolocumab binding antibodies at baseline and 1 (0.2%) participant in the evolocumab group (with a negative result at baseline) developed anti-evolocumab binding antibodies transiently postbaseline. This participant had a positive result at Weeks 12 and 36 and a negative result at Week 24 and End of Study. No participants tested positive for anti-evolocumab neutralizing antibodies.

Vital Signs
A review of mean and median changes in systolic and diastolic blood pressure as well as heart rate at various timepoints during the trial (Weeks 12, 13, 24, 36, 37 and 52) did not reveal any clinically meaningful changes from baseline or compared to placebo.

ECG

A review of mean and median changes in PR, QRS, and QT interval at various timepoints during the trial (Weeks 13, 24, 37 and 52) did not reveal any clinically meaningful changes from baseline or compared to placebo.

Using Bazett's correction method for QTc (QTcB), at baseline, > 450 msec intervals were reported for 50 (8.3%) evolocumab participants and 38 (12.6%) placebo; maximum postbaseline QTcB intervals > 450 msec were reported for 117 (19.5%) evolocumab participants and 68 (22.5%) placebo. Postbaseline QTcB intervals > 480 msec were reported for 7 (1.2%) evolocumab participants and 3 (1.0%) placebo. A maximum increase of > 30 msec from baseline was reported for 44 (7.3%) evolocumab participants and 15 (5.0%) placebo; no individual in either group had a maximum increase > 60 msec from baseline.

Using Fridericia's correction method (QTcF), at baseline, > 450 msec intervals were reported for 21 (3.5%) evolocumab participants and 9 (3.0%) placebo; maximum postbaseline QTcF intervals > 450 msec were reported for 59 (9.8%) evolocumab participants and 29 (9.6%) placebo. Postbaseline QTcB intervals > 480 msec were reported for 4 (0.7%) evolocumab participants and no placebo participants. A maximum increase of > 30 msec from baseline was reported for 32 (5.3%) evolocumab participants and 10 (3.3%) placebo; 1 participant in the evolocumab group had a maximum increase > 60 msec from baseline.

Conclusions:

Efficacy

- The primary efficacy endpoint, percent change from baseline in ultracentrifugation (UC) LDL-C at Week 52 for evolocumab (420 mg SC QM) compared with placebo QM when added to background lipid-lowering therapy, was -57.0% (2.1%) (multiplicity adjusted $p < 0.001$).
- Compared with placebo, the treatment difference for the percent change from baseline at Week 52 in UC LDL-C (SE) for the evolocumab QM group was -55.7% (4.2%) in the diet alone group, -61.6% (2.6%) in the diet plus atorvastatin 10 mg group, -56.8% (5.3%) in the diet plus atorvastatin 80 mg group, and -48.5% (5.2%) in the diet plus atorvastatin 80 mg plus ezetimibe 10 mg group.
- Statistically significant reductions in UC LDL-C from baseline occurred during the first 12 weeks on study for participants treated with evolocumab; these reductions were maintained through Week 52.
- Evolocumab treatment, as compared with placebo, resulted in statistically significant mean percent reductions from baseline in total cholesterol, non-HDL-C, apolipoprotein B, lipoprotein(a), and triglycerides and a statistically significant increase in HDL-C.
- Evolocumab was effective across all subgroups with no significant differences; however, there was a trend toward greater LDL-C reduction with lower BMIs.

Safety

- Two fatal adverse events occurred in the evolocumab group during the study treatment period. A third fatal adverse event occurred 21 days after the EOS (49 days after the last dose of evolocumab). The 3 deaths were cardiac in nature (cardiac failure, myocardial infarction and sudden cardiac death).
- Serious adverse events (SAEs) were reported in 33 (5.5%) of participants in the evolocumab group and 13 (4.3%) of participants in the placebo group.
    - SAEs reported by 2 participants each (0.3%) in the evolocumab group included angina pectoris, palpitation, ventricular extrasystoles, vertigo positional, back pain, and pulmonary embolism; angina pectoris was reported by 2 participants (0.7%) in the placebo group.
- Adverse events leading to discontinuation of IP were reported in 13 (2.2%) of participants in the evolocumab group and 3 (1.0%) of participants in the placebo group. Small increases in discontinuations in the EvoMab group as compared to the placebo group include
    - cardiac disorders (cardiac failure, myocardial infarction, supraventricular extrasystoles) [3 (0.5%) vs 0]
    - general disorders (chills; injection site erythema/ pruritus/swelling/urticaria) [2 (0.3%) vs 0]
    - investigations (CPK or hepatic enzyme increased) [2 (0.3%) vs 0]
    - myalgia [2 (0.3%) vs 0]
    - injection-site reactions reported in 34 participants (5.7%) in the evolocumab group and 15 (5.0%) in the placebo group, resulting in discontinuation of evolocumab in 1 participant
- Adverse events occurred in 74.8% of the evolocumab group and 74.2% of the placebo group.
    - Adverse events reported in ≥ 5% of participants in either group were nasopharyngitis (10.5% evolocumab, 9.6% placebo), upper respiratory tract infection (9.3% evolocumab, 6.3% placebo), influenza (7.5% evolocumab, 6.3% placebo), and back pain (6.2% evolocumab, 5.6% placebo).
    - Adverse events (by preferred term) where there was a ≥ 1% increase in the EvoMab group as compared to the placebo group include: anemia (1.2% evolocumab, 0% placebo); abdominal pain upper (2.2% evolocumab, 0.7% placebo); dyspepsia (1.8% evolocumab, 0.7% placebo); non-cardiac chest pain (1.3% evolocumab, 0% placebo); sinusitis (4.2% evolocumab, 3.0% placebo); gastroenteritis (3.0% evolocumab, 2.0% placebo); CK increased (1.5% evolocumab, 0.3% placebo); ALT increased (1.0% evolocumab, 0% placebo); myalgia (4.0% evolocumab, 3.0% placebo); dizziness (3.7% evolocumab, 2.6% placebo); anxiety (1.7% evolocumab, 0.7% placebo); nephrolithiasis (1.2% evolocumab, 0% placebo); oropharyngeal pain (2.5%

evolocumab, 1.3% placebo); and rash (1.8% evolocumab, 0.3% placebo).

- Positively Adjudicated Events
  - Six (1.0%) participants[51] in the evolocumab group and 2 (0.7%) participants in the placebo group had positively adjudicated events.
    - cardiovascular death (evolocumab: 3 [0.5%]; placebo: 0 [0%])
    - non-fatal MI (evolocumab: 1 [0.2%]; placebo: 0 [0%])
    - PCI (evolocumab: 1 [0.2%]; placebo: 1 [0.3%])
    - CABG (evolocumab: 0 subjects [0%]; placebo: 1 [0.3%])
    - transient ischemic attack (evolocumab: 1 [0.2%]; placebo: 0 [0%])
    - myalgia with creatine kinase (CK) elevation (evolocumab: 1 [0.2%]; placebo: 0 [0%])
- Steroid hormones
  - No notable trends were seen for changes from baseline in the steroid hormones of ACTH, FSH, LH and testosterone. There was an increase in cortisol seen in the EvoMab group at Week 52 that was not observed in the placebo group.
- Vitamin E
  - The mean and median concentration of normalized serum vitamin E at Week 52 was similar to baseline concentrations for both the evolocumab and placebo groups. The mean and median concentration of total serum vitamin E at all postbaseline timepoints was decreased in the evolocumab group as compared to placebo and baseline values. This was expected as vitamin E is a fat-soluble vitamin and plasma concentrations decrease as the concentration of lipoproteins (such as HDL-C and LDL-C) transporting vitamin E decrease. The concentration of vitamin E in red blood cells (RBCs) was evaluated to assess for tissue levels of vitamin E. Although limited by both a very small sample size and substantial missing data, mean and median RBC vitamin E values in both the placebo and evolocumab groups were stable from baseline to Week 12 and Week 52 for those with measurements. RBC vitamin E normalized by hematocrit also remained stable in both groups.
- Anti-evolocumab binding antibodies:
  - 1 (0.2%) participant in the evolocumab group (with a negative result at baseline) developed anti-evolocumab binding antibodies transiently postbaseline.
  - No participants tested positive for anti-evolocumab neutralizing antibodies.
- Vital signs and ECG
  - There were no notable changes between the 2 groups.

51 One adjudicated event of death occurred in an evolocumab subject during the 30 day follow up. This subject completed study 3 weeks prior to death.

Limitations:

- This trial did not use the to-be-marketed devices or formulation.
- As classified by NCEP ATP III criteria, the majority of participants (64%) were at moderate or low CHD risk and only 26% were considered at high risk for CHD. Only 15% of participants had a medical history of coronary artery disease, with <8% having a history of prior myocardial infarction. Only 4% of participants had a medical history of cerebrovascular or peripheral arterial disease, with <1% having a history of prior stroke. Only 12% of participants had a history of diabetes. Thus, the overall trial population did not represent a population at high CV risk with substantial CVD burden.
- 12% of participants were on no background lipid-lowering drug therapy and 43% were on low dose atorvastatin. Thus, at least 55% of the trial population was not on optimally or maximally titrated background statin treatment.
- According to the trial design, the majority of participants, regardless of their CV risk, were at NCEP ATP III goal prior to adding evolocumab.

5.3.2 Trial 20110116: GAUSS-2

While the efficacy results of the four phase 3 trials were similar, the baseline CV risk factors and the tolerability data from this group of subjects who had difficulty tolerating statins was felt to be potentially the most informative of the four phase 3 trials. In the statin-intolerant trial 20110116, as compared to the other three Phase 3 trials, the participants were older, were more likely to be at high or moderately high CHD risk, had a similar background incidence of CAD as the HeFH trial but higher than the monotherapy or combination with statin trials, had a higher incidence of diabetes and hypertension, and had higher baseline LDL values.

20110116: A Double-blind, Randomized, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor

Investigators: This study was conducted at 51 centers in the United States, Australia, Netherlands, Denmark, Spain, Germany, United Kingdom, Belgium, France, Canada, Switzerland, Hong Kong, and Poland.

Study period: The first subject was enrolled on 23 January 2013, and the last subject completed follow-up on 19 November 2013.

Phase of Development: 3

Publications Based on the Study: Cho L, Rocco M, Colquhoun D, et al. Design and

Rationale of the GAUSS-2 Study Trial: A Double-Blind, Ezetimibe-Controlled Phase 3 Study of the Efficacy and Tolerability of Evolocumab (AMG 145) in Subjects With Hypercholesterolemia Who Are Intolerant of Statin Therapy. Clin Cardiol. 2014 Jan 29.

Primary Objectives: Statin intolerance was defined as subjects who had tried at least 2 statins and were unable to tolerate any dose or an increase in statin dose above total weekly maximum doses of statins specified in the protocol (ie, atorvastatin 70 mg, simvastatin 140 mg, pravastatin 140 mg, rosuvastatin 35 mg, lovastatin 140 mg, or fluvastatin 280 mg or 7 times the smallest tablet size for any other statins) due to intolerable myopathy. The primary objective was to evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab administered every 2 weeks (Q2W) and monthly (QM) compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

Secondary Objectives:

- to evaluate the safety and tolerability of evolocumab SC Q2W and QM, compared with ezetimibe
- to evaluate the effect of 12 weeks of evolocumab SC Q2W and QM, compared with ezetimibe, on percent change from baseline in LDL-C
- to assess the effects of 12 weeks of evolocumab SC Q2W and QM, compared with ezetimibe, on change from baseline in LDL-C and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and HDL-C
- to assess the effects of 12 weeks evolocumab SC Q2W and QM, compared with ezetimibe, on % of subjects attaining LDL-C < 70 mg/dL

Design: Phase 3, multicenter, double-blind, randomized, double-dummy, ezetimibe-controlled, parallel-group study designed to evaluate the efficacy and safety of evolocumab, compared with ezetimibe in subjects with hypercholesterolemia who have tried at least 2 statins and were unable to tolerate any dose or an increase in statin dose above total weekly maximum doses listed in the protocol due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without creatine kinase [CK] elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). Prior to randomization, subjects entered a 6-week screening period to determine eligibility. During screening, placebo was administered to confirm tolerance of SC administration prior to randomization. All subjects received placebo SC that corresponded to the QM dose volume (ie, 3.0 mL) using 3 consecutively administered autoinjector/pens (AI/pens). After the 6-week screening period, eligible subjects were randomized with an allocation ratio of 2:2:1:1 into 4 treatment groups. Randomization

was stratified by screening LDL-C level (< 180 mg/dL vs ≥ 180 mg/dL) and by baseline statin use (yes vs no).

Treatment Group	Investigational Product and Dose	Planned Number of Subjects
Evolocumab Q2W	Evolocumab 140 mg SC Q2W and placebo PO QD	100
Evolocumab QM	Evolocumab 420 mg SC QM and placebo PO QD	100
Ezetimibe Q2W	Placebo SC Q2W and ezetimibe 10 mg PO QD	50
Ezetimibe QM	Placebo SC QM and ezetimibe 10 mg PO QD	50

Subjects received their first dose of SC (evolocumab or placebo) and oral (PO) (ezetimibe or placebo) investigational product (IP) on day 1, and returned to the study center at weeks 2 (Q2W group), 8, 10, and 12 for study assessments, including collection of samples for the determination of lipid parameters. Each Q2W dose of evolocumab was administered using a single AI/pen that delivered a 140 mg dose; each QM dose was administered via 3 AI/pens for a total evolocumab dose of 420 mg.

Patient Population: Men and women ≥ 18 to ≤ 80 years of age with documented evidence that they tried at least 2 statins and have been unable to tolerate any dose or an increase in statin dose to the weekly maximum doses due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). Symptoms must have resolved when the statin was discontinued or the dose reduced. Depending on a subject's risk category (based on National Cholesterol Education Program Adult Treatment Panel [NCEP ATP III] treatment goals), subjects must have met the following fasting LDL-C (by central laboratory) criteria at screening:

- ≥ 100 mg/dL for subjects with diagnosed coronary heart disease (CHD) or CHD risk equivalent
- ≥ 130 mg/dL for subjects without diagnosed CHD or risk equivalent and 2 or more risk factors
- ≥ 160 mg/dL for subjects without diagnosed CHD or risk equivalent and with 1 risk factor
- ≥ 190 mg/dL for subjects without diagnosed CHD or risk equivalent and with no risk factors

Fasting triglycerides must have been ≤ 400 mg/dL as determined by the central laboratory analysis at screening.

Duration of Treatment: This study included a maximum 6-week screening period, followed by a 12-week treatment period.

Endpoints:
The co-primary efficacy endpoints were:

- percent change from baseline in LDL-C at week 12
- percent change from baseline in LDL-C at the mean of weeks 10 and 12

The co-secondary efficacy endpoints were at week 12 and at the mean of weeks 10 and 12 for:

- tier 1
  - absolute change from baseline in LDL-C
  - percent of subjects with LDL-C < 70 mg/dL
  - percent change from baseline in non-HDL-C
  - percent change from baseline in ApoB
  - percent change from baseline in the total cholesterol/HDL-C ratio
  - percent change from baseline in ApoB/ApoA1 ratio
- tier 2
  - percent change from baseline in Lp(a)
  - percent change from baseline in triglycerides
  - percent change from baseline in VLDL-C
  - percent change from baseline in HDL-C

Statistical Analyses: Efficacy and safety analyses were performed on the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of IP (either SC or PO). Efficacy analyses were also performed on the monotherapy analysis set (MAS) which included subjects in the FAS who did not take any baseline lipid-regulating medications at study entry. Analyses were performed separately by dose frequency (Q2W and QM), unless specified otherwise. The superiority of evolocumab to ezetimibe was assessed for all efficacy endpoints. Testing of each co-endpoint pair in each analysis set (FAS and MAS) resulted in a single p-value; for co-secondary endpoints in the FAS and all co-endpoints in the MAS, these p-values were then used in the Hochberg procedure. The following method was used to preserve the familywise error rate at 0.05 for testing the co-primary and co-secondary efficacy endpoints within each dose frequency:

1. If the treatment effect from the primary analysis of the co-primary endpoints in the FAS was significant at a significance level of 0.05, statistical testing of the tier 1 co-secondary efficacy endpoints followed the Hochberg procedure at a significance level of 0.005.
2. If all tier 1 co-secondary efficacy endpoints were significant in the FAS, the tier 2 co-secondary efficacy endpoints in the FAS, co-primary and all co-secondary efficacy endpoints in the MAS were tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 co-secondary efficacy endpoints were significant in the FAS, the tier 2 co-secondary efficacy endpoints in FAS, co-primary and all co-secondary efficacy endpoints in the MAS were tested using the Hochberg procedure at a significance level of 0.045

For all analyses related to LDL-C, unless specified otherwise, a reflexive approach was used, where the calculated LDL-C was employed unless the calculated LDL-C

was < 40 mg/dL or triglycerides were > 400 mg/dL in which case ultracentrifugation (UC) LDL-C was determined and utilized.

Analyses of Co-Primary Endpoints
To assess the co-primary endpoints of the percent change in LDL-C from baseline at week 12 and the mean percent change in LDL-C from baseline at weeks 10 and 12, a repeated measures linear effects model was used within each dose frequency to compare the efficacy of evolocumab with ezetimibe. The repeated measures model included terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values were not imputed when the repeated measures linear effects model was used.

Analyses of Secondary and Tertiary Endpoints
The statistical model for the co-secondary endpoints and tertiary endpoints was similar to the co-primary endpoints. However, the co-secondary endpoints of LDL-C response were analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by stratification factors.

Results:

Patient Demographics
Sex: 46% women; 54% men
Age: mean (SD) 61.5 (9.8) years
Ethnicity: 2.3% Hispanic or Latino
Race: 93.5% white, 3.3% Asian, 2.3% black/African American, 0.3% Native Hawaiian or Other Pacific Islander, and 0.7% other race.

- Mean (SD) serum concentration of reflexive LDL-C at baseline was 193.1 (58.5) mg/dL overall and was similar across treatment groups.
- 51% of subjects had a screening LDL-C concentration of < 180 mg/dL and 49% of subjects had a screening LDL-C concentration of ≥ 180 mg/dL
- 81% of subjects had no baseline statin use and 19% recorded baseline statin use
- At baseline, 90 (29.3%) subjects overall had coronary artery disease and 49 (16.0%) subjects overall had cerebrovascular or peripheral arterial disease.
- 59% of subjects were < 65 years of age and 41% of subjects were ≥ 65 years of age

The applicant states that all subjects (100%) were intolerant to 2 or more statins, 55% of subjects were intolerant to 3 or more statins, and 21% of subjects were intolerant to 4 or more statins. Of note, the subjects were not intolerant necessarily to the lowest statin dose but to any dose or an increase in dose above the total maximum weekly doses (such ≤70 mg atorvastatin, ≤140 mg simvastatin, pravastatin, or lovastatin or ≤35 mg rosuvastatin) due to intolerable myopathy. Thus, a subject could be taking

atorvastatin 10 mg/day, simvastatin 20 mg/day or rosuvastatin 5 mg/day and be categorized as statin-intolerant, according to this definition. Atorvastatin, simvastatin, and rosuvastatin were the most commonly reported statins associated with muscle intolerance, reported in 77%, 73%, and 71% of subjects, respectively (see table).

Table 29: Summary of Statin Intolerance Medical History (Full Analysis Set) – Trial 20110116

	Ezetimibe Overall (N = 102) n (%)	EvoMab Overall (N = 205) n (%)	Total (N = 307) n (%)
Number of subjects reporting statin intolerance medical history	102 (100.0)	205 (100.0)	307 (100.0)
LDL-C treatment goals based on risk category			
LDL-C < 100 mg/dL for diagnosed CHD or CHD risk equivalent	50 (49.0)	103 (50.2)	153 (49.8)
LDL-C < 130 mg/dL for 2 or more risk factors without diagnosed CHD or CHD risk equivalent	33 (32.4)	53 (25.9)	86 (28.0)
LDL-C < 160 mg/dL for 1 risk factor without diagnosed CHD or CHD risk equivalent	12 (11.8)	35 (17.1)	47 (15.3)
LDL-C < 190 mg/dL for no risk factors without diagnosed CHD or CHD risk equivalent	7 (6.9)	14 (6.8)	21 (6.8)
Intolerance to statins (number of statins per subject)			
Two statins	42 (41.2)	96 (46.8)	138 (45.0)
Three statins	35 (34.3)	69 (33.7)	104 (33.9)
Four or more statins	25 (24.5)	40 (19.5)	65 (21.2)
Family history of muscular symptoms			
Yes	23 (22.5)	33 (16.1)	56 (18.2)
No	78 (76.5)	172 (83.9)	250 (81.4)
Unknown	1 (1.0)	0 (0.0)	1 (0.3)
Family history of muscular symptoms with statin(s)			
Yes	20 (19.6)	30 (14.6)	50 (16.3)
No	82 (80.4)	175 (85.4)	257 (83.7)
Muscle related intolerance to statins (statin name)			
Atorvastatin	82 (80.4)	155 (75.6)	237 (77.2)
Simvastatin	77 (75.5)	147 (71.7)	224 (73.0)
Rosuvastatin	73 (71.6)	145 (70.7)	218 (71.0)
Pravastatin	29 (28.4)	53 (25.9)	82 (26.7)
Fluvastatin	17 (16.7)	38 (18.5)	55 (17.9)
Lovastatin	9 (8.8)	10 (4.9)	19 (6.2)
Pitavastatin	4 (3.9)	6 (2.9)	10 (3.3)
Other statin	2 (2.0)	2 (1.0)	4 (1.3)

Worst muscle related side effect for any statin - n (%)			
Myalgia (muscle symptoms without CK elevation)	85 (83.3)	161 (78.5)	246 (80.1)
Myositis (muscle symptoms with CK elevation)	15 (14.7)	39 (19.0)	54 (17.6)
Rhabdomyolysis (muscle symptoms with significant CK elevation)	2 (2.0)	4 (2.0)	6 (2.0)
Distribution of muscle-related side effect – n (%)			
Bilateral	101 (99.0)	196 (95.6)	297 (96.7)
Unilateral	0 (0.0)	7 (3.4)	7 (2.3)
Predominant body site of muscle-related side effect - n (%)			
Upper extremity	24 (23.5)	42 (20.5)	66 (21.5)
Lower extremity	44 (43.1)	104 (50.7)	148 (48.2)
Trunk	6 (5.9)	14 (6.8)	20 (6.5)
All over	44 (43.1)	86 (42.0)	130 (42.3)
History of CK elevation – n (%)			
None	79 (77.5)	157 (76.6)	236 (76.9)
> 1 x ULN and < 10 x ULN	11 (10.8)	37 (18.0)	48 (15.6)
10 x ULN and < 40 x ULN	2 (2.0)	3 (1.5)	5 (1.6)
40 x ULN	0 (0.0)	1 (0.5)	1 (0.3)
Unknown	10 (9.8)	6 (2.9)	16 (5.2)
Associated with CK elevation – n (%)			
Serum creatinine elevation	5 (4.9)	3 (1.5)	8 (2.6)
Brown urine or elevated urinary myoglobin	3 (2.9)	0 (0.0)	3 (1.0)
Medical intervention with intravenous hydration	1 (1.0)	3 (1.5)	4 (1.3)

CHD = coronary heart disease; EvoMab = Evolocumab (AMG 145); LDL-C = low-density lipoprotein; N = number of subjects randomized and dosed in the full analysis set.
Source: Modified from applicant's Table 14-2.6.1, Table 14-2.6.2, and Table 9-4 from CSR: 20110116

Patient Disposition

A total of 307 subjects were randomized to 1 of the 4 groups, as follows:

- 205 to the evolocumab groups (103 Q2W, 102 QM)
- 102 to the ezetimibe groups (51 Q2W, 51 QM).

All 307 (100%) subjects received IP (205 evolocumab and 102 ezetimibe) and were included in the FAS. A total of 293 (95.4%) subjects completed SC IP, 276 (89.9%) completed PO IP, and 273 (88.9%) completed both SC and PO IP. A total of 290 (94.5%) subjects completed the study. Of the 17 (5.5%) subjects who did not complete the study, 13 (4.2%) subjects completed IP and week 12 visits but entered an open-label extension study [20120138] before they completed the EOS phone call at week 14 (category of "sponsor decision"), 3 (1.0%) subjects withdrew consent, and 1 (0.3%) subject was lost to follow-up.

Exposure to Study Drug

A total of 307 subjects received ≥ 1 dose of IP (evolocumab: 205, ezetimibe: 102) and were included in the full analysis set. The mean (SD) duration of exposure to SC IP was 2.7 (0.3) months for the overall evolocumab group and 2.7 (0.4) months for the overall ezetimibe group. The mean (SD) cumulative dose of evolocumab was 803.3 (117.6) mg for evolocumab Q2W and 1240.8 (78.9) mg for evolocumab QM.

Concomitant Medication Use

At baseline, 134 (65.4%) subjects in the overall evolocumab group and 71 (69.6%) subjects in the overall ezetimibe group were not taking lipid modifying therapy. Of these subjects, 3 (2.2%) subjects in the overall evolocumab group and 1 (1.4%) subject in the overall ezetimibe group added a non-statin lipid modifying therapy postbaseline and 1 (0.5%) subject in the overall evolocumab group added a statin postbaseline.

A total of 47 (15.3%) subjects in the overall evolocumab group and 12 (11.8%) subjects in the overall ezetimibe group received a non-statin lipid modifying therapy at baseline. All of these subjects remained on non-statin lipid modifying therapy and none received a statin therapy postbaseline. The most commonly administered nonstatin lipid modifying therapy was fish oil, which was taken by 39 (19%) subjects in the overall evolocumab group and 14 (13.7%) subjects in the overall ezetimibe group.

A total of 37 (18.0%) subjects in the overall evolocumab group and 19 (18.6%) subjects in the overall ezetimibe group reported statin usage at baseline. All of these subjects remained on statin therapy postbaseline (see table).

Table 30: Subject Incidence of Concomitant Statin Therapies: Trial 20110116 (Full Analysis Set – Actual Treatment)

	Ezetimibe			EvoMab		
	Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Placebo QM + Ezetimibe QD (N = 51) n (%)	Overall (N = 102) n (%)	140 mg Q2W + Placebo QD (N = 103) n (%)	420 mg QM + Placebo QD (N = 102) n (%)	EvoMab Overall (N = 205) n (%)
STATINS	9 (17.6)	10 (19.6)	19 (18.6)	19 (18.4)	18 (17.6)	37 (18.0)
Rosuvastatin	6 (11.8)	2 (3.9)	8 (7.8)	10 (9.7)	9 (8.8)	19 (9.3)
Simvastatin	0 (0.0)	3 (5.9)	3 (2.9)	1 (1.0)	4 (3.9)	5 (2.4)
Atorvastatin	1 (2.0)	2 (3.9)	3 (2.9)	1 (1.0)	2 (2.0)	3 (1.5)
Fluvastatin	0 (0.0)	1 (2.0)	1 (1.0)	3 (2.9)	2 (2.0)	5 (2.4)
Pravastatin	0 (0.0)	1 (2.0)	1 (1.0)	3 (2.9)	1 (1.0)	4 (2.0)
Lovastatin	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pitavastatin	2 (3.9)	0 (0.0)	2 (2.0)	1 (1.0)	0 (0.0)	1 (0.5)

EvoMab = Evolocumab (AMG 145); N = number of subjects randomized and dosed in the Full Analysis Set - Actual Treatment; Q2W = every 2 weeks (subcutaneous); QD = once a day (oral tablet); QM = monthly (subcutaneous).
Source: Modified from Applicant's Table 14-8.8.1 and Table 12-10 from CSR: 20110116

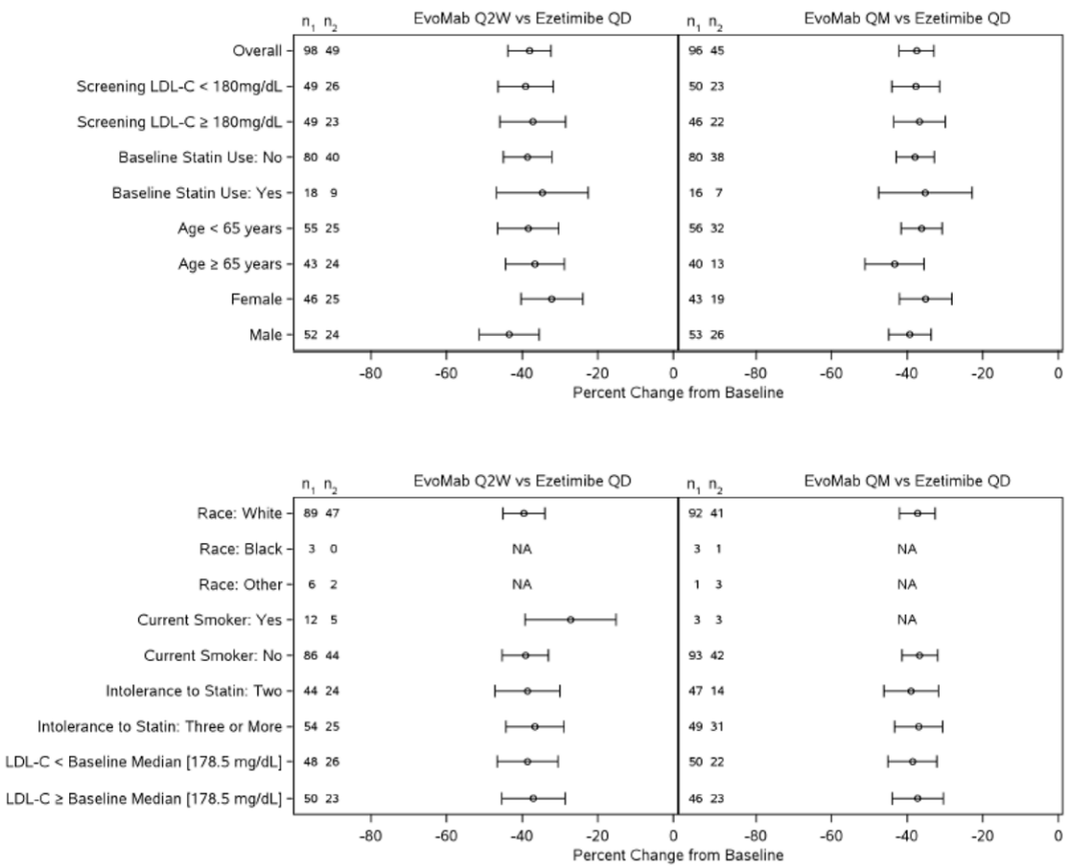
Primary Efficacy Outcomes

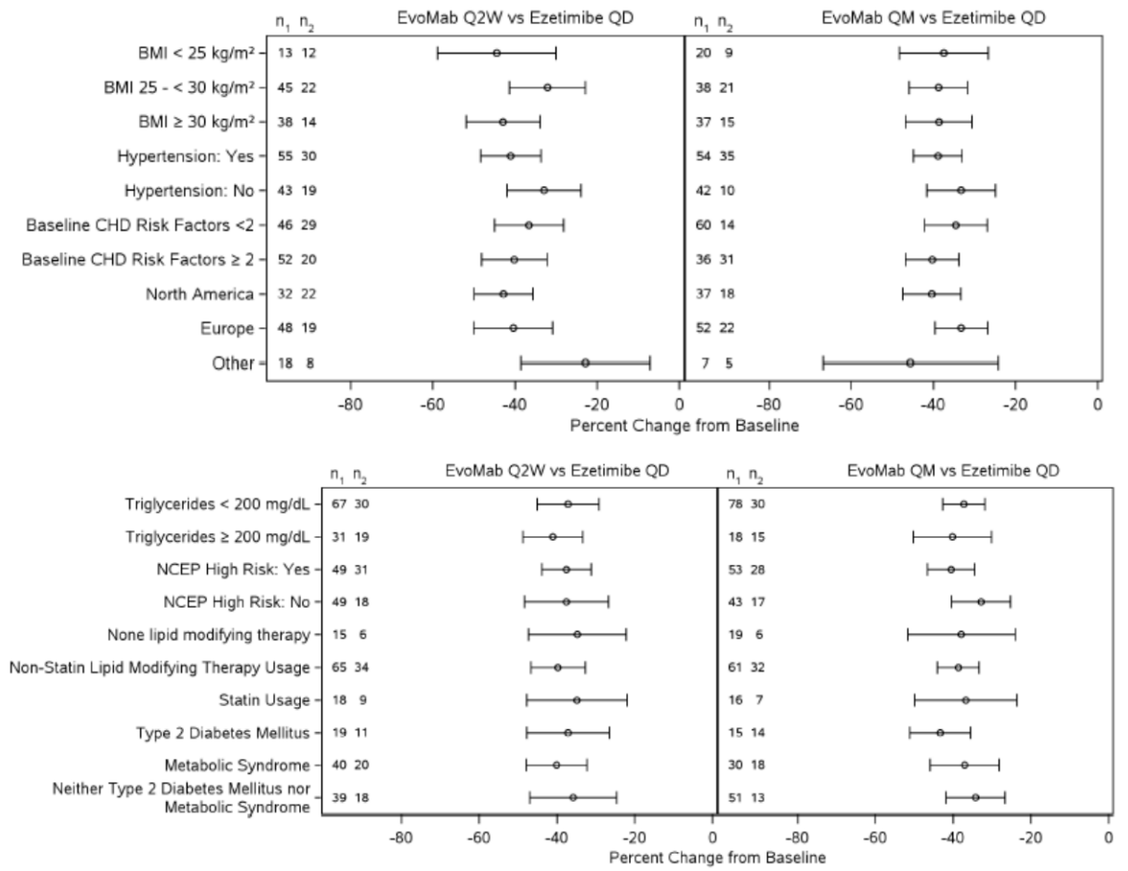
Compared with ezetimibe, evolocumab treatment resulted in statistically significant reductions in reflexive LDL-C from baseline to week 12 in both the Q2W and QM

treatment groups (treatment differences [standard error; SE]: 38% [3%] and 38% [2%], respectively). Compared with ezetimibe, evolocumab also resulted in statistically significant reductions in reflexive LDL-C from baseline to the mean of weeks 10 and 12 in the Q2W and QM treatment groups (treatment differences [SE]: 37% [3%] and 39% [2%], respectively).

Evolocumab Q2W and QM were effective in reducing LDL-C in all subgroups (eg, by sex, age, and race) relative to ezetimibe, with no notable differences between subgroups (see forest plots).

Figure 5: Forest Plot of Treatment Differences in Percent Change from Baseline in LDL-C at Week 12 - Subgroup Analyses Trial 20110116 (Full Analysis Set)





BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; EvoMab = Evolocumab; LDL-C = low-density lipoprotein cholesterol; n1 = number of subjects in the subgroup of interest included in the repeated measures model receiving EvoMab; n2 = number of subjects in the subgroup of interest included in the repeated measures model receiving ezetimibe; NCEP = National Cholesterol Education Program; QD = once a day (oral tablet); Q2W = once every 2 weeks; QM = once monthly.
When the calculated LDL-C is < 40 mg/dL, or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
Least squares mean differences and 95% CI are from the repeated measures model. No imputation is used for missing values.
Source: Modified from applicant's Figure 14-4.6.1 and Figure 10-3 from CSR: 20110116

Secondary Efficacy Outcomes

The co-secondary efficacy endpoints were at week 12 and at the mean of weeks 10 and 12 for:

- tier 1
  - change from baseline in LDL-C
  - percent of subjects with LDL-C < 70 mg/dL
  - percent change from baseline in non-HDL-C
  - percent change from baseline in ApoB

  - percent change from baseline in the total cholesterol/HDL-C ratio
  - percent change from baseline in ApoB/ApoA1 ratio
- tier 2
  - percent change from baseline in Lp(a)
  - percent change from baseline in triglycerides: not significant (NS)
  - percent change from baseline in VLDL-C: NS
  - percent change from baseline in HDL-C: NS

As shown in the following table, treatment with evolocumab Q2W and QM resulted in significant changes compared with ezetimibe (all multiplicity adjusted p-values < 0.001) for all tier 1 co-secondary efficacy endpoints.

Table 31: Summary of Treatment Difference in Tier 1 Co-secondary Endpoints: Trial 20110116 (Full Analysis Set)

	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
Reflexive LDL-C		
Change from baseline at week 12 (95% CI) – mg/dL	-69.7 (-82.0, -57.5)	-68.8 (-79.2, -58.4)
Mean change from baseline at weeks 10 and 12 (95% CI) – mg/dL	-66.3 (-77.9, -54.7)	-70.6 (-80.5, -60.7)
Change from baseline at week 12 (95% CI) – mmol/L	-1.806 (-2.125, -1.488)	-1.781 (-2.051, -1.511)
Mean change from baseline at weeks 10 and 12 (95% CI) – mmol/L	-1.717 (-2.018, -1.416)	-1.827 (-2.084, -1.571)
Least significant p-value	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**
Percent of subjects with reflexive LDL-C < 70 mg/dL [1.8 mmol/L]		
At week 12 (95% CI)	47.96 (34.95, 57.81)	37.50 (25.53, 47.49)
Mean of weeks 10 and 12 (95% CI)	43.54 (30.90, 53.38)	42.00 (30.27, 51.79)
Least significant CMH p-value	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**
Non-HDL-C		
% change from baseline at week 12 (95% CI)	-32.09 (-37.28, -26.90)	-32.99 (-37.19, -28.79)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-31.53 (-36.34, -26.73)	-34.58 (-38.63, -30.54)
Least significant p-value	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**
ApoB		
% change from baseline at week 12 (95% CI)	-32.86 (-38.04, -27.68)	-33.10 (-38.04, -28.17)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-32.20 (-36.92, -27.49)	-34.99 (-39.59, -30.39)
Least significant p-value	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**

	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
Total cholesterol/HDL-C ratio		
% change from baseline at week 12 (95% CI)	-26.28 (-31.42, -21.15)	-28.66 (-33.88, -23.43)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-27.39 (-32.11, -22.67)	-29.94 (-34.72, -25.17)
Least significant p-value	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**
Total cholesterol [a]		
% change from baseline at week 12 (95% CI)	-25.01 (-29.32, -20.70)	-25.21 (-28.73, -21.69)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-24.37 (-28.40, -20.34)	-26.26 (-29.61, -22.91)
Least significant p-value	<0.001	<0.001
ApoB/ApoA1 ratio		
% change from baseline at week 12 (95% CI)	-34.53 (-40.05, -29.00)	-34.13 (-39.87, -28.39)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-34.86 (-39.84, -29.88)	-36.37 (-41.73, -31.01)
Least significant p-value	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**

ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EvoMab = Evolocumab (AMG 145); HDL-C = high-density lipoprotein cholesterol; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; QD = once a day (oral tablet); Q2W = once every 2 weeks; QM = once monthly

When the calculated LDL-C is < 40 mg/dL, or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
[a] Analysis of the component of the total cholesterol/HDL-C ratio
Treatment differences are within each dose frequency using subcutaneous placebo + ezetimibe as reference
Treatment difference is from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates for all endpoints except LDL-C achievement where the treatment difference is from the CMH model stratified by the stratification factors
Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.
Source: Modified from Table 14-4.19.1 and Table 10-6 from CSR: 20110116

Compared with ezetimibe, evolocumab treatment resulted in statistically significant improvements (multiplicity adjusted p < 0.001) in Lp(a) at week 12 and at the mean of weeks 10 and 12 for both the Q2W and QM treatment groups. The added clinical significance of these Lp(a) changes, in the setting of robust LDL-C lowering, is not clear. There were no statistically significant improvements in other co-secondary tier 2 endpoints of HDL-C, triglycerides, and VLDL-C relative to ezetimibe (see table).

Table 32: Summary of Treatment Difference in Tier 2 Co-secondary Endpoints: Trial 20110116 (Full Analysis Set)

	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
Lp(a)		
% change from baseline at week 12 (95% CI)	-25.29 (-33.26, -17.33)	-27.88 (-39.21, -16.56)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-23.90 (-31.27, -16.54)	-25.26 (-33.75, -16.77)
Joint p-value [a]	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**
Triglycerides		
% change from baseline at week 12 (95% CI)	1.58 (-8.14, 11.31)	-4.69 (-17.04, 7.67)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-2.59 (-11.38, 6.20)	-6.42 (-16.55, 3.71)
Joint p-value [a]	0.28	0.33
Adjusted p-value	**0.97**	**0.33**
HDL-C		
% change from baseline at week 12 (95% CI)	3.57 (-1.49, 8.63)	4.83 (-0.16, 9.81)
Mean % change from baseline at weeks 10 and 12 (95% CI)	5.15 (0.74, 9.56)	5.74 (1.23, 10.24)
Joint p-value [a]	0.011	0.022
Adjusted p-value	**0.068**	**0.13**
VLDL-C		
% change from baseline at week 12 (95% CI)	-0.67 (-9.96, 8.61)	0.08 (-11.24, 11.39)
Mean % change from baseline at weeks 10 and 12 (95% CI)	-1.84 (-10.43, 6.75)	-3.53 (-13.12, 6.06)
Joint p-value [a]	0.84	0.32
Adjusted p-value	**0.97**	**0.33**

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EvoMab = Evolocumab (AMG 145); HDL-C = high-density lipoprotein cholesterol; IVRS = interactive voice response system; Lp(a) = lipoprotein(a); Q2W = once every 2 weeks; QD = once a day (oral tablet); QM = once monthly; VLDL-C = very low-density lipoprotein cholesterol
[a] The p-value from the union-intersection test
Treatment differences are within each dose frequency using subcutaneous placebo + ezetimibe as reference
Treatment difference is from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates for all endpoints except LDL-C achievement where the treatment difference is from the CMH model stratified by the stratification factors
Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.
Source: Modified from Applicant's Table 14-4.19.1 and Table 10-7 from CSR: 20110116

Safety Data:

Deaths
No deaths occurred during the study.

Serious Adverse Events
Six (2.9%) subjects in the overall evolocumab group and 4 (3.9%) subjects in the overall ezetimibe group reported serious adverse events. The SAEs reported by the 6 subjects in the evolocumab group were: hepatic enzyme increased, back pain, bladder transitional cell cancer, lipoma, neuroendocrine carcinoma, cartilage graft and osteotomy. The SAEs reported by the 4 subjects in the ezetimibe group were: spinal decompression, gastrointestinal motility disorder, inguinal hernia and kidney infection.

Adverse Events that Led to Study Drug Withdrawal
Thirty subjects discontinued IP (SC and/or PO) due to adverse events, including 17 (8.3%) in the overall evolocumab group and 13 (12.7%) in the overall ezetimibe group. Myalgia was the most frequently reported adverse event that led to discontinuation of IP and occurred in 4 (2.0%) subjects in the overall evolocumab group and 4 (3.9%) subjects in the overall ezetimibe group. Other frequently reported AEs that led to withdrawal include the preferred terms of back pain, muscle spasms, and pain in extremity each reported by 2 (1.0%) in the overall evolocumab group and 0 (0%) in the overall ezetimibe group; abdominal pain reported by 2 (1.0%) in the overall evolocumab group and 2 (2.0%) in the overall ezetimibe group; and nausea reported by 2 (1.0%) in the overall evolocumab group and 1 (1.0%) in the overall ezetimibe group. One subject in the evolocumab group discontinued IP due to a serious adverse event (metastatic neuroendocrine carcinoma).

Adverse Events
The subject incidence of adverse events was numerically lower for the evolocumab group as compared to the ezetimibe group and was also lower in the Q2W dosing group as compared to the QM group for both evolocumab and ezetimibe. The incidence was 65.9% for the overall evolocumab group (61.2% evolocumab Q2W and 70.6% evolocumab QM) and 72.5% for the overall ezetimibe group (68.6% ezetimibe + placebo Q2W and 76.5% ezetimibe + placebo QM).

Adverse events reported by ≥ 5% of subjects who received evolocumab or ezetimibe were headache (7.8%, 8.8%), myalgia (7.8%, 17.6%), pain in extremity (6.8%, 1.0%), muscle spasms (6.3%, 3.9%), fatigue (4.4%, 9.8%), nausea (4.4%, 6.9%), and diarrhea (2.4%, 6.9%). Of note, there was a greater incidence of myalgia in the ezetimibe group vs evolocumab but the incidence for pain in extremity and muscle spasms was greater in the evolocumab group vs ezetimibe. The table below shows the adverse events reported by ≥ 2% of subjects in the overall evolocumab or ezetimibe group. Adverse events reported in ≥ 2% of subjects in the overall

evolocumab group with a ≥ 2% higher subject incidence in the overall evolocumab group than the overall ezetimibe group included (evolocumab, ezetimibe) pain in extremity (6.8%, 1.0%), muscle spasms (6.3%, 3.9%), and constipation (2.9%, 0%).Treatment emergent adverse events reported in ≥ 2% of subjects in the overall ezetimibe group with a ≥ 2% higher incidence in the overall ezetimibe group than the overall evolocumab group included (evolocumab, ezetimibe) myalgia (7.8%, 17.6%), fatigue (4.4%, 9.8%), nausea (4.4%, 6.9%), diarrhea (2.4%, 6.9%), parasthesia (1.0%, 4.9%), depression (0.5%, 2.9%), influenza (0.5%, 2.9%), rash (0.5%, 2.9%), pain (0.0%, 2.9%), and pruritus (0.0%, 3.9%).

Table 33: Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency of Preferred Terms Reported for ≥ 2% of Subjects in the Overall Evolocumab or Overall Ezetimibe Group: Trial 20110116 (Full Analysis Set - Actual Treatment)

	Ezetimibe			EvoMab		
Preferred Term	Placebo Q2W + Ezetimibe QD (N=51) n (%)	Placebo QM + Ezetimibe QD (N=51) n (%)	Ezetimibe Overall (N=102) n (%)	140 mg Q2W + Placebo QD (N=103) n (%)	420 mg QM + Placebo QD (N=102) n (%)	EvoMab Overall (N=205) n (%)
Number of subjects reporting treatment emergent adverse events	35 (68.6)	39 (76.5)	74 (72.5)	63 (61.2)	72 (70.6)	135 (65.9)
Headache	3 (5.9)	6 (11.8)	9 (8.8)	4 (3.9)	12 (11.8)	16 (7.8)
Myalgia	7 (13.7)	11 (21.6)	18 (17.6)	7 (6.8)	9 (8.8)	16 (7.8)
Pain In Extremity	0 (0.0)	1 (2.0)	1 (1.0)	2 (1.9)	12 (11.8)	14 (6.8)
Muscle Spasms	3 (5.9)	1 (2.0)	4 (3.9)	5 (4.9)	8 (7.8)	13 (6.3)
Back Pain	1 (2.0)	2 (3.9)	3 (2.9)	4 (3.9)	5 (4.9)	9 (4.4)
Fatigue	4 (7.8)	6 (11.8)	10 (9.8)	3 (2.9)	6 (5.9)	9 (4.4)
Nausea	2 (3.9)	5 (9.8)	7 (6.9)	3 (2.9)	6 (5.9)	9 (4.4)
Arthralgia	2 (3.9)	2 (3.9)	4 (3.9)	5 (4.9)	3 (2.9)	8 (3.9)
Nasopharyngitis	3 (5.9)	0 (0.0)	3 (2.9)	5 (4.9)	2 (2.0)	7 (3.4)
Abdominal Distension	1 (2.0)	0 (0.0)	1 (1.0)	4 (3.9)	2 (2.0)	6 (2.9)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	4 (3.9)	6 (2.9)
Diarrhoea	3 (5.9)	4 (7.8)	7 (6.9)	3 (2.9)	2 (2.0)	5 (2.4)
Dizziness	0 (0.0)	2 (3.9)	2 (2.0)	3 (2.9)	2 (2.0)	5 (2.4)
Musculoskeletal Stiffness	0 (0.0)	1 (2.0)	1 (1.0)	2 (1.9)	3 (2.9)	5 (2.4)
Sinusitis	2 (3.9)	0 (0.0)	2 (2.0)	1 (1.0)	4 (3.9)	5 (2.4)
Abdominal Pain	1 (2.0)	1 (2.0)	2 (2.0)	1 (1.0)	3 (2.9)	4 (2.0)
Hypertension	1 (2.0)	1 (2.0)	2 (2.0)	2 (1.9)	2 (2.0)	4 (2.0)
Injection Site Erythema	0 (0.0)	3 (5.9)	3 (2.9)	2 (1.9)	2 (2.0)	4 (2.0)
Vomiting	1 (2.0)	1 (2.0)	2 (2.0)	3 (2.9)	1 (1.0)	4 (2.0)
Abdominal Pain Upper	0 (0.0)	2 (3.9)	2 (2.0)	1 (1.0)	2 (2.0)	3 (1.5)
Chest Pain	0 (0.0)	2 (3.9)	2 (2.0)	2 (1.9)	1 (1.0)	3 (1.5)
Musculoskeletal Pain	1 (2.0)	2 (3.9)	3 (2.9)	1 (1.0)	2 (2.0)	3 (1.5)
Urinary Tract Infection	1 (2.0)	1 (2.0)	2 (2.0)	1 (1.0)	2 (2.0)	3 (1.5)
Cough	0 (0.0)	2 (3.9)	2 (2.0)	1 (1.0)	1 (1.0)	2 (1.0)
Cystitis	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	2 (2.0)	2 (1.0)
Oedema Peripheral	2 (3.9)	1 (2.0)	3 (2.9)	0 (0.0)	2 (2.0)	2 (1.0)
Paraesthesia	1 (2.0)	4 (7.8)	5 (4.9)	0 (0.0)	2 (2.0)	2 (1.0)
Pyrexia	1 (2.0)	1 (2.0)	2 (2.0)	1 (1.0)	1 (1.0)	2 (1.0)
Chest Discomfort	0 (0.0)	2 (3.9)	2 (2.0)	1 (1.0)	0 (0.0)	1 (0.5)

	Ezetimibe			EvoMab		
Preferred Term	Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Placebo QM + Ezetimibe QD (N = 51) n (%)	Overall (N = 102) n (%)	140 mg Q2W + Placebo QD (N = 103) n (%)	420 mg QM + Placebo QD (N = 102) n (%)	Overall (N = 205) n (%)
Depression	1 (2.0)	2 (3.9)	3 (2.9)	0 (0.0)	1 (1.0)	1 (0.5)
Hypoaesthesia	1 (2.0)	1 (2.0)	2 (2.0)	0 (0.0)	1 (1.0)	1 (0.5)
Influenza	3 (5.9)	0 (0.0)	3 (2.9)	1 (1.0)	0 (0.0)	1 (0.5)
Lethargy	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	1 (1.0)	1 (0.5)
Rash	1 (2.0)	2 (3.9)	3 (2.9)	1 (1.0)	0 (0.0)	1 (0.5)
Sleep Disorder	2 (3.9)	0 (0.0)	2 (2.0)	0 (0.0)	1 (1.0)	1 (0.5)
Injection Site Haematoma	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney Infection	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	2 (3.9)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephrolithiasis	1 (2.0)	1 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	1 (2.0)	2 (3.9)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	1 (2.0)	3 (5.9)	4 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus Generalised	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)

EvoMab = Evolocumab (AMG 145); N = number of subjects randomized and dosed in the full analysis set; Q2W = every 2 weeks (subcutaneous); QD = once a day (oral tablet); QM = monthly (subcutaneous).
Coded using MedDRA version 16.1.
Source: Modified from Applicant's Table 14-6.2.2 and Table 12-2 from CSR: 20110116 and confirmed by JMP analysis

Six subjects (4 [2.0%] receiving evolocumab, 2 [2.0%] receiving ezetimibe) experienced Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 treatment emergent adverse events, including 1 subject (evolocumab Q2W) who experienced a grade 4 adverse event of transitional cell bladder cancer.

Nine (2.9%) subjects had at least 1 device related treatment emergent adverse event; the most common events were consistent with injection site reactions and included injection erythema (3 subjects) and injection site bruising (2 subjects). No device related adverse event led to discontinuation of IP.

Adverse Events of Interest: (events associated with other lipid lowering therapies (ie, diabetes events, liver events, muscle events), other injectable protein therapies (ie, hypersensitivity events, injection site reactions), and with PCSK9 inhibition/LDL receptor upregulation (ie, hepatitis C events) :

The review of various adverse events categorized in MedDRA SMQs and Amgen search strategies to identify AEs of interest for this BLA are summarized in the table below and do not show important differences between the evolocumab and ezetimibe treatment groups. Of note, there was a greater number of liver test abnormalities with evolocumab as compared to ezetimibe [3 (1.5%) vs 0 (0%)]. Not unexpectedly, there was a greater number of hypersensitivity events with evolocumab as compared to ezetimibe [12 (5.9%) vs 4 (3.9%)].

Table 34: Summary of Treatment Emergent Adverse Events Using Narrow Search Strategy for Potential Hepatitis C Infections and Adverse Events Potentially Associated with Lipid Lowering Therapies or Injectible Protein Therapies: Trial 20110116 (Full Analysis Set - Actual Treatment)

Category High Level Term Preferred Term	Ezetimibe Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Ezetimibe Placebo QM + Ezetimibe QD (N = 51) n (%)	Ezetimibe Overall (N = 102) n (%)	EvoMab 140 mg Q2W + Placebo QD (N = 103) n (%)	EvoMab 420 mg QM + Placebo QD (N = 102) n (%)	EvoMab Overall (N = 205) n (%)
Number of subjects reporting treatment emergent adverse events	2 (3.9)	10 (19.6)	12 (11.8)	10 (9.7)	8 (7.8)	18 (8.8)
POTENTIAL DIABETES EVENTS	1 (2.0)	1 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Carbohydrate tolerance analyses (incl diabetes)	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Glucose Increased	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycaemic conditions NEC	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycaemia	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
POTENTIAL HEPATITIS C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Category High Level Term Preferred Term	Ezetimibe Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Ezetimibe Placebo QM + Ezetimibe QD (N = 51) n (%)	Ezetimibe Overall (N = 102) n (%)	EvoMab 140 mg Q2W + Placebo QD (N = 103) n (%)	EvoMab 420 mg QM + Placebo QD (N = 102) n (%)	EvoMab Overall (N = 205) n (%)
POTENTIAL HYPERSENSITIVITY EVENTS	1 (2.0)	3 (5.9)	4 (3.9)	5 (4.9)	7 (6.9)	12 (5.9)
Allergies to foods, food additives, drugs and other chemicals	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Drug Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Dermatitis and eczema	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)	2 (1.0)
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Erythemas	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
Rash Erythematous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
Injection site reactions	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	3 (1.5)
Injection Site Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (1.0)
Injection Site Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)

Category High Level Term Preferred Term	Ezetimibe Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Ezetimibe Placebo QM + Ezetimibe QD (N = 51) n (%)	Ezetimibe Overall (N = 102) n (%)	EvoMab 140 mg Q2W + Placebo QD (N = 103) n (%)	EvoMab 420 mg QM + Placebo QD (N = 102) n (%)	EvoMab Overall (N = 205) n (%)
POTENTIAL HYPERSENSITIVITY EVENTS (Cont'd)						
Oral soft tissue swelling and oedema	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oedema Mouth	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Rash Pruritic	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Rashes, eruptions and exanthems NEC	1 (2.0)	2 (3.9)	3 (2.9)	1 (1.0)	2 (2.0)	3 (1.5)
Rash Macular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (1.0)
Rash	1 (2.0)	2 (3.9)	3 (2.9)	1 (1.0)	0 (0.0)	1 (0.5)
Urticarias	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
POTENTIAL INJECTION SITE REACTION EVENTS	0 (0.0)	7 (13.7)	7 (6.9)	3 (2.9)	3 (2.9)	6 (2.9)

Category High Level Term Preferred Term	Ezetimibe Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Ezetimibe Placebo QM + Ezetimibe QD (N = 51) n (%)	Ezetimibe Overall (N = 102) n (%)	EvoMab 140 mg Q2W + Placebo QD (N = 103) n (%)	EvoMab 420 mg QM + Placebo QD (N = 102) n (%)	EvoMab Overall (N = 205) n (%)
POTENTIAL INJECTION SITE REACTION EVENTS (Cont'd)						
Injection site reactions	0 (0.0)	7 (13.7)	7 (6.9)	3 (2.9)	3 (2.9)	6 (2.9)
Injection Site Erythema	0 (0.0)	3 (5.9)	3 (2.9)	2 (1.9)	2 (2.0)	4 (2.0)
Injection Site Pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	1 (1.0)	3 (1.5)
Injection Site Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (1.0)
Injection Site Bruising	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	1 (1.0)	1 (0.5)
Injection Site Irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Injection Site Swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
Injection Site Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
Injection Site Haematoma	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection Site Vesicles	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

Category High Level Term Preferred Term	Ezetimibe Placebo Q2W + Ezetimibe QD (N = 51) n (%)	Ezetimibe Placebo QM + Ezetimibe QD (N = 51) n (%)	Ezetimibe Overall (N = 102) n (%)	EvoMab 140 mg Q2W + Placebo QD (N = 103) n (%)	EvoMab 420 mg QM + Placebo QD (N = 102) n (%)	EvoMab Overall (N = 205) n (%)
POTENTIAL MUSCLE EVENTS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TRANSAMINASE ELEVATIONS AND POTENTIAL HEPATIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.9)	0 (0.0)	3 (1.5)
Liver function analyses	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.9)	0 (0.0)	3 (1.5)
Liver Function Test Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.0)
Hepatic Enzyme Increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); Q2W = every 2 weeks (subcutaneous); QM = monthly (subcutaneous); QD = once a day (oral tablet)
Event categories are defined using preferred terms (PT) from MedDRA and either Standard MedDRA Queries (SMQ) or internal groupings. Each event category is defined by a unique set of PT while one PT can be categorized into more than one event category.
Coded using MedDRA version 16.1
Source: Applicant's Table 14-6.8.1 from CSR: 20110116 and confirmed with JMP analysis

No subject experienced a positively adjudicated clinical endpoint event or a non-coronary revascularization during this study.

Laboratory Parameters

Creatinine Kinase
A shift in increased CK from baseline to postbaseline occurred in 2 subjects in the evolocumab group (grade 0 to 3 [QM] and grade 1 to 3 [QM]) and 3 subjects in the ezetimibe group (grade 0 to 4 [Q2W] and grade1 to 3 [Q2W], and grade 2 to 3 [Q2W]).

The subject incidence of CK elevations was similar across treatment groups. Four subjects (2 subjects [1.0%] evolocumab and 2 subjects [2.0%] ezetimibe) had CK elevations > 5 x upper limit of normal (ULN) but < 10 x ULN; 3 of the 4 subjects reportedly had strenuous exertion associated with their CK elevations, and the fourth subject had a history of CK elevations. One subject (1.0%) in the ezetimibe group had CK elevations > 10 x ULN. No subjects discontinued IP as a result of CK elevations.

Two subjects (1 evolocumab and 1 ezetimibe) had adverse events of myalgia concurrent with the CK elevation.

Four of the 5 subjects who had CK elevations > 5 x ULN at any postbaseline visit had physical activity associated with their CK elevations and the fifth subject had chronically elevated CK. For 2 subjects, CK returned to < 5 × ULN by the next assessment, and the other 3 subjects did not have repeat assessments available because their elevated CK occurred at week 12. All subjects completed IP treatment. An adverse event of CK increased was reported for 1 subject (ezetimibe [Q2W]) with CK > 5 x ULN at baseline but was not reported for any subject with a postbaseline CK > 5 x ULN; however, myalgia was reported as an adverse event in 2 subjects (1 subject receiving ezetimibe and 1 subject receiving evolocumab).

Liver Related Tests
No subjects had liver related test abnormalities of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN or total bilirubin > 2 x ULN at any postbaseline visit.

Anti-evolocumab Antibodies
Of the 204 subjects in the combined evolocumab groups who were tested for the presence of anti-evolocumab antibodies on study (194 at baseline and 201 postbaseline), no subject tested positive for anti-evolocumab antibodies.

Vital Signs
There were no notable changes from baseline in vital signs (systolic and diastolic blood pressure, heart rate) for either the evolocumab or ezetimibe group.

ECG
No subject had a QTcB value > 480 msec reported at any postbaseline visit and no subject had an increase from baseline that was > 60 msec for QTcB. An increase from baseline > 30 msec for QTcB was reported for 1 (0.5%) subject in the overall evolocumab group. No subject had a maximum postbaseline QTcF value > 480 msec, and 1 (0.5%) subject in the overall evolocumab group had an increase from baseline > 30 msec for QTcF

Conclusions:
One of the limitations of this trial is that the participants were not required to have failed at least one statin at the lowest starting daily dose– e.g., a patient who could tolerate atorvastatin 10 mg per day could be considered “statin-intolerant” by the applicant’s definition.

Another important limitation is that this trial did not include a statin rechallenge arm, which the Division strongly recommended as a method to test whether the inclusion criteria appeared to enroll a “statin intolerant” population successfully. In such a

design, one would expect that there would be more adverse events and a higher discontinuation rate for the adverse event of interest in the statin arm.

Another limitation of Trial 20110116 is the rather short duration of study—12 weeks. It is difficult to consider a marketing claim based on data demonstrating that a serious adverse event, especially a rare event such as rhabdomyolysis, did not occur during a 12-week trial. In addition, when studying a statin-intolerant population, we are interested in the incidence rate of and treatment withdrawal from *all* adverse events that lead to treatment withdrawal. Twelve weeks does not provide an adequate time to assess long-term adherence to therapy.

Data from this trial show the following:

- Compared with ezetimibe, evolocumab treatment resulted in statistically significant reductions in reflexive LDL-C from baseline to week 12 in both the Q2W and QM treatment groups (treatment differences: 38% and 38%, respectively).

- Treatment emergent adverse events with evolocumab were similar to those with ezetimibe, including the incidence and severity of adverse events, the incidence of adverse events leading to treatment discontinuation, and the incidence of serious adverse events. Of note, this trial was not designed to demonstrate similarity with regard to safety endpoints.

- No trends indicative of clinically important treatment related laboratory abnormalities were observed, there was no evidence of anti-evolocumab antibodies, and the overall safety assessment of evolocumab was not changed after the review of the events of interest.

6 Review of Efficacy

Efficacy Summary

Refer to Section 1.2 Risk Benefit Assessment

6.1 Indication

The applicant proposes indications for primary hyperlipidemia and mixed dyslipidemia as well as HoFH.

Primary Hyperlipidemia and Mixed Dyslipidemia
The applicant is seeking the following indication in primary hyperlipidemia and mixed dyslipidemia: Evolocumab is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to

reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides(TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

The proposed dosing regimens are 140 mg SC Q2W or 420 mg SC QM. The applicant proposes that these 2 doses provide dosing flexibility for patients while delivering an "equivalent clinical response." One limitation of this approach is that it does not allow for down-titration of the evolocumab dose based on tolerability or safety issues or because adequate LDL-C lowering has been achieved. For example, if a patient achieves a low LDL-C level (for example, < 25 mg/dL) on the combination of statin plus evolocumab and the physician does not want to push the LDL-C to such a low level, there is no option to lower the dose of evolocumab; only the statin dose can be reduced or titrated to achieve the desired LDL level. This concern was discussed with the applicant at the End-of-Phase 2 meeting in July 2012, but the applicant chose not to study additional dosing regimens in phase 3.

Homozygous Familial Hypercholesterolemia

The applicant is seeking the following indication for HoFH: Evolocumab is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

In HoFH patients, the proposed dosing regimens are 420 mg Q2W or 420 mg QM. The initial proposed dose is 420 mg QM for non-apheresis subjects and 420 mg Q2W for apheresis subjects with the ability to titrate to the more or less frequent dose based on clinical response.

6.1.1 Methods

For the primary hyperlipidemia indication, the integrated efficacy analysis consisted of four 12-week, phase 3 trials in participants with primary hyperlipidemia that utilized the to-be-marketed formulation and dose (trials 20110114/MENDEL-2, 20110115/LAPLACE-2, 20110116/GAUSS-2, and 20110117/RUTHERFORD-2).

These four trials explored the use of evolocumab in four different patient populations: (1) monotherapy in a population at low CV risk (10-year Framingham risk score of 10% or less); (2) in combination with statins; (3) in 'statin-intolerance'; and, (4) in heterozygous familial hypercholesterolemia (HeFH).

In all four trials at screening, participants had to have fasting triglycerides ≤ 400 mg/dL. The entry criteria for LDL-C varied among the 4 trials:

- 114: fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL
- 115: subjects on an intensive statin: fasting LDL-C ≥ 80 mg/dl; subjects on a non-intensive statin: fasting LDL-C ≥ 100 mg/dl; subjects not taking a statin: fasting LDL-C ≥ 150 mg/dl.
- 116: LDL-C ≥ 100 mg/dL with CHD or CHD risk equivalent, LDL-C ≥ 130 mg/dL without diagnosed CHD or risk equivalent and ≥2 risk factors, LDL-C ≥ 160 mg/dL without diagnosed CHD or risk equivalent and with 1 risk factor, LDL-C ≥ 190 mg/dL without diagnosed CHD or risk equivalent and with no risk factors.
- 117: LDL-C ≥ 100 mg/dL

In the phase 3 trial 20110116, statin intolerance was defined as the inability to tolerate at least 2 statins at any dose, or an increase in statin dose above a total weekly maximum due to intolerable myopathy (ie, myalgia, myopathy, rhabdomyolysis), and having a history of symptom improvement or resolution with statin discontinuation.

MO Comment: For the statin-intolerant population, the applicant chose not to use the Division's working definition of statin intolerance. This is discussed at length in Sections 2.6 Other Relevant Background Information and 5.3.2 Trial 20110116: GAUSS-2.

This reviewer finds the monotherapy at low CV risk population problematic because a low CV risk population may not need lipid-lowering medication and may be appropriately treated with lifestyle changes. If drug therapy is deemed appropriate, statins would be the first-line choice given the wealth of efficacy and safety data with statins as well as proven CV morbidity and mortality reduction. I believe it would be inappropriate to indicate a PCSK9 inhibitor for the general population at low-to-moderate CV risk, with the possible exception of the truly statin-intolerant population, before cardiovascular (CV) outcomes data are available (although it is reasonable to study this population prior to CVOT results). The monotherapy group also represents a different safety population than the population who would likely use evolocumab if it is approved. This reviewer expects that the greatest benefit for evolocumab, and PCSK9 inhibitors in general, is in the highest risk population; for example, as add-on therapy in patients with HeFH or patients at significant CV risk despite maximally tolerated lipid lowering therapy. These patients will likely have more concomitant

medications and other CV risk factors, such as CVD, diabetes and hypertension, as compared to the healthier monotherapy group.

For the population in the evolocumab added on to background statin therapy trials, patients should have been enrolled who were not at goal despite taking the maximally tolerated dose of statin, with or without other lipid-modulating agents. In my opinion, this would have reflected an appropriate use of evolocumab for patients who need additional treatment beyond statin therapy. In trial 20110115, this was not the case and it was entirely possible for a patient to be randomized to a less-intensive statin regimen than what the patient was taking prior to the trial. For example, a subject with known coronary heart disease could be assigned to simvastatin 40 mg + placebo despite taking atorvastatin 80 mg + ezetimibe at screening.

The four, 12-week, phase 3 trials (20110114, 20110115, 20110116, and 20110117) shared the following characteristics:

- international, multicenter
- Phase 3, to-be-marketed formulation and device
- double-blind and randomized
- placebo (SC/PO) controlled and/or ezetimibe (PO) controlled (double-dummy)
- 12-week treatment durations
- 140 mg Q2W and 420 mg QM SC administration of evolocumab
- endpoints and LDL-C measurement methodology
- schedule of assessments
- data monitoring and clinical endpoints committees
- Design
    - During screening, SC administration of placebo was performed to confirm tolerability of SC administration prior to randomization. All participants received placebo SC that corresponded to the QM dose volume (3.0 mL) using 3 consecutively administered autoinjector/pens (AI/pens).
    - Participants returned to the study center at Weeks 2, 8, 10, and 12 for collection of study assessments, including blood samples for the determination of lipid parameters. Blood samples for determination of evolocumab and PCSK9 serum concentrations were collected at Day 1 and at Weeks 2, 10, and 12.
    - The end of study occurred at the study center at Week 12 for participants randomized to the QM IP schedule, and by phone call at week 14 for participants randomized to the Q2W IP schedule.
    - The co-primary endpoints were:
        - percent change from baseline in LDL-C at week 12
        - percent change from baseline in LDL-C at the mean of weeks 10 and 12

- For all analyses related to LDL-C, unless specified otherwise, a reflexive approach was used, where the calculated LDL-C[52] was used unless the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, in which case ultracentrifugation LDL-C[53] was used.
- Analyses of Co-primary Endpoints
  - To assess the co-primary endpoints of the percent change from baseline at week 12 and the percent change in LDL-C from baseline at the mean of weeks 10 and 12, a repeated measures linear effects model was used within each dose frequency to compare the efficacy of evolocumab with placebo and ezetimibe. The repeated measures model included terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Missing values were not imputed when the repeated measures linear effects model was used.
- Safety Analyses
  - Adverse events were coded using Version 16.1 of the Medical Dictionary for Regulatory Activities (MedDRA).
  - Events of death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure were adjudicated by an independent clinical events committee.

- Inclusion criteria
  - Men and women ≥ 18 to ≤ 80 years of age, with fasting triglycerides ≤ 400 mg/dL by central laboratory at screening
- Exclusion criteria
  - Lipid-regulating drug in the last 6 weeks (3 months for 20110114) prior to LDL-C screening
  - Uncontrolled serious cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid

52 Calculated LDL-C was determined based on the Friedewald equation which states that LDL-C equals total cholesterol minus (VLDL-C plus HDL-C), where VLDL-C is estimated by the concentration of triglycerides divided by 5 (when using conventional mass based units)
53 Since the Friedewald calculation only estimates VLDL-C by assuming the ratio of triglycerides to cholesterol in VLDL-C is 5:1 (mass/mass), any situation in which VLDL-C composition is altered can introduce error in the LDL-C estimation. For the most accurate LDL-C measurement, VLDL-C needs to be removed prior to measuring LDL-C. The applicant states that VLDL-C was separated from the other lipoproteins by UC. Preparative UC separates lipoproteins by density, and direct measurement of each sub-fraction can occur. Following UC, VLDL-C is found in the top fraction of the tube while the other lipoproteins are found in the bottom fraction. LDL-C is then determined by measuring the cholesterol in the bottom fraction and subtracting HDL-C from this value. The UC method of assessing LDL-C eliminates the inaccuracies introduced when VLDL-C is estimated by triglycerides divided by 5. VLDL-C can then also be quantified by measuring cholesterol in the top fraction.

ventricular response, or supraventricular tachycardia that are not controlled by medications, in the past 3 months prior to randomization
- NYHA III or IV heart failure, or last known left ventricular ejection fraction < 30% (NYHA II - IV heart failure for 20110114)
- Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg
- Uncontrolled hypothyroidism or hyperthyroidism as defined by thyroid stimulating hormone (TSH) < 1.0 time the lower limit of normal (LLN) or > 1.5 times the ULN, respectively, at screening
- Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2 at screening
- Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x ULN
- CK > 3 times the ULN at screening
- Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator
- Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to randomization
- Female subject who has either (1) not used at least 1 highly effective method of birth control for at least 1 month prior to screening or (2) is not willing to use such a method during treatment and for an additional 15 weeks after the end of treatment, unless the subject is sterilized or postmenopausal
- Subject is pregnant or breast feeding, or planning to become pregnant during treatment and/or within 15 weeks after the end of treatment
- Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years

The unique characteristics of each of the four Phase 3 trials for primary hyperlipidemia are summarized below.

20110114: A Double-blind, Randomized, Placebo- and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 in Subjects With a 10-Year Framingham Risk Score of 10% or Less

Publication: Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 Monotherapy for Hypercholesterolemia The MENDEL-2 Randomized, Controlled Phase III Clinical Trial of Evolocumab. J Am Coll Cardiol 2014;63:2531–40)

Design: double-blind, randomized, double-dummy, placebo-and ezetimibe-controlled, parallel-group study evaluating the effect of 12 weeks of evolocumab SC compared with placebo when administered as monotherapy Q2W or QM on percent change from baseline in LDL-C in hyperlipidemic participants with a 10-year Framingham risk score of 10% or less. After the 6 week screening period, eligible participants were randomized with an allocation ratio of 2:2:1:1:1:1 into 6 treatment groups as shown below. Randomization was stratified on the basis of screening LDL-C concentration (< 130 mg/dL or ≥ 130 mg/dL).

Treatment Group	Investigational Product and Dose	Planned Number of Subjects
Evolocumab Q2W	Evolocumab 140 mg SC Q2W and placebo PO QD	150
Evolocumab QM	Evolocumab 420 mg SC QM and placebo PO QD	150
Ezetimibe (Q2W)	Placebo SC Q2W and ezetimibe 10 mg PO QD	75
Ezetimibe (QM)	Placebo SC QM and ezetimibe 10 mg PO QD	75
Placebo Q2W	Placebo SC Q2W and placebo PO QD	75
Placebo QM	Placebo SC QM and placebo PO QD	75

SC = subcutaneously; Q2W = once every 2 weeks; PO = orally; QD = once daily; QM = once monthly.

Main Inclusion Criteria: Fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL and at screening, and a National Cholesterol Education Program (NCEP) Adult Treatment Panel III Framingham risk score of 10% or less.

Main Exclusion Criteria:

- History of coronary heart disease (CHD) or CHD risk-equivalent disease as per NCEP ATP III
- Diabetes mellitus or fasting serum glucose at screening ≥ 126 mg/dL or HbA1c ≥ 6.5%

20110115: A Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

Publications:

1. Robinson JG, Rogers WJ, Nedergaard BS, et al. Rationale and Design of LAPLACE-2: A Phase 3 Randomized, Double-Blind, Placebo- and Ezetimibe-Controlled Trial Evaluating the Efficacy and Safety of Evolocumab in Subjects With Hypercholesterolemia on Background Statin Therapy. Clin Cardiol. 2014 Jan 30.

2. Robinson JG, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014 May 14;311(18):1870-82.

Design: Double-blind, randomized, double-dummy, placebo- and ezetimibe-controlled, parallel group study designed to evaluate the effect of 12 weeks of evolocumab SC administered Q2W or QM, compared with placebo, in combination with a statin on percent change from baseline in LDL-C in hyperlipidemic participants.

After the screening period, eligible participants were first randomized to 1 of 5 open-label statin cohorts (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg) for the lipid stabilization period. Randomization into the statin dose cohorts was stratified by entry statin therapy (no statin use vs non-intensive statin use vs intensive statin use).

After the lipid stabilization period, eligible participants were randomized within each statin dose cohort to blinded investigational product (IP): evolocumab 140 mg SC Q2W or 420 mg QM; placebo SC and/or oral (PO); or ezetimibe 10 mg PO (for the atorvastatin cohorts only). Within each statin dose cohort, 100 participants were planned to be randomized to each evolocumab group and 50 participants to each placebo and ezetimibe group (ezetimibe group was only in the atorvastatin cohorts).

Main Inclusion Criteria: Participants already receiving intensive statin therapy were required to have fasting LDL-C at screening of ≥ 80 mg/dL (i.e., before the lipid stabilization period). Participants receiving non-intensive statin therapy were required to have a fasting LDL-C at screening of ≥ 100 mg/dL. Participants not receiving a statin at screening were required to have a fasting LDL-C of ≥ 150 mg/dL.

Main Exclusion Criteria:

- Current or prior history of statin intolerance (as determined by investigator), or any intolerance to rosuvastatin, atorvastatin, or simvastatin.
- Subject, who in the opinion of the investigator, requires maximal statin therapy
- Personal or family history of hereditary muscular disorders
- Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 6 months prior to randomization
- Planned cardiac surgery or revascularization
- Type 1 diabetes, poorly controlled type 2 diabetes (HbA1c > 8.5%), newly diagnosed type 2 diabetes (within 6 months of randomization), or laboratory evidence of diabetes during screening (fasting serum glucose ≥ 126 mg or HbA1c ≥ 6.5%) without prior diagnosis of diabetes)

20110116: A Double-blind, Randomized, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor

Publications:

1. Cho L, Rocco M, Colquhoun D, et al. Design and Rationale of the GAUSS-2 Study Trial: A Double-Blind, Ezetimibe-Controlled Phase 3 Study of the Efficacy and Tolerability of Evolocumab (AMG 145) in Subjects With Hypercholesterolemia Who Are Intolerant of Statin Therapy. Clin Cardiol. 2014 Jan 29.
2. Stroes E, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun17;63(23):2541-8.

This trial is described in detail in Section 5.3.2.

20110117: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Subjects With Heterozygous Familial Hypercholesterolemia (RUTHERFORD-2)

Publication: Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. The Lancet - 2 October 2014 DOI: 10.1016/S0140-6736(14)61399-4

Design: Double-blind, randomized, placebo-controlled, parallel-group study was designed to evaluate the effect of 12 weeks of evolocumab SC compared with placebo when administered Q2W or QM on percent change from baseline in LDL-C in subjects with HeFH on stable doses of a statin and other lipid-lowering therapies.

After the 6 week screening period, eligible subjects were randomized with an allocation ratio of 2:2:1:1 into 4 treatment groups, as shown below. Randomization was stratified on the basis of screening LDL-C concentration (< 160 mg/dL vs ≥ 160 mg/dL) and ezetimibe use at baseline (yes vs no).

Treatment Group	Investigational Product and Dose	Planned Number of Subjects
Evolocumab Q2W	Evolocumab 140 mg SC Q2W	100
Evolocumab QM	Evolocumab 420 mg SC QM	100
Placebo Q2W	Placebo SC Q2W	50
Placebo QM	Placebo SC QM	50

SC = subcutaneously; Q2W = once every 2 weeks; QM = once monthly.

Main Inclusion Criteria:

- Diagnosis of HeFH by the diagnostic criteria of the Simon Broome Register Group (SBRG) (Scientific Steering Committee, 1991) as defined by the documentation of one of the following in the patient's past medical record:
  1. A total cholesterol concentration > 290 mg/dL in adulthood or a total cholesterol concentration > 260 mg/dL in childhood at an age of less than 16 years, or a LDL-C concentration > 190 mg/dL in adulthood or > 155 mg/dL in childhood AND tendinous xanthomas in the patient or first- or second-degree relative
  2. Deoxyribonucleic acid (DNA)-based evidence of mutation in the LDLR, ApoB, or PCSK9 gene
  3. A total cholesterol concentration > 290 mg/dL in adulthood or a total cholesterol concentration > 260 mg/dL in childhood at an age of less than 16 years, or a LDL-C concentration > 190 mg/dL in adulthood or > 155 mg/dL in childhood AND family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
  4. A total cholesterol concentration > 290 mg/dL in adulthood or a total cholesterol concentration > 260 mg/dL in childhood at an age of less than 16 years, or a LDL-C concentration > 190 mg/dL in adulthood or > 155 mg/dL in childhood AND family history of raised total cholesterol concentration > 290 mg/dL in a first or second-degree adult relative or > 260 mg/dL in child, brother, or sister aged younger than 16 years
- On a stable dose(s) of a statin and other allowed lipid-regulating drugs for at least 4 weeks before LDL-C screening, with fasting LDL-C ≥ 100 mg/dL

Main Exclusion Criteria:

- Homozygous familial hypercholesterolemia
- LDL or plasma apheresis within 4 months prior to randomization
- Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 6 months prior to randomization
- Planned cardiac surgery or revascularization
- Type 1 diabetes, poorly controlled type 2 diabetes (HbA1c > 8.5%), newly diagnosed type 2 diabetes (within 6 months of randomization), or laboratory evidence of diabetes during screening (fasting serum glucose ≥ 126 mg or HbA1c ≥ 6.5%) without prior diagnosis of diabetes)
- Subject requires uptitration of their current statin dose (these subjects can be uptitrated and rescreened one month later)

HoFH
The indication for HoFH is supported by 2 trials, trial 20110233 and ongoing trial 20110271. Trial 20110233 used an evolocumab dose of 420 mg QM and ongoing trial

20110271 is using doses of 420 mg QM and 420 mg Q2W. The duration of exposure is 12 weeks in trial 20110233 and up to 84 weeks in trial 20110271.

Trial 20110233 was a 2-part phase 2/3 study and is complete. Part A was a phase 2, open-label, single-arm pilot HoFH trial in which all participants (N = 8) received evolocumab 420 mg QM for 12 weeks. Part B was a phase 3, double-blind, randomized, placebo-controlled HoFH trial in which participants (N = 49) were randomized to receive either evolocumab 420 mg QM or placebo QM for 12 weeks. Participants were on background statin therapy with or without ezetimibe and not receiving apheresis. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents.

Trial 20110271 is an ongoing, phase 2/3, open-label extension trial in participants with HoFH or FH. This trial enrolled 96 HoFH participants in the interim analysis set (based on a data cutoff date of 01 April 2014) who completed Part A or Part B of Study 20110233 as well as participants who rolled over from other parent trials or had not received treatment in any parent trial (referred to as non-parent). Participants on apheresis initiated Study 20110271 with 420 mg evolocumab Q2W, while participants not on apheresis initiated treatment with 420 mg QM. Participants were subsequently allowed to switch between the evolocumab 420 mg Q2W and QM dose, depending on their response to the current dose.[54]

6.1.2 Demographics

Primary Hyperlipidemia
The four Phase 3 trials that evaluated the efficacy of evolocumab were heterogeneous and varied in terms of baseline CHD risk, CV risk factors (such as diabetes and hypertension) and baseline LDL-C. This is detailed in Table 35: Demographics of the Integrated Four Phase 3 Trials in the ISE.

In the integrated analysis of efficacy of the four 12-week trials for primary hyperlipidemia, participants were from Europe, North America, and Asia Pacific. The mean (SD) age at baseline in the integrated efficacy analysis population was 58 (11) years, and approximately 49% of participants were female. Most participants were white (92%) and non-Hispanic (95%). Approximately 52% of participants were enrolled at sites in Europe, 40% in North America and 8% Asia Pacific. Approximately 30% (n = 958) of participants were ≥ 65 years old.

54 (b) (4) .

Approximately 20% and 10% of participants in the integrated efficacy analysis population had a prior diagnosis of CAD and cerebrovascular or peripheral arterial disease, respectively. Approximately 300 (9.6%) participants had a history of myocardial infarction; only 69 (2.2%) participants had a history of stroke at baseline. Approximately 4% (136) had a history of congestive heart failure of which 1.7% of participants had CHF NYHA class I and 2.6% had CHF NYHA class II.

Additional baseline characteristics include 12% had Type 2 diabetes mellitus; 49% had hypertension; approximately 34% were high, 10% were moderately-high and 29% were moderate risk by NCEP ATP-III risk categories. Thus, less than 45% (1370 participants) were at moderate-high or higher CHD risk at baseline.

In the integrated efficacy analysis population, 72.4% of the participants were on statins. Approximately 33% of participants were using high-intensity statin therapy (per ACC/AHA definition statins such as atorvastatin 80 mg or rosuvastatin 40 mg) and 38% were using moderate intensity statin therapy (such as atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 20-40 mg). Twenty-eight percent were not on any statin therapy. Participants who received ezetimibe were less likely to use high-intensity statin therapy, this was due to the parent study designs in which ezetimibe was used as a randomized active control in trials 20110114, 20110115 (atorvastatin cohorts), and 20110116. Statin use was lower in the ezetimibe group (50.3%) compared with the placebo (74.2%) and evolocumab (81.1%) groups in part because ezetimibe was used as the active control in trial 20110116 (statin intolerance); this trial did not have a placebo arm. Trials 20110114 (monotherapy) and 20110115 (combination therapy) had both placebo and ezetimibe controls, although the ezetimibe control in trial 20110115 was limited to the atorvastatin cohorts. In addition to statins, subjects were using other lipid-regulating medications (as allowed by individual parent study criteria) such as fish oil (4%), niacin (0.3%), and bile acid sequestrants (1.3%) which were similar across the treatment groups.

Mean (SD) serum concentration of LDL C at baseline in the integrated efficacy analysis population was 128.7 (49.1) mg/dL, mean HDL-C was 54.1 mg/dL and median triglyceride was 119.0 mg/dL.

Table 35: Demographics of the Integrated Four Phase 3 Trials in the ISE

	Control				**EvoMab**		**Total**
	Placebo SC Q2W (N =411) n (%)	Placebo SC QM (N = 410) n (%)	Placebo SC Q2W+Eze. (N = 240) n (%)	Placebo SC QM +Eze. (N =237) n (%)	140 mg Q2W (N=921) n (%)	420 mg QM (N=927) n (%)	(N=3146) n (%)
Sex Female	207 (50.4)	204 (49.8)	133 (55.4)	130 (54.9)	432 (46.9)	447 (48.2)	1553 (49.4)
Age (yrs) Mean	57.6	56.9	58.7	58.2	57.4	58.2	57.8

	Control				EvoMab		Total
	Placebo SC Q2W (N =411) n (%)	Placebo SC QM (N = 410) n (%)	Placebo SC Q2W+Eze. (N = 240) n (%)	Placebo SC QM +Eze. (N =237) n (%)	140 mg Q2W (N=921) n (%)	420 mg QM (N=927) n (%)	(N=3146) n (%)
Age ≥ 65 years	116 (28.2)	118 (28.8)	87 (36.3)	71 (30.0)	272 (29.5)	294 (31.7)	958 (30.5)
White	376 (91.5)	382 (93.2)	218 (90.8)	205 (86.5)	839 (91.1)	858 (92.6)	2878 (91.5)
Asian	14 (3.4)	12 (2.9)	10 (4.2)	16 (6.8)	28 (3.0)	28 (3.0)	108 (3.4)
Black	14 (3.4)	13 (3.2)	10 (4.2)	12 (5.1)	41 (4.5)	34 (3.7)	124 (3.9)
Europe	229 (55.7)	224 (54.6)	112 (46.7)	116 (48.9)	462 (50.2)	496 (53.5)	1639 (52.1)
North America	151 (36.7)	160 (39.0)	106 (44.2)	103 (43.5)	385 (41.8)	366 (39.5)	1271 (40.4)
Asia Pacific	31 (7.5)	26 (6.3)	22 (9.2)	18 (7.6)	74 (8.0)	65 (7.0)	236 (7.5)
National cholesterol education program (NCEP) CHD risk categories							
High	121 (29.4)	136 (33.2)	76 (31.7)	77 (32.5)	333 (36.2)	319 (34.4)	1062 (33.8)
Mod-high	44 (10.7)	31 (7.6)	19 (7.9)	25 (10.5)	84 (9.1)	105 (11.3)	308 (9.8)
Moderate	116 (28.2)	112 (27.3)	76 (31.7)	70 (29.5)	278 (30.2)	250 (27.0)	902 (28.7)
Low	130 (31.6)	131 (32.0)	69 (28.8)	65 (27.4)	226 (24.5)	253 (27.3)	874 (27.8)
Coronary artery disease	78 (19.0)	72 (17.6)	35 (14.6)	32 (13.5)	197 (21.4)	208 (22.4)	622 (19.8)
Angina	42 (10.2)	41 (10.0)	17 (7.1)	20 (8.4)	96 (10.4)	112 (12.1)	328 (10.4)
Myocardial infarction	38 (9.2)	33 (8.0)	15 (6.3)	13 (5.5)	101 (11.0)	102 (11.0)	302 (9.6)
Coronary artery bypass graft	20 (4.9)	18 (4.4)	11 (4.6)	4 (1.7)	63 (6.8)	72 (7.8)	188 (6.0)
Percutaneous coronary intervention	48 (11.7)	42 (10.2)	18 (7.5)	25 (10.5)	119 (12.9)	118 (12.7)	370 (11.8)
Cerebrovascular or peripheral arterial disease	370 (11.8)	41 (10.0)	25 (10.4)	13 (5.5)	93 (10.1)	102 (11.0)	307 (9.8)
Transient ischemic attack	8 (1.9)	9 (2.2)	2 (0.8)	6 (2.5)	17 (1.8)	22 (2.4)	64 (2.0)
Stroke	9 (2.2)	11 (2.7)	6 (2.5)	4 (1.7)	18 (2.0)	21 (2.3)	69 (2.2)
Carotid or vertebral artery disease	9 (2.2)	19 (4.6)	9 (3.8)	2 (0.8)	44 (4.8)	45 (4.9)	133 (4.2)
Peripheral arterial disease	9 (2.2)	11 (2.7)	9 (3.8)	5 (2.1)	37 (4.0)	32 (3.5)	105 (3.3)
Current cigarette use	48 (11.7)	66 (16.1)	37 (15.4)	35 (14.8)	135 (14.7)	118 (12.7)	439 (14.0)
Type 2 diabetes mellitus	35 (8.5)	49 (12.0)	27 (11.3)	44 (18.6)	128 (13.9)	97 (10.5)	380 (12.1)

	Control				EvoMab		Total
	Placebo SC Q2W (N =411) n (%)	Placebo SC QM (N = 410) n (%)	Placebo SC Q2W+Eze. (N = 240) n (%)	Placebo SC QM +Eze. (N =237) n (%)	140 mg Q2W (N=921) n (%)	420 mg QM (N=927) n (%)	(N=3146) n (%)
Hypertension	189 (46.0)	188 (45.9)	111 (46.3)	123 (51.9)	482 (52.3)	455 (49.1)	1548 (49.2)
LDL-C (mg/dL) Mean	117.7	122.1	140.0	137.3	129.5	130.6	128.7
LDL-C (mg/dL) Q1, Q3	90.0, 139.5	93.0, 143.0	106.5, 162.5	104.0, 162.0	93.0, 154.0	95.0, 156.0	95.0, 153.0
HDL-C (mg/dL) Mean	54.6	55.2	54.4	52.5	53.0	54.8	54.1
TG (mg/dL) Median	112.0	113.0	131.3	125.0	121.0	118.0	119.0
Lp(a) (nmol/L) Median	34.0	36.5	36.0	28.0	36.0	35.0	34.0
hsCRP (mg/L)∞ Median	1.29	1.34	1.36	1.76	1.42	1.40	1.40
Statin therapy intensity per ACC/AHA definition*							
High	149 (36.3)	152 (37.1)	56 (23.3)	55 (23.2)	305 (33.1)	307 (33.1)	1024 (32.5)
Moderate	181 (44.0)	179 (43.7)	60 (25.0)	59 (24.9)	360 (39.1)	365 (39.4)	1204 (38.3)
Low	5 (1.2)	0	5 (2.1)	5 (2.1)	16 (1.7)	16 (1.7)	47 (1.5)
Unknown	0	0	0	0	2 (0.2)	0	2 (0.1)
None	76 (18.5)	79 (19.3)	119 (49.6)	118 (49.8)	238 (25.8)	16 (1.7)	869 (27.6)

CHD = coronary heart disease; EvoMab = Evolocumab (AMG 145); QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; CHD = coronary heart disease;
*ACC = American College of Cardiology; AHA = American Heart Association; High-Intensity Statin Therapy (such as atorvastatin 80 mg or rosuvastatin 40 mg) and Moderate-Intensity Statin Therapy (such as atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 20-40 mg).; Amgen definition: intensive if atorvastatin ≥ 40 mg QD, rosuvastatin ≥ 20 mg QD, simvastatin ≥ 80 mg QD, or any statin use with concurrent ezetimibe use and nonintensive is any statin use not classified as intensive.
∞ According to the American Heart Association: Low risk of developing cardiovascular disease if hs-CRP level is < 1.0mg/L; average risk of developing cardiovascular disease if levels are between 1.0 and 3.0 mg/L; high risk for cardiovascular disease if hs-CRP level is > 3.0 mg/L.
Includes the following studies: 20110114, 20110115, 20110116, 20110117.
Subjects from countries with an undefined risk are classed as low risk.
Source: Modified from ISE Table 14-2.1.1, ISE Table 14-2.4.1, ISE Table 14-2.6.1, ISE Table 14-2.7.1., ISE Table 14-2.5.401.and ISE Table 14-2.2.1

The table below summarizes the demographics of the four Phase 3 trials presented by trial. Some notable differences among the trials is that the monotherapy trial (20110114) is primarily comprised of individuals at low or moderate CHD risk and has only a small percentage of individuals with risk factors such as diabetes and hypertension. The statin-intolerant trial (20110116) and the HeFH trial (20110117) have a higher percentage of individuals with high CHD risk. Baseline LDL values are lowest in the statin combination trial (20110115) and highest in the statin intolerant trial.

Baseline statin therapy varied among the trials. No participants received statin therapy at baseline in the monotherapy trial 20110114 and participants were randomized to statin therapy at baseline in the combination trial 20110115. Prior to enrollment in trial 20110115, intensive statin therapy was used by 29% of participants, nonintensive statin by 41%, and 30% were using no statin. In trial 20110116, which evaluated evolocumab compared with ezetimibe in participants with statin intolerance, the majority of participants (252 of 307 [82%] total; 82% evolocumab, 81% ezetimibe) were not receiving a statin at baseline. A total of 13 participants (4%; 7 [3.4%] evolocumab, 6 [5.9%] ezetimibe) were taking moderate-intensity statins and 40 participants (13%; 28 [13.7%] evolocumab, 12 [11.8%] ezetimibe) were taking low-intensity statins. In trial 20110117, which evaluated evolocumab in participants with HeFH, the majority of participants in each treatment group (170 [77%] evolocumab, 80 [73%] placebo) were taking high-intensity statins. Moderate intensity statins were taken by 47 participants (21%) in the evolocumab group and 25 participants (23%) in the placebo group. Less than 1% and 4% of participants in the evolocumab group (2 [0.9%]) and placebo group (4 subjects [3.7%]), respectively, were taking low-intensity statins.

Table 36: Demographics of the Individual Four Phase 3 Trials in the ISE

	20110114 (Monotherapy)	20110115 (Statin Combination)	20110116 (Statin-Intolerant)	20110117 (HeFH)
	Total (N = 614) n (%)	Total (N = 1896) n (%)	Total (N=307) n (%)	Total (N=329) n (%)
Sex Female	405 (66.0)	868 (45.8)	141 (45.9)	139 (42.2)
Age (yrs) Mean	55.1	59.8	61.5	51.2
Age ≥ 65 years	111 (18.1)	671 (35.4)	127 (41.4)	49 (14.9)
White	510 (83.1)	1782 (94.0)	287 (93.5)	296 (90.0)
Asian	58 (9.4)	25 (1.3)	10 (3.3)	16 (4.9)
Black	40 (6.5)	75 (4.0)	7 (2.3)	3 (0.9)
Europe	199 (32.4)	1108 (58.4)	154 (50.2)	178 (54.1)
North America	351 (57.2)	734 (38.7)	112 (36.5)	74 (22.5)
Asia Pacific	64 (10.4)	54 (2.8)	41 (13.4)	77 (23.4)
National cholesterol education program (NCEP) CHD risk categories				
High	7 (1.1)	740 (39.0)	173 (56.4)	142 (43.2)
Mod-high	30 (4.9)	214 (11.3)	45 (14.7)	19 (5.8)
Moderate	226 (36.8)	533 (28.1)	53 (17.3)	90 (27.4)
Low	351 (57.2)	409 (21.6)	36 (11.7)	78 (23.7)
Coronary artery disease	2 (0.3)	427 (22.5)	90 (29.3)	103 (31.3)
Angina	2 (0.3)	223 (11.8)	43 (14.0)	60 (18.2)

	20110114 (Monotherapy)	20110115 (Statin Combination)	20110116 (Statin-Intolerant)	20110117 (HeFH)
	Total (N = 614) n (%)	Total (N = 1896) n (%)	Total (N=307) n (%)	Total (N=329) n (%)
Myocardial infarction	0	212 (11.2)	45 (14.7)	45 (13.7)
Coronary artery bypass graft	0	108 (5.7)	28 (9.1)	52 (15.8)
Percutaneous coronary intervention	0	248 (13.1)	60 (19.5)	62 (18.8)
Cerebrovascular or peripheral arterial disease	4 (0.7)	198 (10.4)	49 (16.0)	56 (17.0)
Transient ischemic attack	1 (0.2)	38 (2.0)	12 (3.9)	13 (4.0)
Stroke	1(0.2)	48 (2.5)	10 (3.3)	10 (3.0)
Carotid or vertebral artery disease	3 (0.5)	77 (4.1)	17 (5.5)	36 (10.9)
Peripheral arterial disease	0	72 (3.8)	18 (5.9)	15 (4.6)
Current cigarette use	72 (11.7)	291 (15.3)	24 (7.8)	52 (15.8)
Type 2 diabetes mellitus	1 (0.2)	293 (15.5)	62 (20.2)	24 (7.3)
Hypertension	176 (28.7)	1084 (57.2)	181 (59.0)	107 (32.5)
LDL-C (mg/dL) Mean	142.9	After lipid stabilization period 109.1	193.1	155.5
LDL-C (mg/dL) Q1, Q3	126.5, 159.0	83.0, 124.0	154.0, 215.0	123.5, 174.0
HDL-C (mg/dL) Mean	58.5	53.5	51.8	51.1
TG (mg/dL) Median	115.3	116.0	152.0	110.0
Lp(a) (nmol/L) Median	25.0	34.0	32.0	65.0
hsCRP (mg/L) Median	1.37	1.45	1.71	0.99
Baseline Statin Therapy	0%	100% Assigned by protocol	17.9%	100%
Atorvastatin	0%	46.5%	2.0%	35.0%
Rosuvastatin	0%	35.8%	8.8%	48.9%
Simvastatin	0%	17.8%	2.3%	12.2%
Other statins	0%	0%	4.8%	3.9%

	20110114 (Monotherapy)	20110115 (Statin Combination)	20110116 (Statin-Intolerant)	20110117 (HeFH)
	Total (N = 614) n (%)	Total (N = 1896) n (%)	Total (N=307) n (%)	Total (N=329) n (%)

CHD = coronary heart disease; EvoMab = Evolocumab (AMG 145); QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; CHD = coronary heart disease;
Includes the following studies: 20110114, 20110115, 20110116, 20110117.
Subjects with an undefined risk are classed as low risk.
Source: Modified from CSR 20110114: Tables 9-3, 14-2.4.1, 14-2.5.1; CSR 20110115: Tables 14-2.2.2, 14-2.4.1, 14-2.5.2; CSR 20110116: Tables 14-2.2.1, 14-2.4.1, 14-2.5.1 and CSR 20110117: Tables 14-2.2.1, 14-2.4.1, 14-2.5.1 and 14-2.7.1

HoFH
For the trial 20110233 (TESLA), Part B, the mean age was 31 years (range, 13-57 years), with 10 (20%) participants younger than 18 years. The mean (SD) baseline LDL-C, determined directly by ultracentrifugation, was 349 (137) mg/dL despite all 49 participants being on statins at baseline (48 on intensive statin, defined as atorvastatin ≥ 40 mg daily or equivalent or any statin plus ezetimibe; and 1 participant on atorvastatin 20 mg).

As the HoFH population was the same for the integrated efficacy as well as the integrated safety evaluation, the demographics of this HoFH population is described in more detail in Section 7.2.1.2 Demographics in the Safety Population.

6.1.3 Subject Disposition

Primary Hyperlipidemia
Of the 3152 participants randomized, 3146 (99.8%) received IP:

- 1848 evolocumab (921 evolocumab SC Q2W, 927 evolocumab SC QM)
- 821 placebo (411 placebo SC Q2W, 410 placebo SC QM)
- 477 ezetimibe (240 ezetimibe [placebo SC Q2W], 237 ezetimibe [placebo SC QM])

In these trials of 12 weeks duration, a total of 3026 (96.0%) participants completed the study. A total of 126 (4.0%) participants discontinued the study: 65 (2.1%) participants discontinued the trial early primarily due to ‘consent withdrawn’ (52; 1.6%) and ‘lost-to-follow up’ (13; 0.4%), and 57 (1.8%) participants enrolled into extension studies without completing the final follow-up visit in the parent trials. This last group made up the majority of the 60 participants who left the trial due to ‘decision by sponsor’. This is summarized in the following table which presents the disposition data for each of the four Phase 3 trials and the combined cohort of the 4 trials.

Table 37: Participant Disposition- Phase 3 Parent Trial and Integrated Cohort

Category	20110114 (Monotherapy)	20110115 (Statin Combination Therapy)	20110116 (Statin-Intolerant)	20110117 (HeFH)	Integrated Cohort (Combined parent trials)
Randomized, n	615	1899	307	331	3152
Received IP, n (%)	614 (99.8)	1896 (99.8)	307 (100.0)	329 (99.4)	3146 (99.8)
Completed IP, n (%)	581 (94.5)	1807 (95.2)	293 (95.4)	324 (97.9)	3005 (95.3)
Completed Study, n (%)	598 (97.2)	1826 (96.2)	290 (94.5)	312 (94.3)	3026 (96.0)
Discontinued Study, n (%)	17 (2.8)	73 (3.8)	17 (5.5)	19 (5.7)	126 (4.0)
Withdrawal of consent	3 (0.5)	40 (2.1)	3 (1.0)	6 (1.8)	52 (1.6)
Death	-	1 (0.1)	-	-	1 (0.03)
Decision by sponsor	8 (1.3)	26 (1.4)	13 (4.2)	13 (3.9)	60 (1.9)
For enrollment into extension study	8 (1.3)	23 (1.2)	13 (4.2)	13 (3.9)	57 (1.8)
Lost to follow-up	6 (1.0)	6 (0.3)	1 (0.3)	-	13 (0.4)

HeFH = heterozygous familial hypercholesterolemia; IP = investigational product; EvoMab = Evolocumab; Q2W = every 2 weeks (subcutaneous), QM = monthly (subcutaneous); QD = once a day (oral tablet);
Source: Modified from ISE Table 14-1.1.1, Table 14-1.1.1 of Study 20110114, Table 14-1.1.2 of Study 20110115, Table 14-1.1.1 of Study 20110116, Table 14-1.1.1 of Study 20110117, Table 13 (2.7.3).

In these four trials of 12 weeks duration, a total of 3005 (95.3%) completed IP, which was balanced among the different treatment groups. The table below summarizes the disposition for the integrated cohort of four Phase 3 trials. A total of 141 (4.5%) participants discontinued IP, primarily due to adverse reactions and subject request. Adverse reactions as a reason to discontinue IP were numerically greater in the EvoMab Q2W dosing compared to EvoMab QM dosing (2.2% and 1.1%, respectively), and compared to the Placebo Q2W dosing (2.0%) and Placebo QM dosing (1.5%).

Table 38: Disposition in the Integrated Cohort of Phase 3 Trials for Primary Hyperlipidemia Indication

	Control				**EvoMab**		**All Total**
	Placebo SC Q2W (N =413) n (%)	Placebo SC QM (N =411) n (%)	Placebo SC Q2W+Eze .(N = 240) n (%)	Placebo SC QM +Eze. (N =237) n (%)	140 mg Q2W (N=924) n (%)	420 mg QM (N=927) n (%)	(N=3152) n (%)
Study Completion Accounting							
Completed study	386 (93.5)	406 (98.8)	222 (92.5)	234 (98.7)	868 (93.9)	910 (98.2)	3026 (96.0)

Discontinued study	27 (6.5)	5 (1.2)	18 (7.5)	3 (1.3)	56 (6.1)	17 (1.8)	126 (4.0)
Consent withdrawn	13(3.2)	4 (1.0)	6 (2.5)	2 (0.8)	14 (1.5)	13 (1.4)	52 (1.6)
Death	1(0.2)	0	0	0	0	0	1 (0.03)
*Decision by sponsor**	11(2.7)	0	11(4.6)	0	37 (4.0)	1 (0.1)	60 (1.9)
Lost to follow-up	2 (0.5)	1(0.2)	1 (0.4)	1(0.4)	5 (0.5)	3 (0.3)	13 (0.4)
Investigational Product Accounting							
Never received IP	2	1	1	0	3	0	6
Received IP	411	410	240	237	921	927	3146 (99.8)
Completed IP	389 (94.6)	392 (95.6)	221 (92.1)	227 (95.8)	879 (95.4)	897 (96.8)	3005 (95.3)
Discontinued IP	**22 (5.4)**	**18 (4.4)**	**19 (7.9)**	**10 (4.2)**	**42 (4.6)**	**30 (3.2)**	**141 (4.5)**
Adverse reaction	8 (1.9)	6 (1.5)	8 (3.3)	5 (2.1)	20 (2.2)	10 (1.1)	57 (1.8)
Pregnancy	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0
Subject request	9 (2.2)	6 (1.5)	6 (2.5)	4 (1.7)	12 (1.3)	12 (1.3)	49 (1.6)
Decision by sponsor	0	0	0	0	1 (0.1)	2 (0.2)	3 (0.1)
Physician decision	0	1 (0.2)	2 (0.8)	0	0	0	3 (0.1)
Lost to follow-up	2 (0.5)	1 (0.2)	1 (0.4)	1 (0.4)	4 (0.4)	1 (0.1)	10 (0.3)
Other	3 (0.7)	4 (1.0)	2 (0.8)	0	5 (0.5)	5 (0.5)	19 (0.6)

Includes the following studies: 20110114, 20110115, 20110116, 20110117.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab;
Eze=ezetimibe; QD = once a day; Q2W = every 2 weeks; QM = monthly;
SC = subcutaneous; IP = investigational product;
*Majority of subjects labeled as decision by sponsor enrolled in the extension study prior to completing the last follow up visit in this study.
Source: Table1-2 IR response 06Nov2014

HoFH

Because the HoFH population was the same for the integrated efficacy and integrated safety evaluation, the disposition of this HoFH population is described in Section 7.2.1.1 Disposition in the Safety Population.

6.1.4 Analysis of Primary Endpoint(s)

Primary Hyperlipidemia
The percent change from baseline in LDL-C at Week 12 was used by the applicant as a co-primary endpoint in the phase 3 trials 20110114, 20110115, 20110116 and 20110117. The other co-primary endpoint used by the applicant was the percent change in LDL-C at the mean of Weeks 10 and 12 to convey information about time-averaged LDL-C reduction with evolocumab therapy over the dosing interval. In the phase 3 trials, the repeated measures linear effects model was used in each dose frequency (Q2W and QM) to compare the efficacy of evolocumab with control groups (placebo or ezetimibe). Multiplicity adjustment method used Hochberg and the fall back procedure to control the familywise error rate at 0.05 for the co-primary endpoints.

The calculation of LDL-C by the Friedewald equation can return underestimated values (ie, greater estimated reductions) when calculated LDL-C concentrations are < 40 mg/dL or triglycerides are high. In the phase 3 trials, the applicant used a reflexive approach, where the calculated LDL-C was used unless the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, in which case LDL-C by preparative ultracentrifugation (UC) was determined and utilized.

Because LDL-C by UC is not routinely used in clinical practice, the applicant proposes to use the calculated LDL-C value for labeling as this method of LDL-C measurement is the more common way in which LDL-C is assessed in the clinical setting.

The table below provides a summary of the primary endpoint efficacy results for the four Phase 3 trials that make up the integrative efficacy assessment. Across the different patient populations and background therapies, evolocumab provides significant LDL-C reduction as compared to placebo and ezetimibe in these trials of 12 weeks duration. In the monotherapy trial 20110114, evolocumab use yielded LDL-C reduction ranging from 55% for the 420 mg QM dose to 57% for the 140 mg Q2W dose. For comparison, high-intensity statins (atorvastatin 40-80 mg; rosuvastatin 20-40 mg) yield LDL-C reductions ranging from 48% to 64%, according to their prescribing information, and some of these doses have proven benefit in CV outcomes trials.

Table 39: Summary of Evolocumab Efficacy Results from the Four Individual Phase 3 Trials in Primary Hyperlipidemia and Mixed Dyslipidemia

<table>
<tr><th>Study</th><th>Description</th><th>Efficacy Results</th></tr>
<tr><td><u>20110114</u>
(N = 615)</td><td><u>Monotherapy (12 weeks):</u>
• EvoMab 140 mg SC Q2W + placebo PO QD
• EvoMab 420 mg SC QM + placebo PO QD
• placebo SC Q2W + placebo PO QD
• placebo SC QM + placebo PO QD
• placebo SC Q2W + 10 mg ezetimibe PO QD
• placebo SC QM + 10 mg ezetimibe PO QD</td><td><u>LDL-C percent change from baseline to week 12</u>
(relative to placebo and ezetimibe)[a] (p value is significant after adjustment for multiplicity; p < 0.001 for all):
• 140 mg SC Q2W:
Reflexive: -57 vs placebo; -39 vs ezetimibe
Calculated: -59 vs placebo; -40 vs ezetimibe
• 420 mg SC QM:
Reflexive: -55 vs placebo; -38 vs ezetimibe
Calculated: -57 vs placebo; -38 vs ezetimibe</td></tr>
<tr><td><u>20110115</u>
(N = 1899)</td><td><u>Combination with atorvastatin, rosuvastatin, or simvastatin (12 weeks):</u>
• EvoMab 140 mg SC Q2W
• EvoMab 420 mg SC QM
• Placebo SC Q2W
• Placebo SC QM
For atorvastatin arms, added ezetimibe 10 mg or placebo PO QD</td><td><u>LDL-C percent change from baseline to week 12</u>
(relative to placebo and ezetimibe)[a, b] (p value is significant after adjustment for multiplicity; p < 0.001 for all):
<table>
<tr><th></th><th colspan="2">140 mg Q2W</th><th colspan="2">420 mg QM</th></tr>
<tr><th></th><th>Reflex.</th><th>Calc.</th><th>Reflex.</th><th>Calc.</th></tr>
<tr><td>Atorv 10 mg (vs pbo)</td><td>-71</td><td>-74</td><td>-59</td><td>-61</td></tr>
<tr><td>Atorv 10 mg (vs eze)</td><td>-40</td><td>-44</td><td>-41</td><td>-43</td></tr>
<tr><td>Atorv 80 mg (vs pbo)</td><td>-76</td><td>-80</td><td>-71</td><td>-74</td></tr>
<tr><td>Atorv 80 mg (vs eze)</td><td>-47</td><td>-50</td><td>-39</td><td>-41</td></tr>
<tr><td>Rosu 5 mg (vs pbo)</td><td>-68</td><td>-71</td><td>-65</td><td>-66</td></tr>
<tr><td>Rosu 40 mg (vs pbo)</td><td>-68</td><td>-71</td><td>-55</td><td>-59</td></tr>
<tr><td>Simv 40 mg (vs pbo)</td><td>-71</td><td>-74</td><td>-60</td><td>-62</td></tr>
</table></td></tr>
<tr><td><u>20110116</u>
(N = 307)</td><td><u>In ‘statin-intolerant’ subjects (12 weeks):</u>
• EvoMab 140 mg SC Q2W and placebo PO QD
• EvoMab 420 mg SC QM and placebo PO QD
• placebo SC Q2W and 10 mg ezetimibe PO QD
• placebo SC QM and 10 mg ezetimibe PO QD</td><td><u>LDL-C percent change from baseline to week 12</u>
(relative to ezetimibe)[a] (p value is significant after adjustment for multiplicity; p < 0.001 for all):
• 140 mg SC Q2W:
Reflexive: -38 vs ezetimibe
Calculated: -39 vs ezetimibe
• 420 mg SC QM:
Reflexive: -38 vs ezetimibe
Calculated: -38 vs ezetimibe</td></tr>
</table>

20110117 (N = 331)	In HeFH subjects (12 weeks): • EvoMab 140 mg SC Q2W • EvoMab 420 mg SC QM • Placebo SC Q2W • Placebo SC QM	LDL-C percent change from baseline to week 12 (relative to placebo)[a] (p value is significant after adjustment for multiplicity; p < 0.001 for all): • 140 mg SC Q2W: Reflexive: -59 vs placebo Calculated: -61 vs placebo • 420 mg SC QM: Reflexive: -61 vs placebo Calculated: -60 vs placebo
a Least squares mean estimate (95% CI) from the repeated measures model which included treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates for all endpoints except LDL-C achievement where the treatment difference is from the CMH model stratified by the stratification factor. b atorvastatin arms only N = number of subjects randomized Source: Modified from applicant's Table 10; Module 2.7.3-Summary of Clinical Efficacy		

The efficacy results for the four integrated Phase 3 trials demonstrate that treatment with evolocumab yielded statistically significant reductions in reflexive LDL-C for both co-primary endpoints (percent change from baseline in LDL-C at week 12 and percent change at mean of weeks 10 and 12). The integrated analyses demonstrated statistically significant reductions in LDL-C for both dosing regimens (evolocumab 140 mg Q2W and 420 mg QM dosing) (multiplicity-adjusted p < 0.001), with random-effects treatment differences (SE) that ranged from reductions of 60.4% (2.1%) for the 420 mg QM dose to 66.7% (2.8%) for the 140 mg Q2W dose compared with placebo, and 38.2% (1.3%) for the 420 mg QM dose to 39.6% (1.4%) for the 140 mg Q2W dose, compared with ezetimibe.

HoFH
Trial 20110233 (part B): The percent change from baseline in LDL-C at Week 12 was used as the primary efficacy endpoint in Study 20110233 part B for the indication of HoFH.

A repeated measures linear effects model was used on participants randomized and receiving at least one dose of IP. The primary analysis model included terms for treatment group, stratification factor, scheduled visit, and the interaction of treatment with scheduled visit, to compare evolocumab with placebo.

In Part A of Trial 20110233, which was a phase 2, open-label pilot study in 8 participants with HoFH, the mean (SD) serum concentration of UC LDL-C at baseline was 442 (113) mg/dL. LDL-C percent change from baseline to Week 12 was -17% for both methods of LDL-C measurement: calculation of LDL-C by the Friedewald equation or by preparative ultracentrifugation (UC).

Part B of Trial 20110233 was a phase 3, double-blind, placebo-controlled trial in 49 participants (33 evolocumab, 16 placebo). Mean (SD) serum concentration of UC LDL-C at baseline was 349 (137) mg/dL. Compared with placebo, evolocumab resulted in statistically significant reductions in LDL-C of approximately 31% at Week 12. Compared to baseline, the mean (SE) percent change in UC LDL-C was -23.1 (3.8) % for evolocumab and 7.9 (5.3)% for placebo.

Trial 20110271 is an ongoing, phase 2/3, open-label long-term extension trial in participants with FH (including, but not limited to, HoFH). Participants with HoFH who completed trial 20110233 and those with FH who rolled over from other parent trials or had not received treatment in any parent trial were eligible to participate in this extension trial. Participants on apheresis as well as those not on apheresis were eligible for this trial. The efficacy evaluation in this section is based on the HoFH interim analysis set which includes all HoFH participants (n=96) enrolled in this trial at the time of the data cutoff date (4/1/14) who have received at least 1 dose of evolocumab. Mean (SD) UC LDL-C at baseline was 321 (131) mg/dL. Evolocumab resulted in UC LDL-C reductions of 19% at Week 12 and 23% at Week 24 in the HoFH analysis set. If serum unbound PCSK9 was ≥ 100 ng/mL with QM dosing, the participant could switch to evolocumab 420 mg Q2W treatment.Increasing the frequency of dosing from 420 mg QM to 420 mg Q2W in participants with HoFH resulted in approximately 6% greater reduction of LDL-C. Of note, the participants who are being treated with apheresis appear to have a reduced response to evolocumab compared to the non-apheresis participants. The reasons for this potential difference are only speculative at the moment – but possibilities include differences in baseline characteristics (apheresis participants may have been more refractory to other therapies, such as statins, perhaps as a result of greater functional defects in LDLR) or an interaction between the apheresis procedure itself with drug PK.

The results from part B of trial 20110233 and the open-label trial 20110271 are summarized in the table below.

Table 40: Summary of Evolocumab Efficacy Results from Individual Trials in HoFH

<table>
<tr><th>Study</th><th>Description</th><th>Efficacy Results</th></tr>
<tr><td><u>20110223</u>
Part B
(N = 49)</td><td><u>Phase 2/3 HoFH trial (12 weeks):</u>
Phase 3 randomized, double-blind, placebo-controlled
• EvoMab 420 mg QM
• placebo QM</td><td><u>UC and calculated LDL-C percent change from baseline to week 12</u> (relative to placebo) (Bold font indicates p < 0.001):
<table>
<tr><th></th><th>Placebo (n=16)</th><th>EvoMab (n=33)</th><th>Treatment difference (n=49)</th></tr>
<tr><td>UC LDL-C</td><td>7.9</td><td>-23.1</td><td>-31†</td></tr>
<tr><td>Calc LDL-C</td><td>9.0</td><td>-23.1</td><td>-32*</td></tr>
</table></td></tr>
<tr><td><u>20110271</u></td><td><u>Phase 2/3 HoFH open</u></td><td><u>UC and calculated LDL-C percent change from baseline[a] to week 24</u>:</td></tr>
</table>

(N = 96) ongoing; interim analysis based on 01 April 2014	label, long-term study (5 years): • EvoMab 420 mg Q2W • EvoMab 420 mg QM		Overall HoFH (n=46)	Apheresis (n=13)	Non-apheresis (N=33)	EvoMab 420 mg Titration[b] (Non-apheresis)(n=25)	
						QM	Q2W
		UC LDL-C:	-23	-20	-25	-16	-22
		Calc LDL-C:	-23	-20	-24	-15	-21

N = number of subjects randomized
a Baseline values for parent study rollover subjects are defined at parent study baseline.
b The 25 subjects in this set initially received ≥ 12 weeks of EvoMab 420 mg QM and then switched to ≥ 12 weeks of EvoMab 420 mg Q2W. Percent change is from baseline to OLE week 12.
† adjusted p-value <0.001
*no formal statistical testing performed, nominal p-value < 0.001
Source: Modified from applicant's Table 12; Module 2.7.3-Summary of Clinical Efficacy

A larger LDL-C reduction was seen in participants with LDL receptor (LDLR) defective HoFH as compared to participants that were not identified as LDLR defective (ie, those with indeterminate/negative LDLR functional status). Based on the type of mutation identified, 28 participants (20 evolocumab, 8 placebo) were considered LDLR-defective (some residual function) in one or both alleles (i.e., as opposed to LDLR-negative, little to no residual function). Among these participants, UC LDL-C was reduced a mean 40.8% from baseline to Week 12, compared to placebo. Those known to have two LDLR-defective alleles had a greater response than those known to have one LDLR-defective paired with one LDLR-negative allele, as summarized in the table below.

Table 41: Percent Change from Baseline in UC LDL-C by Receptor Mutation Status

	Mean Change in UC LDL-C from Baseline to Week 12		
Mutation Status (partial list)	**Evolocumab**	**Placebo**	**Treatment Difference**
Defective in 1 or both alleles	-29.6% (n=20)	+11.2% (n=8)	-40.8% (P<0.001)
Defective/defective	-31.8% (n=8)	+15.1% (n=5)	-46.9% (P<0.001)
Defective/negative	-21.0% (n=6)	+3.5% (n=3)	-24.5% (P=0.013)
Negative/negative	+10.3% (n=1)	-	-

Note: For 6 pts in evolocumab arm, one LDLR was defective and the other was unknown.
Source: Modified from applicant's Appendix 5, supporting document 339, dated 6/18/14 under IND 105188

The clinical team noted that despite two of the eight participants subjects being reported as LDLR-negative in Part A of trial 20110233 (presumably negative/negative

given the apparent lack of response to drug), only 1 of the 49 participants in Part B was reported to be negative/negative; this individual did not show a reduction in LDL-C. Although the clinical team is not aware of detailed genotype/phenotype epidemiological data for HoFH patients in the United States, there was a recent publication that investigated the spectrum of mutations and phenotypic expression in patients with HeFH and HoFH in Italy that found that 11 of 40 patients with HoFH had LDLR-negative phenotypes. Furthermore, approximately 50% of nearly 800 patients with HeFH had a LDLR-negative mutation[55]. In addition, the treatment effect reported in Part B of 20110233 is larger than the effect described from the interim analysis of Study 20110271. The randomized HoFH trial (Part B) may have been enriched (using available genetic information or a previous known response to statin therapy or by chance) with participants who would be expected to have an effect (i.e., LDLR-defective as opposed to LDLR-negative). Although this does not negate the potential benefit that these patients with HoFH may achieve from the drug, it is likely that treatment of the entire HoFH population – where assessment of genetic mutations and their functional significance is not widely performed or understood – would yield a lesser treatment effect, on average.

6.1.5 Secondary Endpoint(s)

Primary Hyperlipidemia
Secondary endpoints in trials 20110114, 20110115, 20110116 and 20110117 were assessed at the mean of Weeks 10 and 12 and at Week 12:

Tier 1 co-secondary endpoints:
- change from baseline in LDL-C
- percent change from baseline in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, total cholesterol, ApoB/ApoA1 ratio

Tier 2 co-secondary endpoints:
- percent change from baseline in Lp(a), triglycerides, HDL-C, VLDL-C

These endpoints were analyzed using a repeated measures linear effects model as used in the primary or co-primary endpoints analysis. Multiplicity adjustment method used Hochberg and the fall back procedure to control the familywise error rate at 0.05 for the primary (or co-primary) and secondary (or co-secondary) endpoints.

As shown in the tables below, the integrated analyses show that evolocumab 140 mg Q2W and 420 mg QM yielded statistically significantly differences in the tier 1 and tier 2 co-secondary endpoints compared with placebo (multiplicity-adjusted $p < 0.001$). It

55 Bertolini S, Pisciotta L, Rabacchi C, et al. Spectrum of mutations and phenotypic expression in patients with autosomal dominant hypercholesterolemia identified in Italy. Atherosclerosis. 2013;227:342-348.

is not known if some of the endpoint changes, such as the modest changes in triglyceride and HDL-C, are clinically meaningful. For the comparison with ezetimibe, triglycerides and VLDL-C did not reach statistically significant differences but the other tier 1 and 2 endpoints did.

Table 42: Summary of Treatment Differences Compared with Placebo and Ezetimibe in Co-Secondary Endpoints Integrated Phase 3 Parent Trials Cohort (Full Analysis Set)

	EvoMab 140 mg Q2W vs Placebo Q2W	EvoMab 420 mg QM vs Placebo QM	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
Tier 1 Secondary Endpoints				
Reflexive LDL-C				
Mean change[a] at weeks 10 and 12 (95% CI) – mg/dL	-76.7 (-85.6, -67.9)	-76.2 (-86.3, -66.1)	-52.9 (-61.4, -44.3)	-55.0 (-66.3, -43.7)
Change[a] at week 12 (95% CI) – mg/dL	-77.6 (-86.1, -69.1)	-71.3 (-81.0, -61.6)	-54.8 (-63.3, -46.3)	-52.1 (-63.9, -40.3)
Mean change[a] at weeks 10 and 12 (95% CI) – mmol/L	-1.987 (-2.216, -1.757)	-1.974 (-2.236, -1.712)	-1.369 (-1.591, -1.147)	-1.425 (-1.716, -1.133)
Change[a] at week 12 (95% CI) – mmol/L	-2.010 (-2.230, -1.791)	-1.846 (-2.098, -1.595)	-1.420 (-1.640, -1.200)	-1.350 (-1.655, -1.044)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
ApoB				
Mean % change[a] at weeks 10 and 12 (95% CI)	-53.36 (-56.99, -49.73)	-54.27 (-56.37, -52.17)	-33.40 (-35.69, -31.11)	-36.55 (-39.31, -33.80)
% change[a] at week 12 (95% CI)	-54.04 (-57.96, -50.13)	-49.87 (-51.97, -47.78)	-34.32 (-36.79, -31.84)	-33.54 (-36.01, -31.06)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Total cholesterol/HDL-C ratio				
Mean % change[a] at weeks 10 and 12 (95% CI)	-43.91 (-46.68, -41.14)	-46.09 (-48.09, -44.10)	-28.08 (-30.15, -26.01)	-29.01 (-31.27, -26.75)
% change[a] at week 12 (95% CI)	-43.91 (-46.44, -41.37)	-43.21 (-45.64, -40.78)	-28.27 (-30.53, -26.01)	-27.13 (-29.65, -24.60)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**

	EvoMab 140 mg Q2W vs Placebo Q2W	EvoMab 420 mg QM vs Placebo QM	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
Triglycerides				
Mean % change[a] at weeks 10 and 12 (95% CI)	-15.65 (-22.37, -8.94)	-21.14 (-24.94, -17.34)	-4.29 (-8.62, 0.03)	-7.96 (-13.20, -2.73)
% change[a] at week 12 (95% CI)	-15.03 (-20.45, -9.61)	-19.90 (-25.53, -14.27)	-3.33 (-8.34, 1.68)	-6.44 (-13.72, 0.85)
Least significant p-value	<0.001	<0.001	0.19	0.083
Adjusted p-value	**<0.001**	**<0.001**	**0.77**	**0.33**
VLDL-C				
Mean % change[a] at weeks 10 and 12 (95% CI)	-16.34 (-23.31, -9.38)	-20.98 (-25.26, -16.69)	-3.09 (-7.29, 1.11)	-6.90 (-12.59, -1.22)
% change[a] at week 12 (95% CI)	-15.80 (-22.04, -9.56)	-19.68 (-26.64, -12.73)	-1.96 (-6.67, 2.76)	-4.18 (-12.04, 3.67)
Least significant p-value	<0.001	<0.001	0.42	0.30
Adjusted p-value	**<0.001**	**<0.001**	**0.83**	**0.59**
HDL-C				
Mean % change[a] at weeks 10 and 12 (95% CI)	6.39 (4.97, 7.82)	8.63 (7.04, 10.23)	6.43 (4.60, 8.26)	6.23 (3.86, 8.59)
% change[a] at week 12 (95% CI)	6.17 (4.51, 7.83)	8.02 (6.26, 9.77)	6.71 (4.50, 8.93)	5.47 (3.27, 7.68)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**

	EvoMab 140 mg Q2W vs Placebo Q2W	EvoMab 420 mg QM vs Placebo QM	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
Total cholesterol				
Mean % change[a] at weeks 10 and 12 (95% CI)	-40.11 (-43.02, -37.21)	-39.73 (-41.89, -37.57)	-24.22 (-26.07, -22.37)	-25.55 (-27.26, -23.85)
% change[a] at week 12 (95% CI)	-40.63 (-43.44, -37.82)	-37.00 (-39.00, -35.01)	-24.71 (-26.73, -22.69)	-23.94 (-25.79, -22.10)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Non-HDL-C				
Mean % change[a] at weeks 10 and 12 (95% CI)	-57.88 (-62.36, -53.40)	-58.59 (-61.86, -55.32)	-34.27 (-36.61, -31.94)	-35.93 (-38.04, -33.82)
% change[a] at week 12 (95% CI)	-58.51 (-63.06, -53.95)	-54.24 (-56.86, -51.62)	-34.88 (-37.36, -32.41)	-33.70 (-36.00, -31.39)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
ApoB/ApoA1 ratio				
Mean % change[a] at weeks 10 and 12 (95% CI)	-54.59 (-57.80, -51.38)	-56.62 (-58.66, -54.58)	-35.81 (-38.28, -33.34)	-39.02 (-42.36, -35.68)
% change[a] at week 12 (95% CI)	-54.64 (-57.95, -51.34)	-52.43 (-54.84, -50.03)	-36.91 (-39.56, -34.27)	-35.42 (-38.22, -32.62)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Tier 2 Secondary Endpoints				
Lp(a)				
Mean % change[a] at weeks 10 and 12 (95% CI)	-29.34 (-33.24, -25.45)	-27.72 (-30.61, -24.84)	-26.28 (-30.60, -21.96)	-27.93 (-35.24, -20.62)
% change[a] at week 12 (95% CI)	-30.90 (-34.77, -27.03)	-26.07 (-29.22, -22.93)	-27.29 (-31.40, -23.19)	-28.15 (-33.16, -23.14)
Least significant p-value	<0.001	<0.001	<0.001	<0.001
Adjusted p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; EvoMab = Evolocumab (AMG 145); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); non-HDL-C = non-high-density lipoprotein cholesterol; Q2W = every 2 weeks (subcutaneous); QD = once a day (oral tablet); QM = monthly (subcutaneous); VLDL-C = very low density lipoprotein cholesterol.
Note: results are based on the random effects meta analysis. When the calculated LDL-C is <40 mg/dL, or triglycerides are > 400 mg/dL, calculated LDL-C is replaced with ultracentrifugation LDL-C from the same blood sample, if available. Treatment difference is within each dose frequency group using placebo in the same group as the reference. Adjusted p-values are based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.
[a]Change from baseline.
Source: Modified from Summary of Clinical Efficacy Table 20, ISE Table 14-4.1.41 and ISE Table 14-4.1.42.

HoFH
Trial 20110233 (part B):

- Percent change from baseline in LDL-C, ApoB and Lp(a) at the mean of Weeks 6 and 12[56]
- Percent change from baseline in ApoB and Lp(a) at Week 12

Secondary endpoints were analyzed using a repeated measures linear effects model as used in the analysis of the primary endpoint. Multiplicity adjustment method used Hochberg and the fall back procedure to control the familywise error rate at 0.05 for the primary and secondary endpoints.

56 The mean of weeks 6 and 12 were used instead of weeks 10 and 12 because the week 10 visit was not compulsory and some subjects did not have an LDL-C assessment done.

As shown in the following table, evolocumab treatment resulted in statistically significant percent reductions in UC and calculated LDL-C at the mean of Weeks 6 and 12, compared with placebo, in the FAS. The changes in ApoB reached statistical significance but changes in Lp(a) did not.

Table 43: Treatment Differences (SE) in Percent Change in Lipid Parameters from Baseline Compared With Placebo in Participants with HoFH: Trial 20110233 (Part B)

Endpoints	Evolocumab 420 mg QM	
	FAS (N = 49)	Age < 18 (N = 10)
Secondary endpoints		
UC LDL-C (mean at weeks 6/12)	-29.8 (5.5)	-26.2 (14.9)
p-Value	<0.001	0.13
Calculated LDL-C (mean at weeks 6/12)	-31.0 (5.6)	NA
p-Value	<0.001	
ApoB (week 12)	-23.1 (5.8)	-16.3 (17.4)
p-Value	<0.001	0.39
ApoB (mean at weeks 6/12)	-22.9 (5.4)	-19.1 (15.2)
p-Value	<0.001	0.25
Lp(a) (week 12)	-11.8 (6.8)	17.3 (22.4)
p-Value	0.088	0.47
Lp (a) (mean at weeks 6/12)	-11.3 (5.9)	3.4 (22.3)
p-Value	0.061	0.89

ApoB = apolipoprotein B; HoFH = homozygous familial hypercholesterolemia; Lp(a) = lipoprotein(a); QM = monthly (subcutaneous); SE = standard error; UC = ultracentrifugation.
Source: Modified from Applicant's Table 33 Summary of Clinical Efficacy

6.1.6 Other Endpoints

Primary Hyperlipidemia
Tertiary endpoint in phase 3 parent trials cohort and in each subpopulation (change from baseline at week 12 and at the mean of weeks 10 and 12):

- Percent change in ApoA1

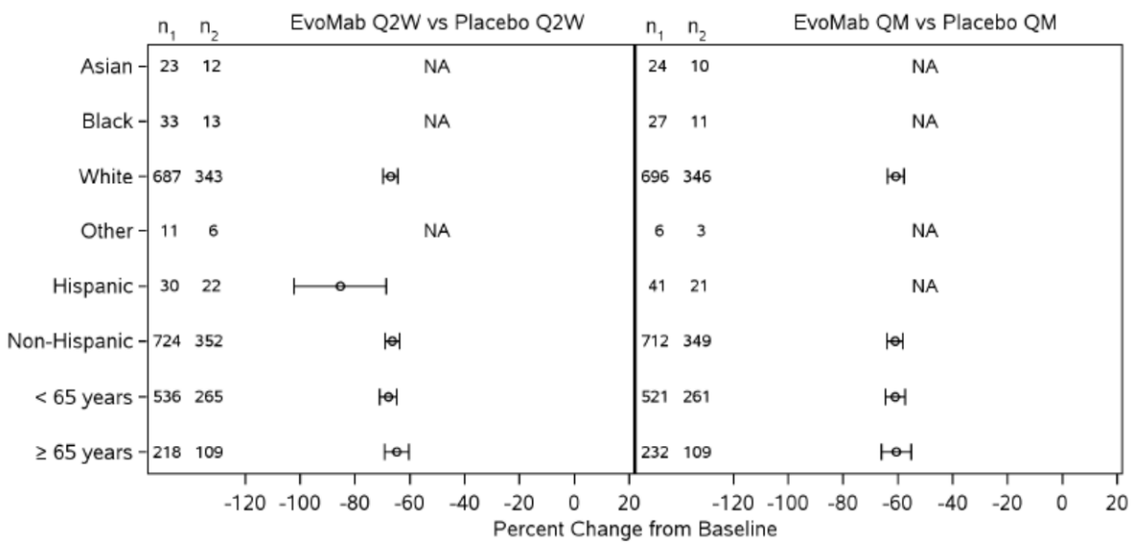
The tertiary endpoint was analyzed in the same way as the co-primary and co-secondary endpoints. However, no multiplicity adjustment was used for the tertiary endpoints.

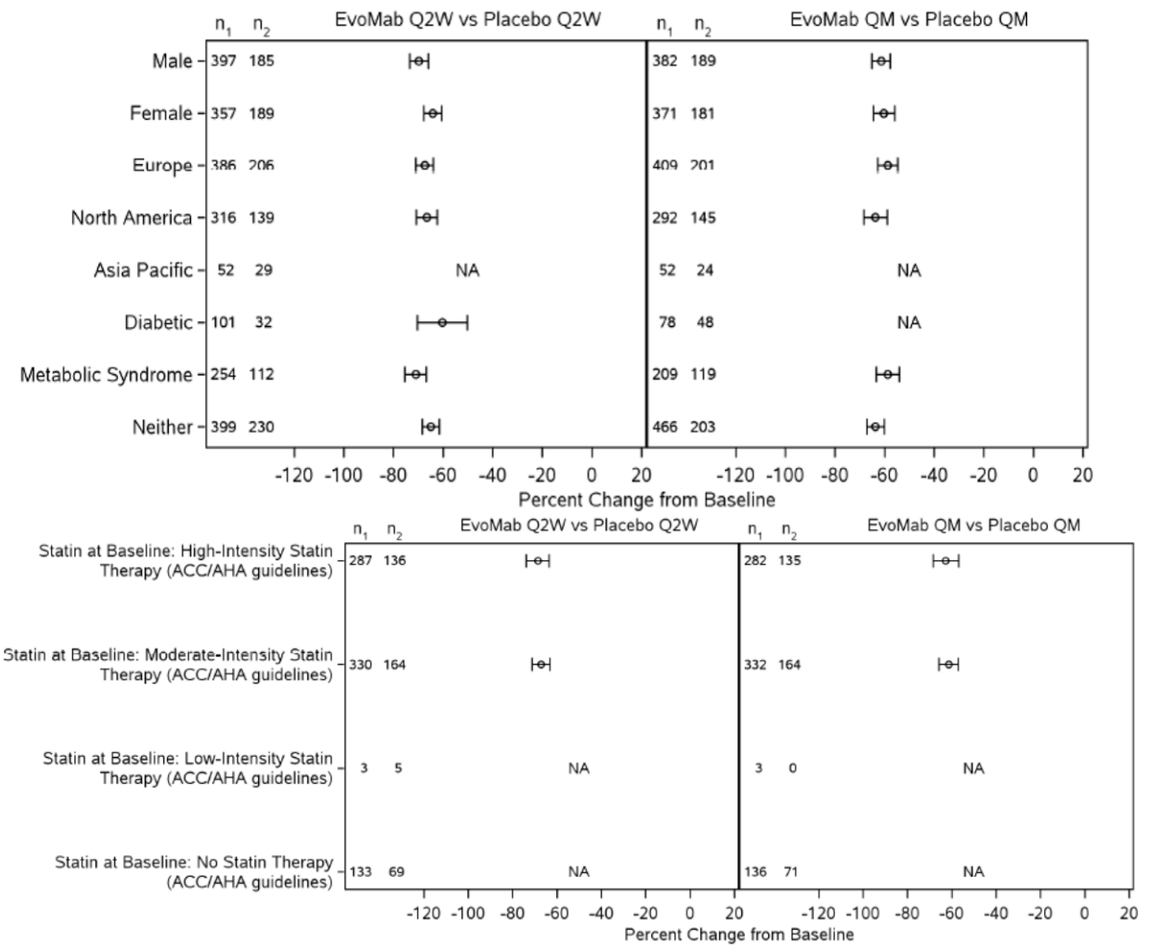
A slight increase in ApoA1 was observed for evolocumab Q2W and QM compared with placebo (4% to 5%) and ezetimibe (4% to 6%) in the integrated analysis but this did not reach statistical significance.

6.1.7 Subpopulations

Evolocumab 140 mg Q2W and 420 mg QM in the integrated phase 3 parent trials cohort were more effective than placebo and ezetimibe in subgroups that were evaluated (race, ethnicity, gender, age, region, glucose tolerance, and statin intensity at baseline). Some of the subgroups were small which limits the interpretability of the comparison. Results of the subgroup analyses of the co-primary endpoint of percent change in LDL-C from baseline at Week 12 compared with placebo are summarized in the following figures.

Figure 6: Forest Plots of Treatment Differences against Placebo in Percent Change from Baseline in LDL-C at Week 12- Subgroup Analyses, Phase 3 Parent Trials Cohort (Full Analysis Set)





Includes Studies 20110114, 20110115 and 20110117; n1 = number of subjects in the subgroup of interest included in the repeated measures model receiving EvoMab; n2 = number of subjects in the subgroup of interest included in the repeated measures model receiving placebo; Q2W = every 2 weeks (subcutaneous); QM = monthly (subcutaneous); EvoMab = Evolocumab (AMG 145)
When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
Least squares mean differences and 95% CI are from the repeated measures model. No imputation is used for missing values.
NA indicates the treatment differences were non-estimable.
Source: Applicant's Figure 14-4.6.401; Module 5.3.5.3.- Integrated Summary of Efficacy

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The evolocumab 140 mg Q2W dose and the 420 mg QM dose yield similar LDL-C reductions but different pharmacodynamic profiles over the dosing interval (QM results in a sawtooth pattern compared to the more-stable LDL C reduction achieved with Q2W dosing). The two different dosing regimens were designed by the applicant

to cater to the patient's preference of taking the injectable every two weeks versus every four weeks and not to allow titration of the magnitude of LDL-C reduction.

The applicant also contends, and this reviewer agrees, that the safety and tolerability profiles of the 140 mg Q2W and 420 mg QM dosing regimens were consistent with those of the other 4 regimens tested in the phase 2 studies (70 and 105 mg Q2W and 280 and 350 mg QM), and there were no notable increased incidence of adverse events with the different doses or dosing frequency of evolocumab in these short-term trials.

For the HoFH population, 420 mg QM was selected as the dose for the non-apheresis participants entering trial 20110233. The 420 mg Q2W dose was evaluated in the open-label extension study 20110271. In the HoFH subjects with unbound PCSK9 ≥ 100 ng/mL with QM dosing who switched to evolocumab 420 mg Q2W treatment, increasing the frequency of dosing from 420 mg QM to 420 mg Q2W resulted in approximately 6% greater reduction of LDL-C.

The applicant proposes that the initial recommended dose is 420 mg QM for non-apheresis patients and 420 mg Q2W for apheresis patients (to coincide with their apheresis schedule), with the option of apheresis and non-apheresis patients to titrate to the more or less frequent dose (Q2W or QM) based on clinical response.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Primary Hyperlipidemia
The persistence of efficacy was explored in trial 20110109, described in detail in Section 5.3.1 Trial 20110109: DESCARTES. The percent change in LDL-C from baseline to Week 52 for evolocumab 420 mg QM compared with placebo QM using UC, reflexive LDL-C, or calculated LDL-C values resulted in treatment differences of -57.0%, -58.0%, and -59.3%, ($p < 0.001$), respectively, when added to 1 of the 4 background lipid-lowering therapies. Overall, 97.8% of participants had at least 1 post baseline UC LDL-C value. Approximately 3% and 10% of participants had a missing UC LDL-C value at weeks 12 and 52, respectively.

The ongoing phase 2 trial 20110110 (data up to Week 112) and phase 3 trial 20120138 (data up to Week 24) are open-label extension trials. Based on a data cutoff date of 01 April 2014, reductions of approximately 50% to 60% in LDL-C concentrations were observed in both trials and maintained in participants receiving long-term administration of evolocumab regardless of parent trial treatment assignment (namely, evolocumab or control).

HoFH

The table below shows the mean LDL-C reduction over time, compared with each participant's baseline, among HoFH participants in the open-label extension trial. Although limited by being an uncontrolled study with variable degrees of follow-up over time, the mean LDL-C observed among non-apheresis patients appears to be approximately 25% whereas that observed among apheresis patients is approximately 18% and appears to be largely consistent over time. It is unfortunate that the patients on apheresis, who would likely benefit from an alternative therapy the most, appear to have the most modest response to this drug. This may be an indication of the severity of their underlying LDLR defect

Table 44: Mean (SE) Percent Change from Baseline in UC LDL C by Study Visit: Subjects with HoFH Study 20110271 (data cutoff date of 01 April 2014)

		OLE Week 4	OLE Week 8	OLE Week 12	OLE Week 16	OLE Week 20	OLE Week 24	OLE Week 36	OLE Week 48
HoFH Interim Analysis Set (N = 96)	n	71	67	68	61	51	45	29	11
	Mean (SE)	-23.8 (3.2)	-21.9 (2.9)	-19.0 (3.0)	-23.7 (2.9)	-22.9 (4.0)	-23.1 (3.6)	-26.2 (4.5)	-19.1 (7.6)
	Median	-21.5	-22.3	-15.6	-22.8	-20.6	-24.1	-27.8	-18.6
	Range	-90.4, 53.7	-90.7, 71.9	-89.1, 47.3	-83.0, 20.8	-83.1, 33.4	-67.8, 43.1	-72.4, 44.9	-62.7, 22.8
Non-apheresis subjects (N = 65)	n	43	43	44	40	35	32	26	9
	Mean (SE)	-27.2 (3.8)	-24.7 (3.0)	-20.4 (3.3)	-26.7 (3.2)	-25.3 (4.4)	-24.5 (4.2)	-27.2 (4.6)	-21.3 (9.2)
	Median	-23.4	-24.0	-18.2	-25.7	-22.1	-23.1	-29.0	-21.7
	Range	-90.4, 53.7	-73.9, 16.9	-80.4, 23.9	-83.0, 15.0	-83.1, 31.5	-67.8, 39.9	-72.4, 44.9	-62.7, 22.8
Apheresis subjects (N = 31)	n	28	24	24	21	16	13	3	2
	Mean (SE)	-18.6 (5.5)	-16.8 (6.0)	-16.6 (6.1)	-18.0 (5.6)	-17.8 (8.4)	-19.5 (7.3)	-17.7 (19.9)	-9.1 (5.1)
	Median	-14.1	-16.3	-14.9	-15.1	-12.0	-24.1	-12.1	-9.1
	Range	-88.3, 31.7	-90.7, 71.9	-89.1, 47.3	-78.2, 20.8	-78.7, 33.4	-59.5, 43.1	-54.6, 13.7	-14.2, -4.0

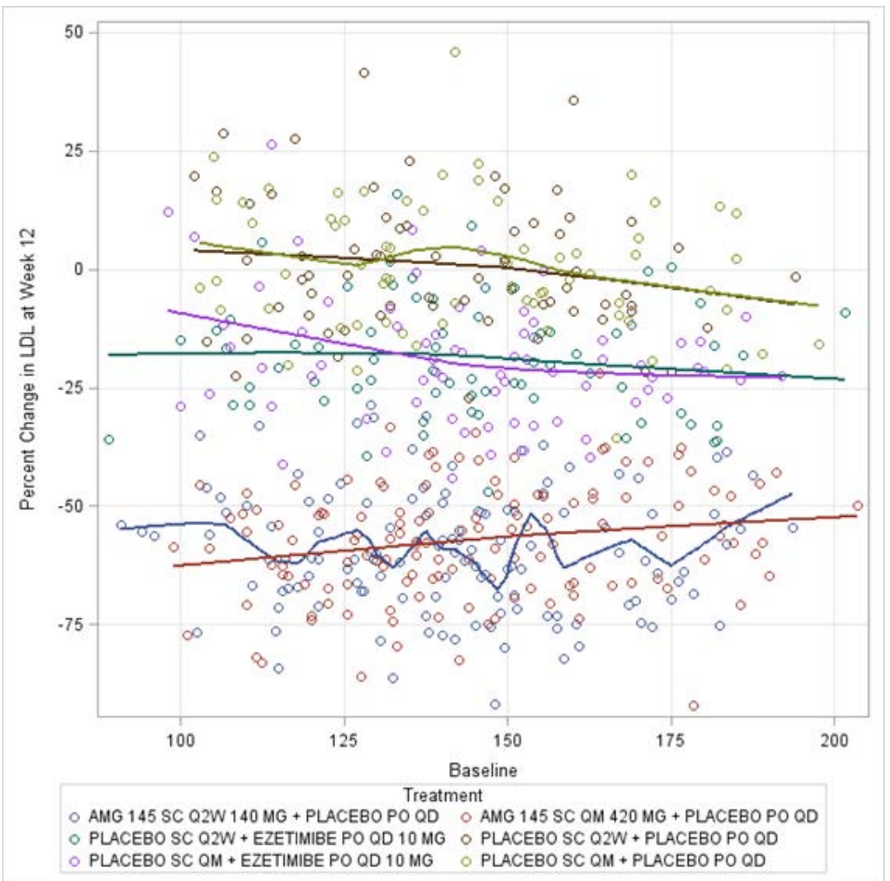
HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; n = number of subjects with observed values at specific visit; OLE = open-label extension; SE = standard error; UC = ultracentrifugation.
Source: Modified from Table 10-1 from CSR-20110271

6.1.10 Additional Efficacy Issues/Analyses

LDL-C Reduction: Percent Change versus Absolute Change

The clinical team explored whether the mean percent reduction in LDL-C with evolocumab is relatively independent of baseline LDL-C. The figure below shows baseline LDL-C on the x-axis versus percent change in LDL-C at Week 12 on the y-axis, using data from trial 20110114. The two uppermost lines are placebo given Q2W and QM. The two lines in the middle are ezetimibe given Q2W and QM. The two lowermost lines are evolocumab given Q2W and QM. The slope of all three sets of lines is fairly horizontal suggesting that the percent reduction in LDL-C for placebo, ezetimibe and evolocumab is relatively independent of baseline LDL-C.

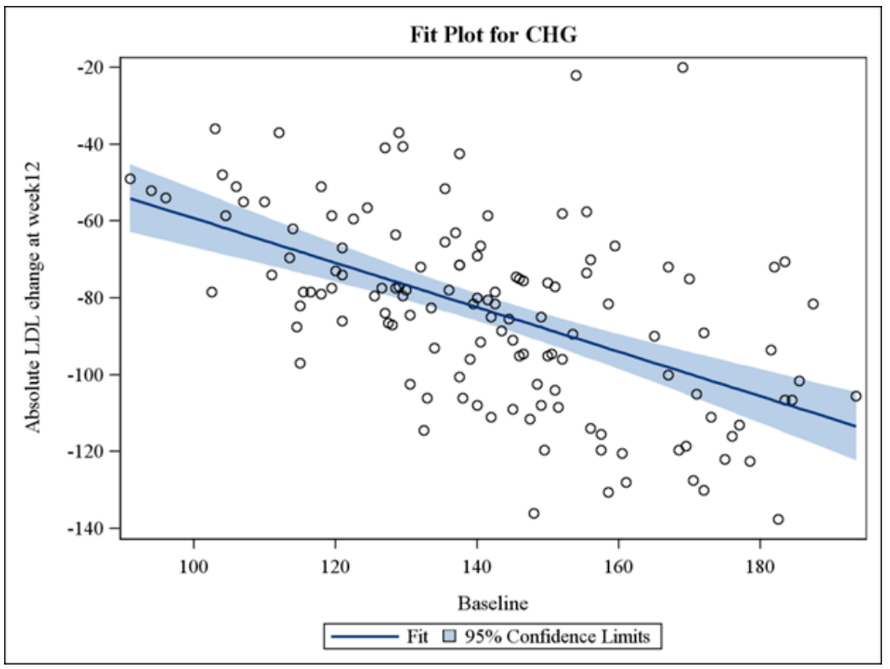
Figure 7: Scatter Plot of LDL-C Percent Change at Week 12 vs Baseline LDL-C (Trial 20110114)



Source: Courtesy of Dr. Shuxian Sinks, FDA statistical reviewer

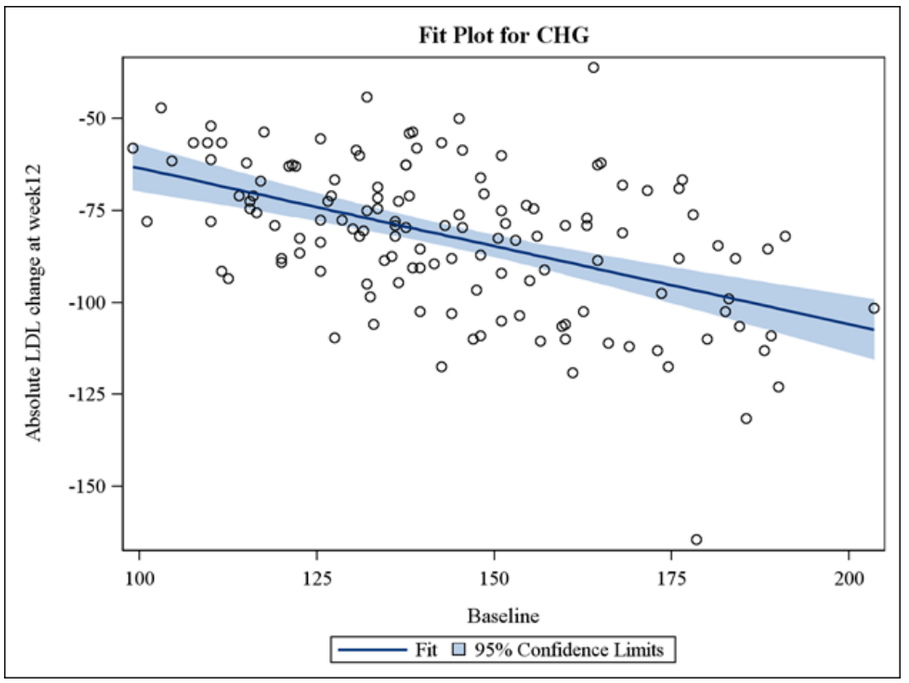
As expected, therefore, higher baseline LDL-C levels are associated with greater reductions in absolute LDL-C, as shown in the following two figures.

Figure 8: Scatter Plot of LDL-C Absolute Change at Week 12 vs Baseline LDL-C for Evolocumab 140 mg Q2W (Trial 20110114)



Source: Courtesy of Dr. Shuxian Sinks, FDA statistical reviewer

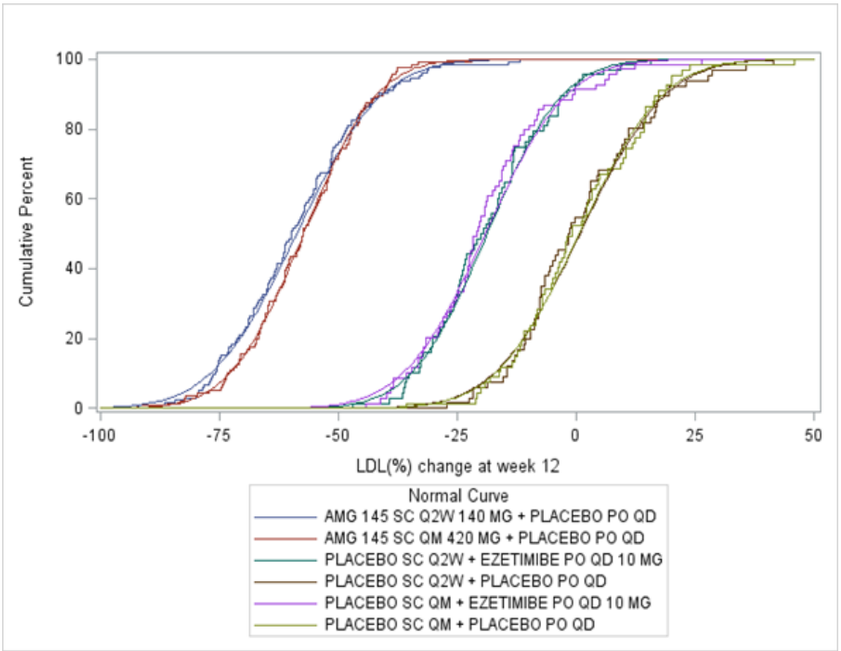
Figure 9: Scatter Plot of LDL-C Absolute Change at Week 12 vs Baseline LDL-C for Evolocumab 420 mg QM (Trial 20110114)



Source: Courtesy of Dr. Shuxian Sinks, FDA statistical reviewer

The following figure is a cumulative distribution plot of LDL-C to examine the distribution of effect of the three treatment arms [evolocumab 140 mg Q2W and 420 mg QM, ezetimibe + SC placebo (given Q2W or QM), and SC placebo (given Q2W or QM)]. Evolocumab has a robust effect on reducing LDL-C as compared to ezetimibe and placebo.

Figure 10: Cumulative Distribution of LDL-C Percent Change at Week 12 (Trial 20110114)



Source: Courtesy of Dr. Shuxian Sinks, FDA statistical reviewer

7 Review of Safety

Safety Summary

Refer to Section 1.3

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Primary Hyperlipidemia

Trials included in the integrated safety analysis set for the indication of primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia are 8 phase 2 and phase 3 lipid-lowering trials, a phase 2 trial done in Japan, 2 device clinical home-use studies, one 52-week placebo-controlled trial (20110109) and two open-label extension studies (20110110 and 20120138). After participating in any of

the phase 2 or phase 3 trials, participants could enroll in a phase 2 (Study 20110110) or phase 3 (Study 20120138) open-label extension trial, respectively. In these trials, participants were randomized (2:1) for the first year of the study to a standard of care (SoC) plus evolocumab versus SoC control arm, followed by open-label evolocumab therapy for all participants beginning in the second year. In Study 20110110, participants received either evolocumab 420 mg QM plus SoC or SoC alone in Year 1, and then switched to evolocumab 420 mg QM starting in Year 2. In Study 20120138, participants received either evolocumab (140 mg Q2W or 420 mg QM) plus SoC or SoC alone in Year 1, and then switched to evolocumab 140 mg Q2W or 420 mg QM starting in Year 2.

The applicant has used three integrated analysis sets to describe the data for the safety analysis of evolocumab:

- The Integrated Parent Analysis Set (**IPAS**) comprises integrated data from the 12-week phase 2 and phase 3 trials in addition to the 52-week study (20110109)
- The Integrated Extension Standard of Care (SoC)-Controlled Period Analysis Set (**IECAS**) comprises integrated data from year 1 (the controlled period) of the open-label extension (OLE) studies.
- The Integrated Extension All-Investigational Product (IP) Period Analysis Set (**IEAAS**) comprises integrated data from year 2+ (the all-IP period) of the open-label, long-term extension studies

Table 45: Safety Analysis Sets in the Integrated Primary Hyperlipidemia and Mixed Dyslipidemia Trials

Analysis Set	**Description**	**Data Source**	**Additional Information**
Integrated Parent Analysis Set (IPAS) N=6026 [3946 Any EvoMab (3201 to-be-marketed doses); 2080 Any Control]	12-week phase 2 and phase 3 trials + the 52-week trial	• primary hyperlipidemia and mixed dyslipidemia trials (12-wk, R, controlled, DB, Phase 2 dose-ranging: 20101154†, 20101155*, 20090158*, 20090159^; 12-wk, R, controlled, DB, Phase 3: 20110114†, 20110115*†, 20110116^, 20110117*) • device home-use studies (20120348 and 20120356) •12-wk, R, controlled, DB, Phase 2, Japanese subjects in trial 20110231* • 52-wk, DB, PC, long-term	• Trials 20110114, 20110115, 20110116, and 20110117 in the IPAS were used to analyze device-related adverse events with the AI/pen. • The analyses of change from baseline in ECG intervals excluded device home-use Studies 20120348 and 20120356 because these studies had ECG data at screening only.

		trial (20110109*)	
Integrated Extension SoC-Controlled Period Analysis Set (IECAS) N=4252 (2833 EvoMab+SoC; 1419 SoC)	year 1 of the OLE trials (controlled period)	Participants randomized in year 1 of the long-term, controlled, OLE Studies 20110110 and 20120138	•Both trials are ongoing with a 01 April 2014 data cutoff date for the submission. • Does not include subjects in Study 20120138 with <12 weeks of potential follow-up time
Integrated Extension All-Investigational Product Period Analysis Set (IEAAS) N=954 all on EvoMab	year 2+ of the OLE trials (open label period)	Participants who were on study at the start of the all-IP period in Trial 20110110 and 20120138 and dosed at least once in that period.	Analysis set primarily comprises participants from trial 20110110.
*Randomized, placebo-controlled trials ^ Enrolled “statin-intolerant” subjects and used a randomized ezetimibe control † Randomized, ezetimibe and placebo as controls (20110155 atorvastatin cohort)			

MO Comment: This reviewer believes that the safety data from the 52-week trial (20110109) and the short-term trials (up to 12 weeks in duration) should be presented separately and not combined together when describing adverse reaction incidence and treatment duration in the label (if approved). The applicant has provided, as background information, safety tables that remove the 52-week trial adverse events from the combined short-term trial data.

Homozygous Familial Hypercholesterolemia (HoFH)
Safety analyses from the 2 HoFH studies are presented separately from the primary integrated analysis set. In HoFH trial 20110233 part A (open-label, pilot phase 2 study) there were 8 HoFH subjects; in trial 20110233 part B (randomized, double-blind, placebo-controlled phase 3 study) there were 49 HoFH subjects, and in HoFH trial 20110271 (OLE, long-term study) there were 99 HoFH subjects. Safety in Trial 20110271 was also assessed in those subjects who had apheresis or non-apheresis at enrollment.

MO Comment: This reviewer concurs with the applicant’s rationale to analyze these participants with HoFH separately based on the genetic component of the disease, which results in much higher LDL-C levels compared with the primary hyperlipidemia and mixed dyslipidemia populations. These trial participants are younger and on more

lipid-lowering agents at baseline than the participants in the primary hyperlipidemia trials.

7.1.2 Categorization of Adverse Events

A data cutoff of 01 April 2014 was used for all ongoing studies included in the marketing application. Adverse events in the integrated analyses were coded using Version 17.0 of the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events in the integrated analyses are treatment emergent adverse events. Adverse events in the individual studies were coded using the most current version of MedDRA at the time of database lock.

An adverse event belongs to the parent study period if the event occurs after the first dose of IP in the parent study and on or prior to the parent study end of study (EOS) date. This definition is consistent with the treatment emergent reporting in parent trials. Post treatment CK, LFT, and ECG abnormalities follow the same period definition. An adverse event belongs to the open label extension period if the event occurs after the later of the informed consent date of the open label extension study and parent EOS date and on or prior to the open label extension study EOS date. Within the open label extension period, event or laboratory data belongs to the SoC-controlled period if they were observed before the All-IP period start date. Any data observed on or after the All-IP period start date will belong to the All-IP period.

Adverse events of special interest for this application include the following categories: adverse events associated with other lipid-lowering therapies (such as diabetes, liver, and muscle events), those associated with other injectable protein therapies (such as hypersensitivity events, injection site reactions), those occurring in participants with LDL-C levels < 40 mg/dL and those that could theoretically be associated with PCSK9 inhibition/LDL receptor upregulation (hepatitis C events). Neurocognitive events in the clinical trials were identified using MedDRA High Level Group Terms.

Potential cardiovascular endpoints (including death) during the phase 2 and phase 3 trials were identified and adjudicated by an Independent Clinical Endpoint Committee (CEC). The CEC coordinator compiled an endpoint event packet consisting of the subject profile and supporting source documentation (eg, relevant electrocardiogram (ECGs), hospitalization records, imaging). Each complete endpoint event packet was randomly assigned to 2 CEC adjudicators who independently reviewed each potential endpoint. If the adjudication results determined by each independent CEC adjudicator were concordant, then the adjudication of that potential endpoint was considered to be complete. If the adjudication results determined by each independent CEC adjudicator were discordant, then the CEC adjudicators discussed the potential endpoint at a moderated CEC meeting until they came to consensus or agreed that they were unable to reach final consensus. If consensus could not be reached, then the case was submitted to the chairperson of the CEC to determine the final

adjudication result. The CV endpoints for the Phase 3 trials were death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, hospitalization for heart failure and cerebrovascular events (transient ischemic attack, stroke). The Phase 2 trials also included non-coronary revascularization. Endpoint definitions in the phase 3 program were updated from the definitions used in the phase 2 program based on an updated draft of the "Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials and the Third Universal Definition of Myocardial Infarction."[57] The subject incidence of adjudicated (positive and negative) cardiovascular events and noncoronary revascularizations was summarized by overall incidence by study period.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For the primary hyperlipidemia indication, the applicant's Integrated Summary of Safety (ISS) includes data from the nine 12-week phase 2 and phase 3 trials, the 8- and 12-week device home-use studies and the 52-week trial (20110109). This reviewer believes that the adverse reaction data from the trials that are up to 12 weeks in duration should also be presented separately and not combined with the 52-week trial in order to explore whether there are differences in adverse event profiles for short-term vs longer duration trials.

It is important to note that the phase 2 and phase 3 statin-intolerant trials (20090159 and 20110116), which where ezetimibe-controlled rather than placebo-controlled, had higher adverse event rates than the non-statin-intolerant trials, regardless of treatment assignment. In the statin-intolerant trial, the control was ezetimibe with placebo (Q2W and/or QM) injections. Comparison of evolocumab Q2W and/or QM to placebo Q2W and/or QM includes statin-intolerant subjects in the evolocumab Q2W and/or QM groups but no statin-intolerant subjects in the placebo Q2W and/or QM groups. Higher event rates were seen in the ezetimibe control arms. The ezetimibe arms were included in two disparate parent trials – trial 114, which enrolled low CV risk subjects (Framingham risk <10%), and trial -116, which generally enrolled high CV risk (statin-intolerant) subjects. The ezetimibe pool does not mirror the population in the EvoMab pool and the higher event rates in the ezetimibe arms are somewhat misleading as it is unclear what the ezetimibe pool really represents. This is a limitation of this pooling strategy.

Another limitation of the applicant's pooling strategy was the different randomization ratio between the Phase 2 and 3 trials. The Phase 2 trials had a 1:1 allocation between evolocumab and placebo whereas the Phase 3 trials used a 2:1 allocation

57 Hicks KA, Hung HM, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, Targum SL, Temple R; on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials and the Third Universal Definition of Myocardial Infarction. 2012

between evolocumab and placebo. This approach could lead to to confounding by study (e.g., Simpson's Paradox). A more appropriate approach may have been to evaluate for study differences through stratification by study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Safety Database
Approximately 6800 participants administered evolocumab (alone or in combination with statins), placebo, or any control (including ezetimibe and SoC) are included in the overall safety analysis. The overall safety database includes a total of 5710 participants exposed to any dose of evolocumab. At the time of database cutoff (1 April 2014), 5416 evolocumab-dosed participants had been on study for at least 3 months, 1824 evolocumab-dosed participants had been on study for at least 12 months, and 614 evolocumab-dosed participants had been on study for 2 years or more.

Participants with the following conditions have been treated with any evolocumab for at least 1 year:

- 345 participants with established CVD
- 504 participants at NCEP high risk for CVD
- 147 participants at NCEP moderately-high risk for CVD
- 183 participants with diabetes
- 463 participants on concomitant high intensity statin; 560 participants on concomitant moderate intensity statin
- 439 participants ≥ 65 years old

Table 46: Overall Summary of Trial Exposure (Phases 1, 2, 3)

Overall	Control		EvoMab		All Unique Participants
	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM or 420mg Q2W[b]	Any EvoMab	
Number of Participants	1578	3079	5456	5710	6801
≥ 3 months	1553	3040	5169	5416	6521
≥ 6 months	294	1444	3340	3350	4638
≥ 12 months	287	718	1787	1824	2462

≥ 24 months	0	1	601	614	923
Primary Hyperlipidemia and Mixed Dyslipidemia (Phase 2 and 3) ISS					
	Control		EvoMab		All Unique Participants
	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM or 420mg Q2W[b]	Any EvoMab	
Number of Participants	1526	3027	4783	4971	6026
≥ 3 months	1501	2988	4654	4839	5904
≥ 6 months	294	1444	3276	3286	4571
≥ 12 months	287	718	1760	1797	2430
≥ 24 months	0	1	598	611	920
Homozygous Familial Hypercholesterolemia					
	Control		EvoMab		All Unique Participants
	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM or 420mg Q2W[b]	Any EvoMab	
Number of Participants[c]	16	16	99	99	99
≥ 3 months	16	16	81	81	85
≥ 6 months	0	0	56	56	59
≥ 12 months	0	0	23	23	28
≥ 24 months	0	0	3	3	3

EvoMab = Evolocumab (AMG 145); Q2W = every 2 weeks; QM = monthly; ISS = Integrated Summary of Safety
Primary hyperlipidemia and mixed dyslipidemia phase 2 and 3 (ISS) studies include 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356, 20110110, and 20120138.
Homozygous familial hypercholesterolemia includes subjects from studies 20110233 and 20110271. Ongoing studies include: 20110110, 20120138, and 20110271 (data cutoff date 01 April 2014).
a Includes placebo, ezetimibe or standard of care.
b Includes 140 mg or 420 mg single dose in phase 1 studies. Subjects in Study 20110271 could switch between 420 mg QM and 420 mg Q2W per protocol.
c Includes 14 adolescent subjects: 13 subjects were enrolled to the extension Study 20110271 (10 subjects were from study 20110233), and 1 subject participated in Study 20110233 but did not continue into Study 20110271.
Patients can contribute data to more than 1 treatment group per designs of parent studies and their extension studies.
Source: Applicant's ISS Table 14-5.1.1and Table 3(2.7.4)

Primary Hyperlipidemia

A total of 6026 participants were included in the integrated parent analysis set for the primary hyperlipidemia indication; of these, 4431 (73.5%) were in the combination

therapy trials. The remaining participants were in the monotherapy trials (1131 [18.8%]) and the statin-intolerant trials (464 [7.7%]) (see table below). The majority of participants were on background statin therapy, which is appropriate as evolocumab, if approved, would be most clinically relevant in participants at higher CV risk not adequately controlled by maximally tolerated statin therapy. The number of participants on high and moderate-intensity statin therapy is described in Table 51.

Table 47: Number of Participants and Treatment Cohort Designation in the Integrated Parent Analysis Set (IPAS)

Cohort	Control			EvoMab				Total
	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N =1245) n (%)	420 mg QM (N =1956) n (%)	420 mg QM + Eze. QD (N = 30) n (%)	(N=6026) n (%)
Monotherapy	121 (20.6)	160 (17.0)	199 (35.9)	181 (25.3)	198 (15.9)	272 (13.9)	NA	1131 (18.8)
Combination with Statins	465 (79.4)	780 (83.0)	221 (39.9)	471 (65.9)	944 (75.8)	1550 (79.2)	NA	4431 (73.5)
Statin Intolerant	NA	NA	134 (24.2)	63 (8.8)	103 (8.3)	134 (6.9)	30 (100.0)	464 (7.7)

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348,20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Eze=ezetimibe; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; IP = investigational product; IPAS = Integrated Parent Analysis Set.
Source Data: adam.adsl; Applicant Table 13 (2.7.4)

The population included in the integrated parent studies has a mean age of 58 years and is approximately 51% female. Approximately 19% and 8% have a prior diagnosis of CAD and cerebrovascular or peripheral arterial disease, respectively. Approximately 13% have Type II diabetes mellitus while approximately one-third have mixed dyslipidemia. Approximately 44% of subjects were high and moderately-high risk by ATP-III; 30% were moderate risk. Approximately 75% of the population studied was on statin lipid-lowering therapy, and 10% received ezetimibe. The exposure to IP and to trial is presented in the following table. The mean duration of evolocumab exposure in the 140 mg Q2W and 420 mg QM treatment groups was 2.6 months and 5.3 months, respectively. The greater duration of exposure in the QM dose was due to trial 20110109 which was 52 weeks in duration and participants were administered only the 420 mg QM dose. The median duration of evolocumab exposure in the 140 mg Q2W and 420 mg QM treatment groups was 2.8 months.

Table 48: Summary of Exposure During the Integrated Parent Studies (IPAS)

	Control			EvoMab			
	Placebo	Placebo	Ezetimibe	Other	140 mg	420 mg	420 mg

	SC Q2W (N = 586)	SC QM (N = 940)	QD (N = 554)	EvoMab Dose (N = 715)	Q2W (N=1245)	QM (N=1956)	QM + Eze. QD (N = 30)
Duration of SC IP exposure (months)							
n	586	940	509	715	1245	1956	30
Mean	2.7	5.5	2.7	2.7	2.6	5.3	2.8
Median	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Min, Max	0.3, 3.4	0.1, 12.3	0.5, 3.4	0.5, 3.3	0.0, 3.3	0.4, 12.3	1.9, 2.9
Duration of trial exposure (months)							
n	586	940	554	715	1245	1956	30
Mean	3.2	5.7	3.0	3.0	3.1	5.6	2.8
Median	3.3	2.8	2.9	2.9	3.3	2.8	2.8
Min, Max	0.3, 4.8	0.1, 17.5	0.5, 5.5	1.0, 6.2	0.0, 5.6	0.4, 17.6	2.6, 3.0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; QD = once a day; Q2W = every 2 weeks; QM = monthly;
SC = subcutaneous; IP = investigational product; IPAS = Integrated Parent Analysis Set.
Source Data: adam.adsl; Applicant Table 4 (2.7.4)

The exposure to IP and to trial for the year 1 SoC-controlled period is presented in the following table. For participants assigned to control during the parent trial and evolocumab plus SoC during the extension trial, the mean duration of evolocumab exposure was 8.1 months and the median duration was 7.3 months. The mean duration of evolocumab exposure for participants who received evolocumab during the parent trial and evolocumab plus SoC during the extension trial was 8.4 months and the median duration was 7.4 months. It is important to note that the safety information and adverse incidence data from this year 1 SoC-controlled period reflects a median exposure of 7 months (not 12 months) of controlled but open-label data.

Table 49: Summary of Exposure During the Year 1 SoC-Controlled Period of the Extension Studies (IECAS)

	Control in Parent Trial		**EvoMab in Parent Trial**	
	SoC (N = 472)	EvoMab + SoC (N = 943)	SoC (N = 947)	EvoMab + SoC (N = 1890)
Duration of SC IP exposure (months)				
n	472	940	947	1890
Mean	0	8.1	0	8.4
Median	0	7.3	0	7.4
Min, Max	0, 0	0, 13.1	0, 0	0.1, 13.1
Duration of trial exposure (months)				
n	472	943	947	1890
Mean	8.1	8.2	8.6	8.6

Median	7.2	7.4	7.8	7.6
Min, Max	0, 13.1	0, 13.1	0, 13.1	0.1, 13.1

Includes the following studies: 20110110, 20120138.
N = number of subjects randomized in the integrated extension SoC-controlled period analysis set; EvoMab = Evolocumab; SoC= standard of care; SC = subcutaneous; IP = investigational product;
Source Data: adam.adsl; Applicant Table 5 (2.7.4)

The exposure to IP and to trial for the Year 2+ OLE period is presented in the following table. The total mean and median duration of evolocumab exposure for the year 2+ OLE period was 12.6 and 12.9 months, respectively.

Table 50: Summary of Exposure During the Year 2+ OLE Period of the Extension Studies (IEAAS)

	SoC in SoC-Controlled period	EvoMab + SoC in SoC-Controlled period	**Total**
	EvoMab + SoC (N = 312)	EvoMab + SoC (N = 642)	(N = 954)
Duration of SC IP exposure (months)			
n	312	642	954
Mean	12.6	12.7	12.6
Median	12.9	13.0	12.9
Min, Max	0, 16.8	0, 16.9	0, 16.9
Duration of trial exposure (months)			
n	312	642	954
Mean	12.8	12.9	12.8
Median	12.9	13.1	13.0
Min, Max	0, 16.8	0, 16.9	0, 16.9

Includes the following studies: 20110110, 20120138.
N = number of subjects randomized in the integrated extension all-IP period analysis set; EvoMab = Evolocumab; SoC= standard of care; IP = investigational product;
Source Data: adam.adsl; Applicant Table 6 (2.7.4)

Exposure in Specific Subpopulations

The extent of exposure in evolocumab-treated participants with ≥ 3 months of evolocumab exposure (combined parent and OLE study periods, regardless of adherence to evolocumab, is denoted in parentheses in the table) and various baseline demographics is presented below. Of note, the exclusion criteria in the phase 2 and 3 trials included poorly controlled or newly diagnosed diabetes; New York Heart Association CHF class III or IV; uncontrolled serious cardiac arrhythmia; uncontrolled hypertension; hypo/hyperthyroidism; severe hepatic impairment (Child-Pugh class C); estimated glomerular filtration rate (eGFR) < 30mL/min/1.73m2; ALT/AST > 2 x ULN; creatine kinase (CK) > 3 x ULN; myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass, or stroke within 3 months prior to randomization; and malignancy (except non-melanoma skin

cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years. Thus, individuals with these conditions were not represented in the trials.

Table 51: Exposure in Subpopulations on Evolocumab and (in trial regardless of adherence to evolocumab)

Number of Subjects	**EvoMab 140 mg Q2W or 420 mg QM**
Subjects with Established Arteriosclerotic Cardiovascular Disease	
≥ 3 months	1074
≥ 6 months	726 (740)
≥ 12 months	345 (366)
≥ 18 months	176 (180)
≥ 24 months	145 (147)
≥ 30 months	8 (8)
Subjects with Congestive Heart Failure or Ischemic Cardiomyopathy	
≥ 3 months	198
≥ 6 months	122 (125)
≥ 12 months	58 (62)
≥ 18 months	33 (34)
≥ 24 months	31 (31)
≥ 30 months	2 (2)
Subjects with NCEP/ATP III High Risk	
≥ 3 months	1550
≥ 6 months	1052 (1074)
≥ 12 months	504 (534)
≥ 18 months	233 (239)
≥ 24 months	192 (195)
≥ 30 months	11 (12)
Subjects with NCEP/ATP III Moderately High Risk	
≥ 3 months	455
≥ 6 months	317 (319)
≥ 12 months	147 (158)
≥ 18 months	85 (85)
≥ 24 months	60 (61)
≥ 30 months	5 (6)
Subjects with Type II Diabetes Mellitus	
≥ 3 months	600
≥ 6 months	397 (408)
≥ 12 months	183 (197)
≥ 18 months	69 (72)
≥ 24 months	55 (56)
≥ 30 months	5 (6)
Subjects with High-Intensity Statin Therapy at Study Day 1	
≥ 3 months	1410
≥ 6 months	962 (984)

≥ 12 months	463 (497)
≥ 18 months	235 (237)
≥ 24 months	148 (149)
≥ 30 months	8 (10)
Subjects with Moderate-Intensity Statin Therapy at Study Day 1	
≥ 3 months	1762
≥ 6 months	1198 (1226)
≥ 12 months	560 (600)
≥ 18 months	303 (308)
≥ 24 months	204 (207)
≥ 30 months	13 (13)
Subjects ≥ 65 Years Old	
≥ 3 months	1357
≥ 6 months	944 (963)
≥ 12 months	439 (470)
≥ 18 months	222 (225)
≥ 24 months	160 (162)
≥ 30 months	30 (17)

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; NCEP/ATP = National Cholesterol Education Program Adult Treatment Panel; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous
Statin therapy intensity defined using the ACC/AHA definition in Table 5 in "ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines" in Circulation (2013). High-Intensity Statin Therapy (such as atorvastatin 80 mg or rosuvastatin 40 mg) and Moderate-Intensity Statin Therapy (such as atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 20-40 mg).
Subjects with Established Arteriosclerotic Cardiovascular Disease defined as any of angina due to atherosclerotic coronary disease, prior myocardial infarction, any coronary artery bypass graft or percutaneous coronary intervention, transient ischemic attack, stroke/cerebral infarction, carotid or vertebral artery disease, or peripheral arterial disease.
Subjects with Congestive Heart Failure or Ischemic Cardiomyopathy where Ischemic cardiomyopathy is defined as left ventricular ejection fraction < 50%.
Subjects can contribute data to more than 1 treatment group.
Source: Modified from Table 9 of 2.7.4; ISS Table 14-5.4.402; ISS Table 14-5.4.403; ISS Table 14-5.4.404; ISS Table 14-5.4.405; ISS Table 14-5.4.406; ISS Table 14-5.4.407; ISS Table 14-5.4.408; ISS Table 14-5.4.409; ISS Table 14-5.4.410; ISS Table 14-5.4.413; ISS Table 14-5.4.414; and Table 4-1 response to 06Nov2014 IR

MO Comment: The overall duration of exposure to evolocumab in this primary hyperlipidemic population, including the proportions of participants with CVD, diabetes, increased age, female sex, concomitant high intensity statin, and in the high and moderate-risk NCEP/ATP risk categories, adequately represents the intended target population and is adequate to make a safety assessment for this indication. More long-term data in patients with CVD and other co-morbidities on maximally tolerated baseline statin therapy in a trial that is blinded and placebo or active agent controlled would have been appreciated and informative.

Evolocumab Exposure in HoFH Trials

Safety data includes 99 participants (96 from trial 20110271 and 3 from trial 20110233 who did not continue into trial 20110271). The population of the 99 HoFH participants included in the HoFH safety analysis set was younger (mean age of approximately 34 years of age at baseline) and presented with higher concentrations of LDL-C than the primary hyperlipidemia population. The HoFH population was exposed to evolocumab at a dose of 420 mg SC either Q2W or QM in trials 20110233 and 20110271; 31 participants received evolocumab 420 mg Q2W and 68 participants received 420 mg QM for the first dose. Across the 2 HoFH trials, 81 HoFH participants received evolocumab for at least 3 months, 56 HoFH participants received evolocumab for at least 6 months, and 23 HoFH participants received evolocumab for at least 12 months. Trial 20110233 included 11 subjects who were ≥ 12 to < 18 years old and trial 20110271 included 10 of those 11 subjects plus an additional 3 subjects; all 14 subjects were diagnosed with HoFH. In Study 20110271, 31 subjects with HoFH were receiving apheresis at enrollment. The exposure to IP for Trial 20110233 is presented in the following table. For Part B, the total mean and median duration of evolocumab exposure was 2.7 and 2.8 months, respectively.

Table 52: Summary of Exposure in Trial 20110233

	20110233 Part A	**20110233 Part B**	
	EvoMab 420 mg QM (N = 8)	**Placebo QM (N = 16)**	**EvoMab 420 mg QM (N = 33)**
Duration of SC IP exposure (months)[a]			
n	8	16	33
Mean	2.8	2.8	2.7
Median	2.7	2.8	2.8
Min, Max	2.7, 2.8	2.8, 2.8	1.0, 2.9

For part A, N = number of subjects enrolled and dosed; for part B, N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly; IP = investigational product
a For QM subjects in part A: IP Exposure Period = [min(end of EOIP date + 28 days, EOS date) - Study day 1 Date + 1] / 365.25 * 12. For QM subjects in part B: [min(Last dose date + 28 days, EOS date) - First dose date +1] /365.25 * 12
Source: Modified from Table 14-5.1.1 Part A of Study 20110233 and Table 14-5.1.1 Part B of Study 20110233 and Applicant Table 7 (2.7.4)

The exposure to IP for Trial 20110271 is presented in the following table and shows the exposure in the OLE for the patients who did or did not rollover from a parent study. The total mean and median duration of evolocumab exposure was 6.4 and 5.1 months, respectively. Exposure to evolocumab for ≥ 12 weeks occurred in 69 participants and for ≥ 24 weeks in 47 participants. A summary of exposure for HoFH participants ≥ 12 to < 18 years old (data not shown in the table) is mean and median exposure to evolocumab of 7.5 months and 10.6 months, respectively. Exposure to evolocumab for ≥ 12 weeks occurred in 11 participants and ≥ 24 weeks in 8 participants.

Table 53: Summary of Exposure in Study 20110271 (HoFH Interim Analysis Set, 01 April 2014 data cutoff date)

	20110233 HoFH Parent Study Rollover			20110271 HoFH Non-Parent / Other Parent Study Rollover			**Total**
	Part A EvoMab (N = 8)	Part B EvoMab (N = 30)	Part B Placebo (N = 16)	Apheresis at Enrollment (N = 31)	Non-apheresis at Enrollment (N = 11)	Total (N = 42)	(N = 96)
Duration of SC IP exposure (months)							
n	8	30	16	31	11	42	96
Mean	18.0	6.3	5.6	5.0	3.8	4.7	6.4
Median	17.3	5.3	4.9	4.6	2.0	4.2	5.1
Min, Max	11.9, 21.1	0.6, 10.6	1.2, 10.6	0.4, 13.9	0.1, 15.4	0.1, 15.4	0.1, 21.1
Participants with Duration of IP exposure (%)							
≥ 12 weeks	8 (100.0)	22 (73.3)	11 (68.8)	24 (77.4)	4 (36.4)	28 (66.7)	69 (71.9)
≥ 24 weeks	8 (100.0)	15 (50.0)	8 (50.0)	13 (41.9)	3 (27.3)	16 (38.1)	47 (49.0)

N = number of HoFH subjects enrolled and dosed in Study 20110271; HoFH=Homozygous Familial Hypercholesterolemia; IP = investigational product;
EvoMab=Evolocumab (AMG 145); SD = standard deviation
Data cutoff date 01APR2014.
Source Data: Table 14-5.1.2 of Study 20110271 and Applicant Table 8 (2.7.4)

Exposure to the 420 mg Q2W Dose

Two groups of participants in Study 20110271 received evolocumab 420 mg Q2W:

1. non-apheresis participants who began the study on 420 mg QM and subsequently had their dose uptitrated to 420 mg Q2W as allowed by protocol, and
2. apheresis participants, all of whom began on the 420 mg Q2W dose.

Non-apheresis HoFH participants: Of the 96 participants in the HoFH Interim Analysis Set of the open-label extension Study 20110271, as of the 01 April 2014 data cutoff date, 25 participants received ≥ 12 weeks of evolocumab 420 mg once monthly (QM) and then switched to ≥ 12 weeks of evolocumab 420 mg Q2W. As of the 01 July 2014 data cutoff date for the 120-day Safety Update, 100 participants were included in the HoFH Interim Analysis Set and 28 participants had been switched 420 mg Q2W.

01 April 2014 data cutoff date: 198 participants with HoFH and HeFH were included in the Interim Analysis Set of Study 20110271. Of these, 65 participants ever received evolocumab 420 mg Q2W (of which 61 were participants with HoFH).

01 July 2014 data cutoff date: 242 participants with HoFH and HeFH were included in the Interim Analysis Set of Study 20110271. Of these, 93 participants ever received evolocumab 420 mg Q2W (of which 75 were participants with HoFH).

The number of participants who used the 420 mg Q2W dose and the duration of exposure are summarized in the following two tables.

Table 54: Participants Who Received Evolocumab by Actual Dose Received Study 20110271 (Interim Analysis Set)

	As of 01 April 2014 (Original BLA) (N = 198)				As of 01 July 2014 (120-day Safety update) (N = 242)			
	Any Q2W				Any Q2W			
Subjects Receiving Evolocumab for Any Duration	Q2W Only[a]	QM and Q2W[b]	Total	QM only[c]	Q2W Only[a]	QM and Q2W[b]	Total	QM only[c]
All subjects	30	35	65	133	43	50	93	149
HoFH subjects	27	34	61	35	28	47	75	25
Non-apheresis subjects (began on QM)	0	30	30	35	0	41	41	25
Apheresis subjects (began on Q2W)	27	4	31	0	28	6	34	0
Severe HeFH subjects[d]	3	1	4	98	15	3	18	124
Non-apheresis subjects (began on QM)	0	1	1	98	0	2	2	124
Apheresis subjects (began on Q2W)	3	0	3	0	15	1	16	0

HoFH = homozygous familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; OLE = open-label extension; Q2W = every 2 weeks; QM = once monthly.
a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.
b Apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM, or non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W.
c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM.
d Subjects in OLE Study 20110271 who did not meet the study criteria for HoFH.
Source: Applicant's response to Feb 2015 Information Request.

Table 55: Exposure in Study 20110271 by Dosing Regimen (420 mg QM only, 420 mg Q2W only, or 420 mg QM and Q2W); (Data cutoff date 01JUL2014)

	20110271: HoFH			20110271: HeFH		
	Q2W Only[a]	QM and Q2W[b]	QM Only[c]	Q2W Only[a]	QM and Q2W[b]	QM Only[c]
Total Number of participants	28	47	25	15	3	124
Median Exposure (months)	7.1	12.5	5.5	2.5	3.3	3.5
Mean Exposure (months)	6.7	11.5	6.3	2.4	4.3	4.5

Data cutoff date 01JUL2014. HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; Q2W = once every 2 weeks; QM = once monthly.
a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.
b Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.

Source: Applicant's response to Feb 2015 Information Request.

The number of participants exposed to the 420 mg Q2W and the duration of exposure at this dose is quite limited. The safety profile of the 420 mg Q2W dose is discussed in Section 7.7.1 120-Day Safety Update for BLA: Primary Hyperlipidemia/Mixed Dyslipidemia and HoFH Populations

The applicant was asked to provide information on the estimated percentage of evolocumab that is cleared by apheresis. The applicant responded that there were 31 participants with HoFH on apheresis who had received evolocumab in OLE Study 20110271 as of the 01 April 2014 data cutoff date for the original BLA. These participants visited the site every 2 weeks and were placed on an evolocumab 420 mg SC Q2W. Unbound serum evolocumab concentrations were measured immediately before and immediately after each apheresis session, followed by evolocumab dosing. The following table shows the mean evolocumab serum concentrations pre- and post-apheresis by visit from week 2 through week 12 as well as the estimated dose lost by apheresis. The applicant states that the mean serum unbound evolocumab concentrations assessed at trough (ie, 2 weeks after administration) were approximately 20% to 30% lower as a result of apheresis, representing an estimated 30 to 60 mg of evolocumab (8% to 15% of the dose).

Table 56: Mean Pre- and Post-Apheresis Unbound Evolocumab Concentrations in Participants with HoFH through Week 12 Receiving Evolocumab 420 mg SC Q2W (Post-Apheresis) in Study 20110271

Study Week	Pre-Apheresis		Post-Apheresis				
	N	Unbound Evolocumab Concentration (µg/mL)	N	Unbound Evolocumab Concentration (µg/mL)	Concentration Difference (µg/mL)	Estimated Drug Loss[a] (mg)	Estimated Dose Lost (%)
2	29	31.1	27	21.5	9.6	32	8
4	27	49.5	25	34.4	15.1	50	12
6	27	61.9	24	43.6	18.3	61	15
8	25	63.4	21	45.8	17.6	59	14
10	24	69.0	20	49.7	19.3	64	15
12	22	77.0	16	61.3	15.7	52	12

01 April 2014 data cutoff date
a Estimated using volume of distribution from Phase 1 IV 420 mg dose = 3.34 L
Source: Table 12 from Feb 2015 Information Request Response.

Device-Exposure
The PFS and the AI/pen provide a single SC administration of 140 mg evolocumab. The AI/pen was used in the majority of the phase 3 trials with 3 consecutively administered (within 30 minutes) AI/pens to deliver the 420 mg dose. The initial drug

substance (Process 1) was administered via the vial and syringe. The 2 devices (PFS, and AI/pen) administered the proposed commercialized drug substance (Process 2). The device exposures with EvoMab 140 mg Q2W or 420 mg QM (IPAS, IECAS, and IEAAS) are as follows:

- AI/pen: 3165 subjects (1595 patient-years); 1680 at ≥ 6 months; 105 at ≥ 12 months
- PFS: 75 subjects (12 patient-years); 0 at ≥ 3 months
- Vial and syringe: 1827 subjects (2497 patient-years) ; 1615 at ≥ 6 months; 1564 at ≥ 12 months (note: the applicant has not requested approval consideration for this method of administration)

Device Exposure in HoFH Trials
In the HoFH trials, most of the participants used the vial and syringe. However, in trial 20110233, a total of 14 participants (9 evolocumab, 5 placebo) used the AI/pen at least once and 8 participants (6 evolocumab, 2 placebo) used the AI/pen at every visit (ie, 9 AI/pens over the course of the trial). One adolescent participant (15 years old; 23371001001) used the AI/pen at each visit; all other participants who used the AI/pen were adults.

In the long-term OLE trial 20110271, of the 96 HoFH participants, evolocumab was administered with an AI/pen in 37 (38.5%) participants. One adolescent participant (15 years old; 27158005001) used AI/pen; all other participants who used the AI/pen were adults.

7.2.1.1 Disposition in the Safety Population

Disposition in Primary Hyperlipidemia and Mixed Dyslipidemia Trials

Discontinuation of investigational product in the IPAS was similar across treatment groups and dosing frequency. Adverse events and subject request were the most common reasons for discontinuation of investigational product across control and EvoMab treatment groups.

Table 57: Summary of Disposition in Primary Hyperlipidemia and Mixed Dyslipidemia Studies: Integrated Parent Studies (IPAS)

	Control			**EvoMab**			
	Placebo Q2W (N =589) n (%)	Placebo QM (N =945) n (%)	EZ QD (N=556) n (%)	Other EvoMab Dose (N =721) n (%)	140 mg Q2W (N=1248) n (%)	420 mg QM (N=1960) n (%)	420 mg QM + EZ QD (N =31) n (%)
Subjects who never received IP	3 (0.5)	5 (0.5)	1 (0.2)	6 (0.8)	3 (0.2)	4 (0.2)	1 (3.2)
Subjects who	586	940	509	715	1245	1956	30 (96.8)

received IP	(99.5)	(99.5)	(99.8)	(99.2)	(99.8)	(99.8)	
Subjects who completed IP	557 (94.6)	885 (93.7)	478 (93.7)	695 (96.4)	1190 (95.4)	1833 (93.5)	29 (93.5)
Subjects who discontinued IP	29 (4.9)	55 (5.8)	31 (6.1)	20 (2.8)	55 (4.4)	123 (6.3)	1 (3.2)
Full consent withdrawn	0	10 (1.1)	0	1 (0.1)	2 (0.2)	9 (0.5)	0
Adverse event	9 (1.5)	12 (1.3)	15 (2.9)	3 (0.4)	26 (2.1)	27 (1.4)	1 (3.2)
Pregnancy	0	0	0	0	0	1 (0.1)	0
Death	0	0	0	0	0	2 (0.1)	0
Subject request	11 (1.9)	17 (1.8)	10 (2.0)	6 (0.8)	16 (1.3)	43 (2.2)	0
Administrative decision by sponsor	0	1 (0.1)	0	0	16 (1.3)	6 (0.3)	0
Physician decision	0	2 (0.2)	2 (0.4)	2 (0.3)	0	1 (0.1)	0
Lost to follow-up	3 (0.5)	3 (0.3)	2 (0.4)	0	4 (0.3)	13 (0.7)	0
Other	6 (1.0)	10 (1.1)	2 (0.4)	8 (1.1)	6 (0.5)	21 (1.1)	0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; EZ=ezetimibe; QD = once a day; Q2W = every 2 weeks; QM = monthly;
SC = subcutaneous; IP = investigational product; IPAS = Integrated Parent Analysis Set.
Source: Table 3-1 response to 06Nov2014 IR

Disposition in HoFH Trials

In trial 20110233 part A, a total of 8 subjects were enrolled and all 8 subjects completed treatment with open-label evolocumab and completed the trial. In trial 20110233 part B, a total of 50 subjects were randomized to the evolocumab (n = 33) and placebo (n = 17) groups. All 33 (100%) subjects in the evolocumab group and 16 (94%) subjects in the placebo group received IP. Two (6.1%) subjects in the evolocumab group discontinued IP, both listed as due to subject request although there were some adverse events occurring around the time of withdrawal.[58] No subject in the placebo group discontinued IP. All 49 subjects who received IP completed the study. All but 3 (n=46) participants continued into trial 20110271.

In trial 20110271, a total of 96 HoFH subjects were enrolled. All 96 HoFH subjects received evolocumab, including 87 (90.6%) subjects who were still receiving

58 For Subject 23356002004, the reason was listed as: Mother attributed adverse event of Achilles tendonitis to IP and did not wish her child to continue; patient did not wish bloods taken or injections to be given. Of note, only the first dose of drug was given. In the AE dataset, AE for Achilles tendonitis is listed as “not related” on day 24-31.

For Subject 23356002005 the reason was listed as: Mother attributed adverse events of upper respiratory tract infection (URI) and atypical chest pain to IP and did not wish her son to receive more IP. Subject received drug at day 1 and 29; the URI [“not related” was day 37-43 (along with gastroenteritis)] and the non-cardiac chest pain was on days 66-68.

evolocumab as of the data cutoff date. Of the 9 (9.4%) subjects who discontinued evolocumab, 5 (5.2%) subjects discontinued due to physician decision, 2 (2.1%) subjects due to subject request, and 1 (1.0%) subject each due to adverse event and pregnancy. One (1.0%) subject discontinued from the study due to “other” reason.

Table 58: Participant Disposition with Discontinuation Reason for HoFH Participants in Trial 20110271 (HoFH Interim Analysis Set) Data cutoff date 01APR2014

	20110233 HoFH Parent Trial Rollover			**20110271 HoFH Non-Parent / Other Parent Study Rollover**			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B Placebo (N = 16) n (%)	Apheresis at Enrollment (N = 31) n (%)	Non-apheresis at Enrollment (N = 11) n (%)	Total (N = 42) n (%)	Total (N = 96) n (%)
Participants who discontinued IP	1 (12.5)	2 (6.7)	1 (6.3)	5 (16.1)	0	5 (11.9)	9 (9.4)
Adverse reaction	0	1 (3.3)	0	0	0	0	1 (1.0)
Pregnancy	0	0	1 (6.3)	0	0	0	1 (1.0)
Subject request	1 (12.5)	0	0	1 (3.2)	0	1 (2.4)	2 (2.1)
Physician decision	0	1 (3.3)	0	4 (12.9)	0	4 (9.5)	5 (5.2)

N = number of HoFH subjects enrolled and dosed in Study 20110271; HoFH=Homozygous Familial Hypercholesterolemia; EvoMab = Evolocumab; IP = investigational product
Source Data: adam.adsl; Applicant Table 16 (2.7.4)

7.2.1.2 Demographics in the Safety Population

Demographics in Primary Hyperlipidemia and Mixed Dyslipidemia Trials

In the integrated parent studies analysis set (see table below), the mean (SD) age was 57.5 (11.2) years; 1779 (29.5%) participants were ≥ 65 years of age and 223 (3.7%) were ≥ 75 years. No pediatric participants (< 18 years of age) were enrolled. A total of 3044 (50.5%) participants were women. Eighty-three percent of participants were white of which only 5% were Hispanic/Latino, 9% were Asian, 6% were black, and 49% were from North America, 39% from Europe, and 12% from Asia Pacific.

Additional baseline characteristics include 1141 (18.9%) participants had coronary artery disease, with 541 (9.1%) having a history of myocardial infarction. Only 145 (2.4%) participants had a history of stroke at baseline. There were 803 (13.3%) participants with type 2 diabetes, 3100 (51.4%) with hypertension, 909 (15.1%) participants with current cigarette use, and 674 (11.2%) participants with renal

impairment (eGFR < 60 mL/min/1.73m2). Only 1.7% of participants had CHF NYHA class I, 1.7% had CHF NYHA class II and one participant had class III CHF.

Approximately one-third of participants were at high CHD risk according to National Cholesterol Education Program Adult Treatment Panel coronary heart disease risk categories whereas < 10% were at moderate-high risk. Thus, less than 50% (2619 participants) were at moderate-high or higher CHD risk at baseline.

At baseline, approximately 30% of participants were using high-intensity statin therapy (per ACC/AHA definition statins such as atorvastatin 40-80 mg or rosuvastatin 20-40 mg) and 38% were using moderate intensity statin therapy (such as atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg). Twenty-five percent were not on any statin therapy. Participants who received ezetimibe were less likely to use high-intensity statin therapy; this was due to the parent study designs in which ezetimibe was used as an active control in trials 20110114, 20110115 (atorvastatin cohorts), and 20110116.

Across the IPAS, baseline LDL-C and other lipid parameters were generally similar and well-controlled between the evolocumab and control groups, with the following exceptions: (1) baseline LDL-C was somewhat higher for the ezetimibe groups due to differences in parent study designs and background therapy (no statin background therapy and statin-intolerance trials used ezetimibe as a control); (2) the “other evolocumab dose” were phase 2 trials that enrolled subjects with higher LDL values; and (3) the baseline LDL-C was markedly higher in the evolocumab 420 mg QM plus ezetimibe group as this randomized treatment paradigm was used as an arm of the statin-intolerance Study 20090159 (GAUSS-1) where the mean baseline LDL-C was 193 mg/dL.

Table 59: Key Baseline Characteristics (IPAS)

	Control			**EvoMab**				**Total**
	Placebo SC Q2W (N =586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N =715) n (%)	140 mg Q2W (N=1245) n (%)	420 mg QM (N=1956) n (%)	420 mg QM + Eze. QD (N = 30) n (%)	(N=6026) n (%)
Sex Female	290 (49.5)	484 (51.5)	307 (55.4)	383 (53.6)	595 (47.8)	962 (49.2)	23 (76.7)	3044 (50.5)
Age (yrs) Mean	57.8	56.5	58.0	57.1	58.1	57.5	62.0	57.5
Age ≥ 65 years	163 (27.8)	249 (26.5)	174 (31.4)	214 (29.9)	392 (31.5)	574 (29.3)	13 (43.3)	1779 (29.5)
Age ≥ 75 years	25 (4.3)	27 (2.9)	13 (2.3)	28 (3.9)	63 (5.1)	67 (3.4)	0	223 (3.7)
White	483	785	486	522	1065	1659	24	5024

	Control			EvoMab				Total
	Placebo SC Q2W (N =586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N =715) n (%)	140 mg Q2W (N=1245) n (%)	420 mg QM (N=1956) n (%)	420 mg QM + Eze. QD (N = 30) n (%)	(N=6026) n (%)
	(82.4)	(83.5)	(87.7)	(73.0)	(85.5)	(84.8)	(80.0)	(83.4)
Asian	68 (11.6)	87 (9.3)	29 (5.2)	121 (16.9)	93 (7.5)	136 (7.0)	5 (16.7)	539 (8.9)
Black	28 (4.8)	45 (4.8)	33 (6.0)	58 (8.1)	72 (5.8)	116 (5.9)	1 (3.3)	353 (5.9)
Europe	262 (44.7)	365 (38.8)	249 (44.9)	212 (29.7)	489 (39.3)	732 (37.4)	15 (50.0)	2324 (38.6)
North America	240 (41.0)	438 (46.6)	261 (47.1)	380 (53.1)	628 (50.4)	998 (51.0)	11 (36.7)	2956 (49.1)
Asia Pacific	84 (14.3)	137 (14.6)	44 (7.9)	123 (17.2)	128 (10.3)	226 (11.6)	4 (13.3)	746 (12.4)
National cholesterol education program (NCEP) CHD risk categories								
High	183 (31.2)	289 (30.7)	168 (30.3)	253 (35.4)	477 (38.3)	648 (33.1)	10 (33.3)	2028 (33.7)
Mod-high	2028 (33.7)	84 (8.9)	49 (8.8)	73 (10.2)	117 (9.4)	211 (10.8)	1 (3.3)	591 (9.8)
Moderate	173 (29.5)	271 (28.8)	172 (31.0)	205 (28.7)	363 (29.2)	578 (29.6)	11 (36.7)	1773 (29.4)
Low	174 (29.7)	296 (31.5)	165 (29.8)	184 (25.7)	288 (23.1)	519 (26.5)	8 (26.7)	1634 (27.1)
Coronary artery disease	115 (19.6)	158 (16.8)	77 (13.9)	126 (17.6)	274 (22.0)	385 (19.7)	6 (20.0)	1141 (18.9)
Angina	67 (11.4)	96 (10.2)	43 (7.8)	89 (12.4)	139 (11.2)	211 (10.8)	5 (16.7)	650 (10.8)
Myocardial infarction	53 (9.0)	79 (8.4)	30 (5.4)	52 (7.3)	145 (11.6)	187 (9.6)	0	546 (9.1)
Coronary artery bypass graft	29 (4.9)	47 (5.0)	16 (2.9)	46 (6.4)	80 (6.4)	136 (7.0)	2 (6.7)	356 (5.9)
Percutaneous coronary intervention	68 (11.6)	88 (9.4)	45 (8.1)	72 (10.1)	168 (13.5)	192 (9.8)	3 (10.0)	636 (10.6)
Cerebrovascular or peripheral arterial disease	48 (8.2)	66 (7.0)	39 (7.0)	61 (8.5)	120 (9.6)	174 (8.9)	1 (3.3)	509 (8.4)
Transient ischemic attack	10 (1.7)	11 (1.2)	9 (1.6)	16 (2.2)	26 (2.1)	43 (2.2)	0	115 (1.9)
Stroke	17 (2.9)	21 (2.2)	10 (1.8)	27 (3.8)	28 (2.2)	42 (2.1)	0	145 (2.4)
Carotid or vertebral artery disease	17 (2.9)	27 (2.9)	11 (2.0)	17 (2.4)	52 (4.2)	74 (3.8)	0	198 (3.3)

	Control			EvoMab				Total
	Placebo SC Q2W (N =586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N =715) n (%)	140 mg Q2W (N=1245) n (%)	420 mg QM (N=1956) n (%)	420 mg QM + Eze. QD (N = 30) n (%)	(N=6026) n (%)
Peripheral arterial disease	17 (2.9)	19 (2.0)	14 (2.5)	22 (3.1)	47 (3.8)	49 (2.5)	1 (3.3)	169 (2.8)
Current cigarette use	82 (14.0)	153 (16.3)	84 (15.2)	126 (17.6)	187 (15.0)	275 (14.1)	2 (6.7)	909 (15.1)
Type 2 diabetes mellitus	60 (10.2)	121 (12.9)	74 (13.4)	107 (15.0)	199 (16.0)	240 (12.3)	2 (6.7)	803 (13.3)
Hypertension	301 (51.4)	445 (47.3)	265 (47.8)	388 (54.3)	692 (55.6)	995 (50.9)	14 (46.7)	3100 (51.4)
Statin therapy intensity per ACC/AHA definition*								
High	165 (28.2)	347 (36.9)	111 (20.0)	132 (18.5)	358 (28.8)	676 (34.6)	0	1789 (29.7)
Moderate	250 (42.7)	385 (41.0)	121 (21.8)	233 (32.6)	515 (41.4)	806 (41.2)	1 (3.3)	2311 (38.4)
Low	50 (8.5)	47 (5.0)	14 (2.5)	113 (15.8)	86 (6.9)	87 (4.4)	3 (10.0)	400 (6.6)
Unknown	0	0	0	1 (0.1)	3 (0.2)	0	0	4 (0.1)
None	121 (20.6)	161 (17.1)	308 (55.6)	236 (33.0)	283 (22.7)	387 (19.8)	26 (86.7)	1522 (25.3)
Baseline Lipid Parameters (mean [SD])								
LDL-C (mg/dL)	122.8 (37.7)	119.4 (38.5)	141.3 (49.7)	137.3 (36.7)	128.2 (45.7)	121.6 (44.0)	193.6 (59.7)	126.8 (43.7)
Total cholesterol (mg/dL)	203.6 (42.5)	199.2 (42.6)	223.9 (56.4)	218.2 (41.4)	208.8 (50.2)	201.3 (48.4)	279.7 (65.3)	207.3 (48.4)
HDL-C (mg/dL)	54.6 (17.0)	54.1 (16.5)	53.6 (16.2)	53.6 (16.4)	53.0 (15.6)	53.4 (16.0)	59.9 (19.2)	53.6 (16.2)
Triglycerides(mg/dL)	132.0 (66.8)	130.2 (68.9)	144.8 (74.4)	137.3 (63.6)	138.9 (73.1)	131.9 (69.8)	130.9 (55.5)	134.9 (69.9)
ApoB (mg/dL)	97.5 (24.6)	96.8 (24.4)	108.4 (31.3)	109.9 (24.0)	101.5 (29.6)	97.9 (27.4)	138.8 (33.1)	101.1 (27.7)
ApoA1 (mg/dL)	152.7 (29.1)	153.1 (28.6)	151.7 (28.3)	154.6 (28.2)	150.9 (28.1)	152.0 (27.8)	163.1 (29.0)	152.4 (28.3)
non-HDL-C (mg/dL)	149.0 (40.3)	145.1 (42.6)	170.3 (55.2)	164.6 (40.4)	155.9 (49.5)	147.9 (47.6)	219.8 (60.5)	153.6 (47.5)
Lp(a) (nmol/L)	79.5 (94.2)	87.8 (106.5)	80.8 (92.3)	80.1 (99.7)	83.2 (103.7)	87.5 (107.1)	105.3 (120.9)	84.4 (102.9)

N = number of subjects randomized in the integrated parent analysis set;
CHD = coronary heart disease; EvoMab = Evolocumab (AMG 145); IPAS = Integrated Parent Analysis Set; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; CHD = coronary heart disease;
*ACC = American College of Cardiology; AHA = American Heart Association; High-Intensity Statin Therapy (such as atorvastatin 80 mg or rosuvastatin 40 mg) and Moderate-Intensity Statin Therapy (such as atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 20-40 mg).; Amgen definition: intensive if atorvastatin ≥ 40 mg QD, rosuvastatin ≥ 20 mg QD, simvastatin ≥ 80 mg QD, or any

	Control			EvoMab				Total
	Placebo SC Q2W (N =586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N =715) n (%)	140 mg Q2W (N=1245) n (%)	420 mg QM (N=1956) n (%)	420 mg QM + Eze. QD (N = 30) n (%)	(N=6026) n (%)
statin use with concurrent ezetimibe use and nonintensive is any statin use not classified as intensive. Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Subjects from countries with an undefined risk are classed as low risk. *Source: Modified from ISS Table 14-2.1.1, ISS Table 14-2.7.401, ISS Table 14-2.8.401, ISS Table 14-2.2.1, Table 17 (2.7.4) and Table 6-1 response to 06Nov2014 IR*								

Demographics in the Integrated Extension Standard of Care (SoC)-Controlled Period Analysis Set (IECAS)

The IECAS comprises integrated data from year 1 (the controlled period) of the open-label extension (OLE) trials. In the IECAS analysis set (see table below), the mean age was 57.9 years; 31% of participants were ≥ 65 years of age and 3.8% were ≥ 75 years. No pediatric participants (< 18 years of age) were enrolled. A total of 2111 (50.0%) participants were women. Eighty-six percent of participants were white of which only 5% were Hispanic/Latino, 8% were Asian, 5% were black, and 48% were from North America, 40% from Europe, and 12% from Asia Pacific. This is very similar to the demographics of the IPAS dataset.

Additional baseline characteristics include 815 (19.2%) participants had coronary artery disease, with 381 (9.0%) having a history of myocardial infarction. Only 2.7% (116) of participants had a history of stroke at baseline. There were 560 (13.2%) participants with type 2 diabetes, 2189 (51.5%) with hypertension, and 656 (15.4%) participants with current cigarette use. Only 1.6% of participants had CHF NYHA class I, 1.2% had CHF NYHA class II and one participant had class III CHF. The number of participants is smaller than what was available in the IPAS dataset but the proportions of participants in each category is similar.

As in the IPAS dataset, approximately one-third of participants were at high CHD risk according to National Cholesterol Education Program Adult Treatment Panel coronary heart disease risk categories and approximately 10% were at moderate-high risk. Thus, less than 50% (2619 participants) were at moderate-high or higher CHD risk at baseline.

As seen in the IPAS dataset, approximately 30% of participants were using high-intensity statin therapy (per ACC/AHA definition statins such as atorvastatin 80 mg or rosuvastatin 40 mg) and 38% were using moderate intensity statin therapy (such as

atorvastatin 20 mg, rosuvastatin 10 mg, and simvastatin 20-40 mg). Twenty-five percent were not on any statin therapy.

Across the IECAS, baseline LDL-C and other lipid parameters were generally similar and well-controlled between the evolocumab and control groups.

Table 60: Baseline Demographics in the Integrated Extension SoC-Controlled Period Analysis Set (IECAS)

	Control in Parent Trial		**EvoMab in Parent Trial**		**All**		**Total**
	SoC (N=472) n (%)	EvoMab+ SoC (N = 943) n (%)	SoC N = 947 n (%)	EvoMab+ SoC (N =1890) n (%)	SoC (N=1419) n (%)	EvoMab+ SoC (N=2833) n (%)	(N=4252) n (%)
Sex Female	247 (52.3)	481 (51.0)	447 (47.2)	936 (49.5)	694 (48.9)	1417 (50.0)	2111 (49.6)
Age (yrs) Mean	58.5	57.3	58.1	58.1	58.2	57.8	57.9
Age ≥ 65 years	147 (31.1)	271 (28.7)	302 (31.9)	581 (30.7)	449 (31.6)	852 (30.1)	1301 (30.6)
Age ≥ 75 years	24 (5.1)	23 (2.4)	34 (3.6)	82 (4.3)	58 (4.1)	105 (3.7)	163 (3.8)
White	413 (87.5)	822 (87.2)	793 (83.7)	1615 (85.4)	1206 (85.0)	2437 (86.0)	3643 (85.7)
Asian	37 (7.8)	72 (7.6)	85 (9.0)	159 (8.4)	122 (8.6)	231 (8.2)	353 (8.3)
Black	15 (3.2)	37 (3.9)	57 (6.0)	95 (5.0)	72 (5.1)	132 (4.7)	204 (4.8)
Europe	227 (48.1)	402 (42.6)	343 (36.2)	744 (39.4)	570 (40.2)	1146 (40.5)	1716 (40.4)
North America	190 (40.3)	431 (45.7)	492 (52.0)	929 (49.2)	682 (48.1)	1360 (48.0)	2042 (48.0)
Asia Pacific	55 (11.7)	110 (11.7)	112 (11.8)	217 (11.5)	167 (11.8)	327 (11.5)	494 (11.6)
National cholesterol education program (NCEP) CHD risk categories							
High	149 (31.6)	294 (31.2)	348 (36.7)	669 (35.4)	497 (35.0)	963 (34.0)	1460 (34.3)
Mod-high	47 (10.0)	90 (9.5)	100 (10.6)	195 (10.3)	147 (10.4)	285 (10.1)	432 (10.2)
Moderate	150 (31.8)	270 (28.6)	268 (28.3)	572 (30.3)	418 (29.5)	842 (29.7)	1260 (29.6)
Low	126 (26.7)	289 (30.6)	231 (24.4)	454 (24.0)	357 (25.2)	743 (26.2)	1100 (25.9)
Coronary artery disease	86 (18.2)	156 (16.5)	194 (20.5)	379 (20.1)	280 (19.7)	535 (18.9)	815 (19.2)
Angina	38 (8.1)	93 (9.9)	104 (11.0)	216 (11.4)	142 (10.0)	309 (10.9)	451 (10.6)
Myocardial infarction	40 (8.5)	69 (7.3)	90 (9.5)	182 (9.6)	130 (9.2)	251 (8.9)	381 (9.0)

	Control in Parent Trial		EvoMab in Parent Trial		All		Total
	SoC (N=472) n (%)	EvoMab+ SoC (N = 943) n (%)	SoC N = 947 n (%)	EvoMab+ SoC (N =1890) n (%)	SoC (N=1419) n (%)	EvoMab+ SoC (N=2833) n (%)	(N=4252) n (%)
Coronary artery bypass graft	28 (5.9)	37 (3.9)	70 (7.4)	129 (6.8)	98 (6.9)	166 (5.9)	264 (6.2)
Percutaneous coronary intervention	50 (10.6)	94 (10.0)	107 (11.3)	208 (11.0)	157 (11.1)	302 (10.7)	459 (10.8)
Cerebrovascular or peripheral arterial disease	44 (9.3)	65 (6.9)	86 (9.1)	188 (9.9)	130 (9.2)	253 (8.9)	383 (9.0)
Transient ischemic attack	7 (1.5)	12 (1.3)	15 (1.6)	48 (2.5)	22 (1.6)	60 (2.1)	82 (1.9)
Stroke	10 (2.1)	32 (3.4)	26 (2.7)	48 (2.5)	36 (2.5)	80 (2.8)	116 (2.7)
Carotid or vertebral artery disease	22 (4.7)	18 (1.9)	37 (3.9)	75 (4.0)	59 (4.2)	93 (3.3)	152 (3.6)
Peripheral arterial disease	16 (3.4)	17 (1.8)	31 (3.3)	60 (3.2)	47 (3.3)	77 (2.7)	124 (2.9)
Current cigarette use	70 (14.8)	147 (15.6)	143 (15.1)	296 (15.7)	213 (15.0)	443 (15.6)	656 (15.4)
Type 2 diabetes mellitus	60 (12.7)	110 (11.7)	141 (14.9)	249 (13.2)	201 (14.2)	359 (12.7)	560 (13.2)
Hypertension	229 (48.5)	464 (49.2)	504 (53.2)	992 (52.5)	733 (51.7)	1456 (51.4)	2189 (51.5)
Statin therapy intensity per ACC/AHA definition*							
High	141 (29.9)	296 (31.4)	289 (30.5)	558 (29.5)	430 (30.3)	854 (30.1)	1284 (30.2)
Moderate	168 (35.6)	358 (38.0)	351 (37.1)	67 (7.1)	519 (36.6)	1082 (38.2)	1601 (37.7)
Low	26 (5.5)	50 (5.3)	67 (7.1)	151 (8.0)	93 (6.6)	201 (7.1)	294 (6.9)
Unknown	0	0	0	3 (0.2)	0	3 (0.1)	3 (0.1)
None	137 (29.0)	239 (25.3)	240 (25.3)	454 (24.0)	377 (26.6)	693 (24.5)	1070 (25.2)
Baseline Lipid Parameters							
LDL-C (mg/dL)	127.0 (44.4)	126.6 (43.0)	130.5 (46.4)	129.4 (45.7)	129.4 (45.8)	128.5 (44.8)	128.8 (45.1)
Total cholesterol (mg/dL)	209.4 (49.8)	209.4 (49.8)	210.9 (51.0)	210.0 (49.8)	210.4 (50.6)	209.0 (49.0)	209.5 (49.5)
HDL-C (mg/dL)	54.8 (16.8)	53.8 (16.3)	53.8 (16.3)	53.8 (16.3)	53.5 (16.2)	53.8 (16.3)	53.7 (16.3)
Triglycerides (mg/dL)	138.7 (81.4)	135.1 (66.4)	139.3 (78.0)	134.3 (65.2)	139.1 (79.1)	134.5 (65.6)	136.1 (70.4)

	Control in Parent Trial		EvoMab in Parent Trial		All		Total
	SoC (N=472) n (%)	EvoMab+ SoC (N = 943) n (%)	SoC N = 947 n (%)	EvoMab+ SoC (N =1890) n (%)	SoC (N=1419) n (%)	EvoMab+ SoC (N=2833) n (%)	(N=4252) n (%)
ApoB (mg/dL)	100.6 (27.9)	100.9 (27.2)	104.1 (28.9)	103.2 (28.5)	102.9 (28.6)	102.4 (28.1)	102.6 (28.3)
ApoA1 (mg/dL)	153.9 (28.4)	152.5 (28.2)	151.5 (28.3)	153.5 (27.8)	152.3 (28.4)	153.1 (27.9)	152.9 (28.1)
non-HDL-C (mg/dL)	154.6 (48.9)	153.3 (47.1)	158.1 (50.2)	156.2 (49.0)	156.9 (49.8)	155.2 (48.4)	155.8 (48.8)
Lp(a) (nmol/L)	82.0 (99.5)	87.0 (103.6)	84.2 (106.6)	84.1 (100.6)	83.4 (104.1)	85.1 (101.7)	84.5 (102.5)

N = number of subjects randomized in the integrated extension SoC-controlled period analysis set; SoC = Standard of Care.; CHD = coronary heart disease; EvoMab = Evolocumab (AMG 145);
*ACC = American College of Cardiology; AHA = American Heart Association; High-Intensity Statin Therapy (such as atorvastatin 80 mg or rosuvastatin 40 mg) and Moderate-Intensity Statin Therapy (such as atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 20-40 mg).; Amgen definition: intensive if atorvastatin ≥ 40 mg QD, rosuvastatin ≥ 20 mg QD, simvastatin ≥ 80 mg QD, or any statin use with concurrent ezetimibe use and nonintensive is any statin use not classified as intensive.
Includes the following studies: 20110110, 20120138Subjects from countries with an undefined risk are classed as low risk.
Source: Modified from ISS Table 14-2.2.3, ISS Table 14-2.1.3, ISS Table 14-2.8.401 and Table 6-2 response to 06Nov2014 IR

As was discussed with the applicant at the End of Phase 2 meeting, the experience with evolocumab, especially the long-term experience in controlled trials, needs to include a heterogeneous population with respect to demographics, high- and moderately-high risk for CVD, concomitant high and moderate-high intensity statin therapy, diabetes, established cardiovascular disease, and CHF or ischemic cardiomyopathy to ensure sufficient representation from the types of patients expected to use evolocumab if approved. The demographics of the IPAS and IECAS datasets show that the trials do provide a good representation of women, North Americans and participants who are 65 years or older. The majority of participants are white and non-Hispanic; there is an under representation of Hispanic, Asian and black populations. Given that patients at higher CV risk are the most appropriate population for evolocumab, there is a good representation of participants with hypertension but underrepresentation of participants with cardiovascular disease, myocardial infarction, congestive heart failure, stroke, moderately high NCEP CHD risk category and diabetes. Approximately 30% of participants were on high intensity statins and 38% were on moderate intensity statin therapy. While this is adequate, this reviewer believes that a greater proportion of participants on high intensity statin would have been more informative for the purposes of the safety evaluation.

Demographics in HoFH Trials

Study 20110233 Part A
All 8 participants were white and non-Hispanic and most (75%) were men.

Mean (SD) age of participants at baseline was 34.3 (12.4) years, with a range from 14 to 54 years. There was one participant younger than 18 years at baseline (age 14). Four (50%) participants had coronary artery disease, and 1 (13%) had cerebrovascular or peripheral arterial disease. Three participants had homozygous genetic defects and 5 participants had compound heterozygous genetic defects. All participants were using a statin (atorvastatin ≥ 40 mg QD or rosuvastatin≥ 10 mg QD) and ezetimibe at baseline. Two (25.0%) participants were using a bile acid sequestrant and 2 (25.0%) were using nicotinic acid at baseline. All participants were using acetylsalicylic acid at baseline.

Study 20110233 Part B
Baseline demographics were similar between the placebo and evolocumab groups. Approximately one half of the participants (25, 51.0%) were men. Race was white (44, 89.8%), Asian (2, 4.1%), or other (3, 6.1%). Ethnicity was Hispanic for 1 (2.0%) participant. Mean (SD) age of participants at baseline was 30.9 (12.8) years, with a range from 13 years to 57 years. Ten (20.4%) participants were ≥ 13 to < 18 years of age at baseline. Twenty-one (43%) participants had coronary artery disease, and 4 (8%) had cerebrovascular or peripheral arterial disease. Twenty-four (49%) participants had homozygous genetic defects, 24 (49%) participants had compound heterozygous genetic defects and one had heterozygous genetic defects. Baseline therapy included a statin for all participants and the doses were rosuvastatin ≥ 10 mg QD or atorvastatin ≥ 40 mg QD for all except 1 in the evolocumab group. Overall, 45 (91.8%) subjects were receiving ezetimibe and 2 (4.1%) subjects were receiving a bile acid sequestrant. Only 3 (19%) participants in the placebo group and 11 (33%) in the evolocumab group were using acetylsalicylic acid at baseline.

Trial 20110271
There were 96 HoFH participants in this trial, which consisted of 46.9% women and the mean (SD) age at baseline was 33.7 (14.3) years (see table below). Eighty-three (86.5%) participants were ≥ 18 years of age and 13 (13.5%) were less than 18 years of age. Most participants were white (81%), followed by Asian (14%), Japanese (7%), other (4%), and American Indian or Alaskan native (1%). Ethnicity was Hispanic or Latino in 2% of participants. Not unexpectedly, more apheresis participants than non-apheresis participants with HoFH had a history of coronary artery disease (51.6% vs 43.1%), cerebrovascular or peripheral arterial disease (32.3% vs 7.7%). One (33.3%) adolescent participant (with apheresis at enrollment) had a history of coronary artery disease and no adolescent participant had a history of cerebrovascular or peripheral arterial disease. Mean (SD) serum concentration of UC LDL-C at baseline in subjects with HoFH was 339 (139) mg/dL in non-apheresis participants and 283 (103) mg/dL in apheresis participants.

Table 61: Baseline Demographics in Trial 20110271 (HoFH Interim Analysis Set, data cutoff 01APR14)

	20110233 HoFH Parent Trial Rollover			**20110271 HoFH Non-Parent / Other Parent Study Rollover**			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B Placebo (N = 16) n (%)	Apheresis at Enrollment (N = 31) n (%)	Non-apheresis at Enrollment (N = 11) n (%)	Total (N = 42) n (%)	Total (N = 96) n (%)
Sex Female	2 (25.0)	15 (50.0)	8 (50.0)	13 (41.9)	7 (63.6)	20 (47.6)	45 (46.9)
Age (yrs) Mean	34.3	31.4	32.1	34.5	40.0	35.9	33.7
Age ≥ 18 years	7 (87.5)	24 (80.0)	13 (81.3)	28 (90.3)	11 (100.0)	39 (92.9)	83 (86.5)
Age < 18 years	1 (12.5)	6 (20.0)	3 (18.8)	3 (9.7)	0	3 (7.1)	13 (13.5)
White	8 (100.0)	27 (90.0)	15 (93.8)	21 (67.7)	7 (63.6)	28 (66.7)	78 (81.3)
Asian	0	1 (3.3)	1 (6.3)	7 (22.6)	4 (36.4)	11 (26.2)	13 (13.5)
Black	0	0	0	0	0	0	0
Coronary artery disease	4 (50.0)	15 (50.0)	6 (37.5)	16 (51.6)	3 (27.3)	19 (45.2)	44 (45.8)
Angina	3 (37.5)	10 (33.3)	5 (31.3)	11 (35.5)	2 (18.2)	13 (31.0)	31 (32.3)
Myocardial infarction	0	3 (10.0)	3 (18.8)	3 (9.7)	2 (18.2)	5 (11.9)	11 (11.5)
Coronary artery bypass graft	2 (25.0)	8 (26.7)	4 (25.0)	11 (35.5)	1 (9.1)	12 (28.6)	26 (27.1)
Percutaneous coronary intervention	3 (37.5)	7 (23.3)	2 (12.5)	7 (22.6)	1 (9.1)	8 (19.0)	20 (20.8)
Cerebrovascular or peripheral arterial disease	1 (12.5)	4 (13.3)	0	10 (32.3)	0	10 (23.8)	15 (15.6)
Transient ischemic attack	0	3 (10.0)	0	1 (3.2)	0	1 (2.4)	4 (4.2)
Stroke	0	0	0	0	0	0	0
Carotid or vertebral artery disease	1 (12.5)	1 (3.3)	0	10 (32.3)	0	10 (23.8)	12 (12.5)
Peripheral arterial disease	1 (12.5)	1 (3.3)	0	2 (6.5)	0	2 (4.8)	4 (4.2)
Current cigarette use	0	5 (16.7)	1 (6.3)	1 (3.2)	0	1 (2.4)	7 (7.3)
Type 2 diabetes mellitus	0	1 (3.3)	1 (6.3)	0	1 (9.1)	1 (2.4)	3 (3.1)

	20110233 HoFH Parent Trial Rollover			20110271 HoFH Non-Parent / Other Parent Study Rollover			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B Placebo (N = 16) n (%)	Apheresis at Enrollment (N = 31) n (%)	Non-apheresis at Enrollment (N = 11) n (%)	Total (N = 42) n (%)	Total (N = 96) n (%)
Hypertension	1 (12.5)	3 (10.0)	1 (6.3)	5 (16.1)	4 (36.4)	9 (21.4)	14 (14.6)

N = number of HoFH subjects enrolled and dosed in Study 20110271; HoFH=Homozygous Familial Hypercholesterolemia; EvoMab = Evolocumab;
Baseline demographics for parent study rollover subjects are defined at the parent study baseline
Data cutoff date 01APR2014.
Source: Modified from Table 14-2.2.2 of Study 20110271 and Table 14-2.5.3 of Study 20110271; adam.adsl; Applicant Table 19 (2.7.4)

7.2.2 Explorations for Dose Response

The evolocumab dosing regimens of a fixed 140 mg dose administered SC Q2W or a fixed 420 mg dose administered SC QM proposed were selected for evaluation in phase 3 trials based on phase 1 and 2 studies of evolocumab in healthy subjects and patients with primary hyperlipidemia and mixed dyslipidemia. Pharmacokinetic sampling evaluated a range of fixed SC doses from 7 to 420 mg and dosing regimens (QW, Q2W, or QM administration). Data from the phase 1 and 2 studies (20101154, 20101155, 20090158, 20090159, and 20110231) explored a total of 6 fixed SC doses (70 to 420 mg) and 2 dosing intervals (Q2W and QM) in patients with primary hyperlipidemia and mixed dyslipidemia.

In the phase 2 studies, there was no notable increased incidence of adverse events with any dose or dosing frequency of evolocumab. Doses up to 420 mg Q2W have been tested in clinical studies in subjects with HoFH with a mean Cmax of 105 µg/mL (Study 20110271). No clinical data are available for doses exceeding 420 mg Q2W.

In the integrated parent studies, the incidence of adverse events in the evolocumab 140 mg Q2W (43.6%) and the placebo Q2W groups (41.0%) was similar as was the incidence of adverse events for evolocumab 420 mg QM group (54.0%) and placebo QM groups (54.6%). In the ezetimibe comparator group, the incidence of adverse events was 278 (50.2%). The QM dosing, regardless if the IP is placebo or EvoMab, has a higher AE incidence than the Q2W dosing because the QM dosing regimen includes the data from the 52-week trial which only used the QM dosing frequency. The incidence of serious AEs, AEs that led to discontinuation and fatal AEs was similar between the evolocumab Q2W and QM dose as well as in the 2 dosing regimens for placebo. The table below shows the AE incidences with the 52-week trial excluded.

Table 62: Incidence of Adverse Events During the Integrated Parent Studies (IPAS) with the 52-week Trial 20110109 Excluded

	Control			EvoMab		
	Placebo SC Q2W (N = 586)	Placebo SC QM (N = 638)	Eze. QD (N = 554)	140 mg Q2W (N=1245)	420 mg QM (N=1357)	420 mg QM + Eze. QD (N = 30)
All adverse events (AE)	240 (41.0)	289 (45.3)	278 (50.2)	543 (43.6)	608 (44.8)	20 (66.7)
Serious AE	12 (2.0)	11 (1.7)	7 (1.3)	36 (2.9)	26 (1.9)	0
Lead to discontinuation of IP	10 (1.7)	11 (1.7)	24 (4.3)	29 (2.3)	28 (2.1)	1 (3.3)

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348,20120356. The 52-week trial, 20110109, is excluded
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Eze=ezetimibe; IP=investigational product; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; IPAS = Integrated Parent Analysis Set. Coded using MedDRA version 17.0.
Source Data: adam.adsl; ISS Tables 14-6.4.3, 14-6.2.3, 14-6.5.3

The incidences of adverse events when data from trial 20110109 were excluded are provided in greater detail in Appendix 9.4. There was a numerical increase in adverse events in the QM dose group in injection site reactions (pain, bruising), pain in extremity, peripheral edema, and CPK increase as compared to Q2W dosing which was seen for study drug and placebo groups. There was a numerical increase in adverse events in the QM dose group for nasopharyngitis, headache and fatigue as compared to Q2W dosing which was seen for the study drug group but not for the placebo group. However, the incidence of nasopharyngitis, headache and fatigue was lower in the evolocumab 420 mg QM group than in the ezetimibe comparator group. The incidence of serious adverse events when data from trial 20110109 was excluded is described in Section 9.6 Serious Adverse Events in the Integrated Parent Analysis Set Excluding Trial 20110109. The incidence of adverse events leading to discontinuation of IP when trial 20110109 was excluded is in Section 9.7 Adverse Events that Led to Discontinuation in the Integrated Parent Analysis Set Excluding Trial 20110109.

Excluding trial 20110109 allows for a similar trial duration to be compared across different dosing regimens. However, when one excludes the long-term data component, you are also reducing the number of injection episodes that you are recording. For example, with the QM dosing regimen in a 12-week trial, there are only 3 dosing episodes during the trial which limits the value of the safety data for a product that will be administered chronically. In conclusion, there does not appear to be a notable safety difference between the Q2W and QM dosing regimen in the short-term trials.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The central laboratory assessments as well as data collection times are summarized for Trial 20110114 below. The schedule of assessments was similar for trials 20110115, 20110116 and 20110117.

Table 63: Schedule of Assessments - Trial 20110114 (All Subjects)

Study Day / Time Point[a]	Screening	D1 Visit	Week 2 Visit	Week 4	Week 6	Week 8 Visit	Week 10 Visit	Week 12 Visit (QM EOS)	Week 14[b] (Q2W EOS)
General Procedures									
Informed consent	X								
Medical history	X								
Vital Signs (sitting BP, HR)	X	X	X			X	X	X	
Review for AEs/SAEs/CV events	X[c]	X	X			X	X	X	X
Concomitant therapy	X	X	X			X	X	X	
Dietary instruction	X	X	X			X	X		
Physical exam	X							X	
Body weight, waist circumference		X						X	
Body height	X								
12 lead ECG	X	X					X	X	
Randomization		X[d]							
Central Laboratory									
Fasting lipids	X	X	X			X	X	X	
ApoA1, ApoB, Lp(a)		X					X	X	
PK (evolocumab)[e], PCSK9		X	X				X	X	
Chemistry	X[f]	X				X		X	
Hematology	X	X				X		X	
hsCRP		X						X	
HbA1c	X							X	
TSH	X								
Biomarkers (blood)[g]		X					X	X	
Anti-evolocumab antibodies		X						X	
HCV antibodies	X[h]								
HCV viral load		X[h]	X[h]			X[h]		X[h]	
Serum pregnancy; FSH[i]	X							X	
Urine pregnancy		X	X			X			
Urinalysis		X						X	
Investigational Product									
Placebo	X								
PO IP dispensation		X	X			X			
PO IP tablet count			X			X		X[j]	
Autoinjector/pen instruction	X	X	X						
Q2W SC IP on-site		X	X			X	X		
Q2W SC IP home-use setting				X	X				
QM SC IP on-site		X				X			
QM SC IP home-use setting				X					
SC IP dispense			X						
SC IP reconcile						X			

AEs = adverse events; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; BP = blood pressure; CV = cardiovascular; D1 = study day 1; ECG = electrocardiogram; EOS = end of study; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; HCV = hepatitis C virus; HR = heart rate; hsCRP = high-sensitivity C-reactive protein; IP = investigational product; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; PO = oral (per os); Q2W = once every 2 weeks; QM = once monthly; SAEs = serious adverse events; SC = subcutaneous(ly); TSH = thyroid stimulating hormone; W = study week.

[a] D1 = day of first administration of IP; a visit window of ± 3 days applied to all other visits.

[b] Subjects on Q2W SC IP schedule; subject was contacted by the site at week 14 (eg, by phone call).

[c] Only AEs poss bly related to study procedures and SAEs were collected during the screening period.

[d] Randomization occurred within 5 - 10 days of the screening LDL-C sample that determined eligibility.

[e] PK samples were taken prior to IP administration, if applicable.

[f] Includes fasting glucose.

[g] If the subject consented to pharmacogenetics analyses, DNA was extracted from some of the blood samples, eg, biomarker samples.

[h] HCV antibodies only in high risk subjects or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV.
[i] Pregnancy testing in females of childbearing potential, FSH only if applicable per exclusion criterion.
[j] All subjects took oral IP (ezetimibe or placebo) daily until the week 12 visit.

Immunogenicity
Validated assays for detecting anti-evolocumab antibodies were used in the clinical trials. Serum samples were collected and tested for anti-evolocumab antibodies per study protocols (tested at day 1 and at week 12 in subjects receiving EvoMab). Samples were tested for anti-evolocumab binding antibodies using an electrochemiluminescent bridging immunoassay. If positive, samples were then tested for neutralizing antibodies using a receptor binding assay based on the binding of proprotein convertase subtilisin/kexin type 9 (PCSK9) to low-density lipoprotein receptor (LDLR).

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology, Section 4.4

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable; evolocumab is first-in-class.

7.3 Major Safety Results

The table below presents a summary of the adverse event findings in the four 12-week and one 52-week Phase 3 trials. Of note, the statin-intolerant trial had the highest percentage of AEs and AEs that led to discontinuation of investigational product—regardless of treatment group.

Table 64: Summary of Subject Incidence of Adverse Events in the Phase 3 Trials

	20110114 (Monotherapy)			**20110115 (Statin Combination)**			**20110116 (Statin-Intolerant)**		**20110117 (HeFH)**		**20110109**	
	12 week (N = 614)			12 week (N = 1896)			12 week (N=307)		12 week (N=329)		52 week (N=601)	
	Pbo	Eze.	EvoMab	Pbo	Eze	EvoMab	Eze	EvoMab	Pbo	EvoMab	Pbo	EvoMab
	N=154	N=154	N=306	N=558	N=221	N=1117	N=102	N=205	N=109	N=220	N=302	N=599
AEs*, %	44	46	44	39	40	36	73	66	49	56	74	75
SAEs, %	<1	<1	1	2	<1	2	4	3	5	3	4	6
AEs that led to D/C of IP, %	4	3	2	2	2	2	13	8	0	0	1	2
Fatal AEs, %	0	0	0	<1	0	0	0	0	0	0	0	<1

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab; Eze=ezetimibe; IP=investigational product
*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Source: modified from CSR 20110114: Table 12-1; CSR 20110115: Tables 14-6.1.1., 14-6.1.3., 14-6.1.2.; CSR 20110116: Table 12-1.; CSR 20110117: Table 12-1.

The table below presents a summary of the adverse event findings in the 12 (phase 2 + phase 3) trials that make up the integrated parent analysis set by detailed treatment groups.

Table 65: Summary of Subject Incidence of Adverse Events During the Parent Studies by Treatment Groups (Integrated Parent Analysis Set)

	Control			**EvoMab**			
	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1956) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Adverse Events*	240 (41.0)	513 (54.6)	278 (50.2)	397 (55.5)	543 (43.6)	1056 (54.0)	20 (66.7)
Grade ≥ 2	104 (17.7)	263 (28.0)	120 (21.7)	158 (22.1)	224 (18.0)	489 (25.0)	7 (23.3)
Grade ≥ 3	18 (3.1)	36 (3.8)	12 (2.2)	20 (2.8)	46 (3.7)	79 (4.0)	2 (6.7)
Grade ≥ 4	2 (0.3)	4 (0.4)	0	4 (0.6)	10 (0.8)	10 (0.5)	0

	Control			EvoMab			
	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1956) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
SAEs	12 (2.0)	24 (2.6)	7 (1.3)	15 (2.1)	36 (2.9)	59 (3.0)	0
AEs that led to D/C of IP	10 (1.7)	14 (1.5)	24 (4.3)	3 (0.4)	29 (2.3)	42 (2.1)	1 (3.3)
Serious	1 (0.2)	3 (0.3)	0	0	9 (0.7)	7 (0.4)	0
Non-serious	9 (1.5)	12 (1.3)	24 (4.3)	3 (0.4)	24 (1.9)	35 (1.8)	1 (3.3)
Fatal AEs	1 (0.2)	0	0	0	1 (0.1)	2 (0.1)	0

*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab (AMG 145); QD = once a day; Q2W = every 2 weeks; QM =monthly; SC = subcutaneous.
Coded using MedDRA version 17.0.
Source: modified from ISS Table 14-6.1.1.

The table below presents a summary of the adverse event findings in the 12 (phase 2 + phase 3) trials that make up the integrated parent analysis set by combined treatment groups.

Table 66: Summary of Subject Incidence of Adverse Events During the Parent Studies by Combined Treatment Groups (Integrated Parent Analysis Set)

	Any Placebo (N = 1526) n (%)	**Any Control (N = 2080) n (%)**	**EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)**	**Any EvoMab (N = 3946) n (%)**
Adverse Events*	753 (49.3)	1031 (49.6)	1599 (50.0)	2016 (51.1)
Grade ≥ 2	367 (24.0)	487 (23.4)	713 (22.3)	878 (22.3)
Grade ≥ 3	54 (3.5)	66 (3.2)	125 (3.9)	147 (3.7)
Grade ≥ 4	6 (0.4)	6 (0.3)	20 (0.6)	24 (0.6)

	Any Placebo (N = 1526) n (%)	**Any Control (N = 2080) n (%)**	**EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)**	**Any EvoMab (N = 3946) n (%)**
SAEs	36 (2.4)	43 (2.1)	95 (3.0)	110 (2.8)
AEs that led to D/C of IP	24 (1.6)	48 (2.3)	71 (2.2)	75 (1.9)
Serious	4 (0.3)	4 (0.2)	16 (0.5)	16 (0.4)
Non-serious	21 (1.4)	45 (2.2)	59 (1.8)	63 (1.6)
Fatal AEs	1 (0.1)	1 (<0.1)	3 (0.1)	3 (0.1)

*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117,
20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab (AMG 145).
IP=investigational product
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects.
Any EvoMab includes any subject with EvoMab as a component of investigational product.
Coded using MedDRA version 17.0.
Source: modified from ISS Table 14-6.1.2.

7.3.1 Deaths

There were 15 deaths reported during the clinical program. Six deaths occurred during the parent trials [4 deaths during the trial and 2 deaths after the end of the parent trial (one death 43 days after last placebo SC injection and one death 50 days after last EvoMab injection)], 7 deaths occurred during the year 1 SoC-controlled period, and 2 deaths occurred during the year 2+ OLE period.

In the integrated parent trials, 3/3231 (0.09%) deaths were reported in the evolocumab group (1 death in the 140 mg Q2W group, 2 deaths in the evolocumab 420 mg QM group), and 1/1526 (0.07%) death was reported in the placebo Q2W group.

In the year 1 SoC-controlled period, 2 (0.11%) deaths were reported in participants who received evolocumab in the parent trial and evolocumab plus SoC in year 1; 3 (0.32%) deaths were reported in those who received evolocumab in the parent trial and SoC alone in year 1; 1 (0.11%) death was reported in a participant who received placebo in the parent trial and evolocumab plus SoC in year 1; and 1 (0.21%) death was reported in a participant who received placebo in the parent trial and in year 1. Thus, 1 death occurred in the group that never received EvoMab (1/472, 0.21%) and 6 deaths occurred in those that had received EvoMab in either the parent trial or the extension trial (6/3780, 0.16%).

In the year 2+ OLE period, 2 (0.31%) deaths were reported in subjects who received evolocumab plus SoC in year 1 and year 2+. Two deaths occurred after the end of study. No deaths were reported in Phase 1 or the HoFH trials.

Table 67: Summary of Deaths

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
Deaths in Subjects Who Ever Received Evolocumab							
10923201053	60 /W/ male	Parent (20110109) EvoMab 420 mg QM	131	131	47	Cardiac failure	atorvastatin,dexamethasone, verapamil, zolpidem, oxycodone, betamethasone, levocetirizine, aminophylline, betahistine, combination of fenoterol and ipratropium, paracetamol and tramadol. dyslipidemia, hypertension, current cigarette use, asthma, chronic bronchitis, peripheral edema, vertigo, varicose ulceration in lower extremities. The subject received the first dose of atorvastatin in April 2012 and of evolocumab in (b) (6). In June 2012, the subject developed sideropenic anemia. On the same day, ultrasound investigation revealed diffuse hepatopathy. Approximately one month later, in July 2012, the subject developed edema of left lower extremity. The subject's last dose of evolocumab prior to the event was in August 2012.Approximately 4 months and 1 week after receiving first dose of evolocumab, in (b) (6), the subject died due to cardiac failure. An autopsy was performed. The cause of death according to the autopsy was heart failure caused by chronic heart insufficiency. Underlying diseases included grade 3 central atherosclerosis, advanced coronary atherosclerosis with multiple stenosis (> 75%) and exacerbation of chronic atrophic bronchitis (acute purulent bronchitis). Complications reported included disperse myofibrosis corresponding to clinical diagnosis of chronic ischemic heart disease, vascular nephrosclerosis, chronic heart insufficiency (cyanotic induration of organs) and evidence of acute circulatory failure (pulmonary edema, brain edema and acute venostasis in organs). Reviewer note: class II-IV CHF was an exclusion criterion, and this patient does not appear to have been on any medications for CHF at baseline. Question if whether this patient's asthma/COPD may have been partly cardiogenic in nature. Not aware of any mechanism where EvoMab could precipate acute/chronic cardiac decompensation.
10923201092	67 /W/ male	Parent (20110109) EvoMab 420 mg	13	13	13	Myocardial infarction	atorvastatin, tamsulosin hydrochloride hypercholesterolemia, obesity (weight of 101.5 kg and height of 176 cm), family history of premature coronary heart disease. The subject received the first dose of atorvastatin in (b) (6) and aprroximately one month later received the first dose of evolocumab on (b) (6). Twelve days later after the evolocumab dose in (b) (6), the subject died. Resuscitation was

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
		QM					performed. An autopsy was performed. Autopsy: cause of death as myocardial infarction complicated with cardiac tamponade. Direct cause of death as heart tamponade, with complications of generalized atherosclerosis of Grade 1-3, predominantly on coronary arteries, and acute myocardial infarction of left ventricular posterior wall, and thrombosis of the right coronary artery.
15566056006	66 /B/ male	Parent (20101155) EvoMab 140 mg Q2W	71	71	2	Cardiac failure congestive	simvastatin, acetylsalicylic acid, isosorbide, metoprolol, glyceryl trinitrate, clopidogrel, losartan, procaterol, amiodarone, benazepril, carvedilol, furosemide, fluticasone / salmeterol, bupropion, ipratropium / albuterol/ albutamol dyslipidemia, asthma, COPD, depression, hypertension, angina, MI, percutaneous coronary intervention, peripheral arterial disease,TIA, CHF NY Heart Association (NYHA) Class II, current cigarette user, family history of premature coronary heart disease. Approximately two months after initiation of first dose, the subject had no complaints. The subject did not have any sign or symptoms of pneumonia. The subject left his sister's house and did not return home. His brother informed the site that the subject crashed into bushes, hit a tree and was found dead the next morning. The subject was taken to the hospital and an autopsy was performed. Autopsy: cause of death as CHF due to ischemic heart disease and broncho-pneumonia; COPD was contributing factor. Pathological findings: severe coronary artery atherosclerosis, nutmeg congestion of the liver, minimal pitting edema of the ankles, prostate hypertrophy and pulmonary edema with patchy consolidation. Reviewer note: At baseline, the subject had eGFR 30.2 mL/min/1.73m2. Other baseline lab values were normal except for Cr 2.3 mg/dL and BUN 30 mg/dL. Creatinine ranged 2.3 to 2.6 mg/dL during the study. The subject had no history of diabetes. Potassium levels were normal during the study (4.1 at baseline and 3.9-4.0 through week 8). Urinalysis results were unremarkable. Other than lipid parameters, most safety labs were last drawn at week 8 (November 2011). With the exception of stable moderately severe renal dysfunction, other labs of interest include LDLC values of 64, 18, and 23 mg/dL at weeks 8, 9, and 10, respectively. While the cause of death is adjudicated as cardiac failure congestive, this case is suggestive of sudden cardiac death given the lack of clinical symptoms on the morning of his death and the extent of his CV disease.

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
11521012010	69/W female	Parent (20110115) EvoMab 420 mg QM Extension (20120138) EvoMab + SoC	129	129	≤49	Sudden death	rosuvastatin, pantoprazole, amlodipine, citalopram, hydrochlorothiazide, valsartan, captopril, and dihydrocodeine hyperlipidemia, metabolic syndrome, elevated C reactive protein (5.26mg/L), hypertension, depression. The subject received evolocumab in the parent study (Study 20110115) from (b) (6) to (b) (6) and received the first dose of evolocumab in Study 20120138 in (b) (6).Approximately 6 weeks later, in (b) (6), the subject died suddenly. Diagnostic tests were not performed at the time of the event. Information regarding the clinical sequence of events leading to death was unknown. Investigational product had not been discontinued at the time of the subject's death. The visiting physician considered acute myocardial infarction as the possible cause of death. However, the final cause of death was not determined. An autopsy was not performed.
15566012006	45 /W/ male	Parent (20101155) EvoMab 70 mg Q2W Extension (20110110) EvoMab+ SoC	259	259	18	Myocardial infarction	rosuvastatin, acetylsalicylic acid, glyceryl trinitrate, diltiazem, prasugrel hydrochloride hyperlipidemia, increased lipoprotein A, CAD, hypertension, angioplasty, stent placement, coronary arteriospasm, coronary artery restenosis, unstable angina, coronary artery bypass, vascular graft, family history of coronary artery disease, former tobacco user Treatments: Parent Study: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + SoC Report: Myocardial infarction (2 events), Unstable angina The subject participated in the parent study, Study 20101155, from November 2011 to (b) (6) and received the last dose on February 2012. The subject received the first dose of evolocumab in Study 20110110 on (b) (6). On the day of completion of parent study, (b) (6), the subject presented to the emergency room (ER) with intermittent left sided chest pain radiating to the left jaw and associated with mild shortness of breath which was not relieved by nitro. He was diagnosed with unstable angina and non-Q-wave myocardial infarction. Balloon angioplasty and deployment of stent in Feb 2012. Approximately 3 months after the first dose of evolocumab in Study 20110110, on (b) (6), the subject presented to the emergency room with unstable angina, recurrent chest pain, and chest discomfort and was hospitalized. A catheterization was performed

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
							and demonstrated total occlusion of right coronary vein graft stent and indicated that no interventional procedure could be performed. The detailed report of coronary anatomy showed unchanged left main which was diffusely diseased; the circumflex was diffusely diseased with 89% proximal lesions and calcified; no retrograde filling at obtuse marginals; the large atrial branch with collateral to right coronary, unchanged; the rest of the obtuse marginals was totally occluded. The LAD was 100% occluded in its proximal portion, and the right was 100% occluded in its mid portion. As the subject was not a candidate for any type of revascularization, he was started on maximal medical therapy that included glyceryl trinitrate. Discharge medications included diltiazem, acetylsalicylic acid, prasugrel, rosuvastatin, and nitroglycerin. The investigator reported "the subject stated that he had trouble buying medication in terms of the cost, therefore, the expensive medication was held until the follow up visit". On July 2012, the subject was started on enhanced external counterpulsation therapy (EECP). The subject had resumed smoking after the stent placement in February 2012. Approximately 5 months after the first dose of evolocumab in Study 20110110, on (b) (6), the subject was found dead. The cause of death was reported as myocardial infarction. No relevant laboratory or diagnostic results were reported. The subject's last dose of evolocumab prior to death was on July 2012.
11416001003	48 /W/ female	Parent (20110114) placebo SC Q2W + ezetimibe 10 mg PO QD Extension (20120138) EvoMab+ SoC	299	299	196	Myocardial infarction	hydrochlorothiazide, losartan, salbutamol, venlafaxine hydrochloride, aripiprazole (ezetimibe in parent study) dyslipidemia, hypertension, depression, smoking The subject received placebo and ezetimibe in the parent study from March 2013 to May 2013. She received the first (and only) dose of evolocumab in Study 20120138 in (b) (6). Approximately 6 months later, in (b) (6), the subject experienced a myocardial infarction with the outcome reported as fatal. The subject's last dose of evolocumab prior to the event (and only dose) was in (b) (6).The investigator reported that there was not a reasonable possibility that the fatal event of myocardial infarction may have been caused by investigational drug or device. According to the investigator, the etiological or predisposing factors associated with the event of myocardial infarction were cigarette smoking and hypertension.
11566045004	73 /W/ male	Parent (20110115)	141	141	85	Clostridium difficile	atorvastatin, diclofenac, metoprolol, isosorbide, nifedipine, acetylsalicylic acid hypertension, atherosclerosis, angina pectoris, myocardial infarction, coronary

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
		EvoMab 420 mg QM + Placebo PO QD Extension (20120138) SoC alone				infection	artery disease, osteoarthritis, obesity The subject received evolocumab and placebo in the parent study (Study 20110115) from April 2013 to July 2013. The subject was randomized to the standard of care arm in Study 20120138 in July 2013. The subject developed Clostridium difficile infection in (b) (6) and was hospitalized on for further evaluation and treatment. According to a family member the subject had a viral eye infection, was placed on antibiotics, and developed Clostridium difficile colitis. He had been hospitalized previously in (b) (6) and readmitted at the beginning of (b) (6). The subject developed ascites and the abdominal fluid was removed once. He was evaluated for cancerous cells and lymph nodes were to be evaluated. The subject died in (b) (6) and the cause of death was reported as Clostridium difficile colitis.
15566037007	40 /B/ female	Parent (20101155) EvoMab 140 mg Q2W Extension (20110110) SoC alone	397	397	327	Pulmonary embolism	simvastatin, escitalopram, lisinopril hypertension, hyperlipidemia, obesity, pulmonary hypertension, anemia, dyspnea, depression, suicide attempt. Parent Study: Evolocumab SC Q2W 140 mg: (b) (6) (last dose EvoMab end of Jan 2012) Year 1 treatment: SoC: (b) (6) - Approximately 10 months after the randomization into Study 20110110, on (b) (6), the subject sent a text message to her friend indicating that she might harm herself; she was advised to contact suicide hotline. Later, on the same day, the subject felt dizzy and she called for the ambulance. The subject had difficulty in breathing and an elevated heart rate. The subject stated that she had a history of hypertension and psychiatric illness, and was not taking her medications. Subsequently, while being transferred from the ambulance stretcher to the emergency room bed, the subject became unresponsive. Resuscitation efforts were made; however, they were unsuccessful and the subject died. Autopsy: pulmonary thromboemboli obstructing pulmonary trunk and arteries within both lungs. No injury was visible on or within the body. Toxicological analysis was negative for ethanol or drugs of abuse.
10957201014	66 /mixed race/ female	Parent (20110109) EvoMab 420 mg	500	500	165	Lung neoplasm malignant	amlodipine, atenolol, isosorbide mononitrate, isosorbide dinitrate, paracetamol, acetylsalicylic acid, carbamazepine, atorvastatin, ezetimibe, tramadol, losartan. ischemic heart disease, hypertension, COPD, heavy smoking The subject received evolocumab in the parent study from August 2012 to July

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
		QM Extension (20120138) SoC alone					2013. The subject was randomized to the standard of care treatment arm in Study 20120138 in November 2013. Approximately 3 weeks later in December 2013, the subject was found to have pleural effusion and diagnosed with metastatic lung cancer (lymph, lung, cerebral involvement). The subject underwent 2 fine needle aspiration biopsies of the lung that confirmed small cell carcinoma of lung (OAT cell type) and squamous cell carcinoma with necrosis. The subject was discharged to home 9 days after entering the hospital (end of (b) (6)). In (b) (6) the subject died due to metastatic lung cancer. The subject's last dose of evolocumab was in the parent study (July 2013).
15516046016	65 /Asian/ male	Parent (20101155) EvoMab 280 mg QM Extension (20110110) EvoMab+ SoC	722	217	135	Cholangio-carcinoma	simvastatin, dutasteride, omeprazole, tamsulosin chronic hepatitis B carrier, antrectomy/vagotomy for peptic ulcer disease, enlarged prostate, elevated prostate-specific antigen The subject was in the parent study from September 2011 to December 2011 and received the last dose of evolocumab in the parent study on November 2011. The subject received the first dose of evolocumab in Study 20110110 on January 2012. Approximately 1 year and 2 months later, on February 2013, the subject developed right upper quadrant pain. On April 2013, the computerized tomogram (CT) scan showed a large lesion spanning segment 8 and measuring 8.1 cm transverse, 8.5 cm anteroposterior, and 9 cm in the axial plane. Nine days later, the subject was diagnosed with cholangiocarcinoma. In July 2013, the subject was diagnosed to have intrathoracic pulmonary metastatic disease and right paracardiac lymph nose metastases. The investigator reported that the subject died in (b) (6) due to progressive metastatic carcinoma. The last dose of evolocumab prior to the event was in April 2013, and the subject discontinued from the study at that point.
15522001033	68 /W/ female	Parent (20101155) Placebo SC QM Extension (20110110) EvoMab 420 QM+	755	279	34	Peripheral ischemia	Simvastatin, amlodipine, mometasone, cyanocobalamin, furosemide, potassium chloride, thiamazole, etodolac, nebivolol, ibuprofen, and estradiol hyperlipidemia, vitamin B complex deficiency, hypertension, pharyngeal edema, edema, current smoker, family history of premature coronary heart disease The subject received her first dose of evolocumab in Study 20110110 on February 2012. Approximately 2 months after the first dose of evolocumab, in April 2012, the subject experienced pain in right lower leg. On October 2013, a computed tomography (CT) lower extremity angiography revealed occlusion of infra-renal abdominal aorta, common iliac artery and internal and external iliac

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
		SoC					artery bilaterally. Multifocal stenosis of the superficial femoral artery and popliteal artery bilaterally was detected. Multifocal stenosis corresponding to deep femoral artery bilaterally, particularly on left side was noted. On (b) (6), the subject developed limb ischemia, and was hospitalized on the same day. Treatment included furosemide, metoprolol, dalteparin, amiodarone, acetazolamide, hydrocortisone sodium succinate, ondansetron, potassium chloride, heparin, combination of fenoterol and ipratropium, loperamide, cefuroxine, and levofloxacin. The subject underwent elective surgery (aortobifemoral bypass). Reportedly, the subject experienced several complications after surgery. Atrial fibrillation was diagnosed and was medically treated. Renal insufficiency was treated with dialysis and medications. Respiratory failure was treated with mechanical respiratory support. Pleural exudate was treated with drainage. Infection was treated with unspecified antibiotics. Pacemaker was inserted due to bradycardia. On (b) (6), the subject's husband reported that the subject had died. It was reported that the subject died due to complications after surgery. The subject's last dose of the evolocumab prior to death was on 31 October 2013.
Deaths in Subjects Who Received Placebo and/or SoC							
11529002014	48 /W/ male	Parent (20110115) Placebo SC Q2W	32	32	17	Acute Myocardial infarction	rosuvastatin, acetylsalicylic acid, metoprolol, ramipril hyperlipidemia, Angina, atherosclerotic coronary disease, hypertension, left ventricular systolic function, myocardial infarction, percutaneous coronary intervention, smoking, family history of premature coronary heart disease. Autopsy: acute myocardial infarction of the anterior wall
15416017006	53 /W/ male	Parent (20101154) Placebo SC Q2W Extension (20110110) SoC alone	335	221	Pbo= 265	Death	paracetamol with codeine, perindopril with indapamide, fluticasone, salbutamol, bupivacaine, docusate, quetiapine, amlodipine hypertension, depression, panic disorder, hepatitis A, back surgery, drug hypersensitivity (to sulfa and morphine drugs). Approximately 7 months after the subject was randomized, on (b) (6), the subject was found dead at home. The investigator reported that an autopsy was performed and the cause of death was reported as unascertained. No further details were provided.
Deaths That Occurred After the End of Study							

Subject ID	Age (yrs) at Start/ Race/ Sex	Trial & Treatment	Parent Study Day	Days Since First Dose	Days Since Last Dose	Cause of Death (Preferred Term)	Relevant Other Medications Relevant Other Conditions/History
11521005031	65/W/ female	Parent (20110115) Placebo SC QM + Ezetimibe 10 mg PO QD	99	-	Eze =11, PBO = 43	Cerebro-vascular Accident; pulmonary embolism	Ezetimibe, fenoterol/ ipratropium, acetylsalicylic acid, gliclazide, escin, aminophyline, beclometasone, levothyroxine, perindopril arginine, metoprolol (atorvastatin during lipid stabilization phase) hyperlipidemia, coronary artery disease status post myocardial infarction, type 2 diabetes mellitus, cigarette use, chronic bronchitis, severe COPD, severe obstructive ventilation disorder, nodular struma with normal thyroid function, asymptomatic atrio ventricular node reentry tachycardia. Autopsy: pulmonary emphysema, chronic pulmonary heart, and hemorrhage to brain and subarachnoid as causes of death; no emboli were found as thrombolytic therapy had been administered.
10957204007	51 /mixed race/ female	Parent (20110109) EvoMab 420 mg QM	389	-	50	Sudden cardiac death	atorvastatin, ezetimibe, amlodipine, furosemide, acetylsalicylic acid, isosorbide mononitrate, fluoxetine, salbutamol, budesonide, theophylline, paracetamol, metformin, amitryptyline hyperlipidemia, peripheral vascular disorder, asthma, type 2 diabetes mellitus, depression, myocardial ischemia, angina pectoris, coronary angioplasty At the end of the study, the subject reported that she was still having angina pectoris, relatively frequently with effort, and using sublinguial nitrates regularly. Approximately 3 weeks after the last dose of the evolocumab, the subject suddenly collapsed and was found unarousable. The subject was taken to the hospital and was pronounced dead on arrival. No resuscitation was attempted; nor interventions were carried out neither treatment medications were administered. No relevant laboratory or diagnostic test results were reported. The investigator reported that the subject had been having increasing frequency of angina pectoris with effort, no rest pain, and that the family of the subject informed them of the subject's death. The family reported she had been having angina pectoris in her usual patterns in the days prior to death. The investigator reported the features of the event were strongly suggestive of sudden cardiac death due to suspected myocardial infarction.

EvoMab = Evolocumab; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous
Parent Study Day is from the start of the parent study. Period Study Day is from the start of the period with the event. Subjects with events not occurring during a study period had the event occur after the end of the study in the parent study.
Coded using MedDRA version 17.0.
Source: Modified from ISS Listing 16-2.7.1 and narratives in the individual CSRs and ISS Appendix 2; Table 38 (2.7.4)

All deaths were reviewed and adjudicated by the CEC as cardiovascular or non-cardiovascular deaths. A total of 11 deaths were deemed to be cardiovascular: 1 (0.2%) death in the placebo Q2W group, 1 (0.2%) death in the ezetimibe group, 1 death in the evolocumab 140 mg Q2W group, and 3 (0.2%) deaths in the evolocumab 420 mg QM group of the integrated parent studies; 3 (0.1%) death in the evolocumab plus SoC group and 1 (0.1%) deaths in the SoC alone group of the year 1+ SoC-controlled period; and 1 (0.1%) death in the year 2+ OLE period.

Table 68: Incidence of Positively Adjudicated Cardiovascular Deaths and Non-cardiovascular Deaths

	Integrated Parent Studies[a] (placebo and active-controlled)		**Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)**		**Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)**
	Any Control (N = 2080) n (%)	**Any EvoMab (N = 3946) n (%)**	**SoC (N = 1419) n (%)**	**EvoMab + SoC (N = 2833) n (%)**	**EvoMab + SoC (N = 954) n (%)**
Death	2 (0.1)	4 (0.1)	4 (0.3)	3 (0.1)	2 (0.2)
Cardiovascular	2 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Non-cardiovascular	0	0	2 (0.1)	0	1 (0.1)
Undetermined	0	0	1 (0.1)	0	0

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; OLE = open-label extension; SoC = standard of care
a Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348,
20120356. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product..
b Includes the following studies: 20110110, 20120138
c Includes the following studies: 20110110, 20120138
Some cases from the phase 2 and phase 3 lipid lowering clinical studies had lipid values present in the adjudication package
Source: Modified from ISS Table 14-8.1.2, ISS Table 14-8.1.3, ISS Table 14-8.1.4, ISS Table 14-8.1.402, ISS Table 14-8.1.403, and ISS Table 14-8.1.404, and Table 43 (2.7.4)

Of the 15 deaths to date, the majority are cardiovascular in nature (11, 73%). The small number of deaths makes it difficult to make any conclusion regarding EvoMab and mortality; there does not appear to be any meaningful imbalances in the incidence of death among treatment groups based on this limited sample.

HoFH
No deaths were reported in trials involving participants with HoFH (trials 20110233 or 20110271).

Deaths in the 120-day Safety Update (01 July 2014 data cutoff)

In addition to the 15 deaths as of 1 April 2014, there were 4 additional deaths before the 1 July 2014 data cutoff for the safety update: 2 in the Year 1 dataset and 2 in the Year 2+ dataset— which are summarized in the table below. All together there were 4 (0.1%) deaths reported in the evolocumab plus SoC group and 5 (0.3%) deaths reported in the SoC alone group, of which 2 deaths were newly reported in the 120-day Safety Update: gastric cancer in the evolocumab plus SoC group in a participant who received placebo in the parent study and evolocumab plus SoC in year 1, and pneumonia in the SoC alone group in a participant who received placebo in the parent study and SoC alone in year 1. Of note, the adjudication of 3 of the 4 deaths (gastric cancer, malignant lung neoplasm, and pneumonia) that were newly reported in the 120-day Safety Update were not completed at the time of the data cutoff date of 01 July 2014.

Table 69: Incidence of Positively Adjudicated Cardiovascular Deaths and Non-cardiovascular Deaths (as of 1 July 2014)

	Integrated Parent Studies[a] (placebo and active-controlled)		**Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)**		**Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)**
	Any Control (N = 2080) n (%)	**Any EvoMab (N = 3946) n (%)**	**SoC (N = 1489) n (%)**	**EvoMab + SoC (N = 2976) n (%)**	**EvoMab + SoC (N = 1675) n (%)**
Death	2 (0.1)	4 (0.1)	5 (0.3)	4 (0.1)	4 (0.2)
Cardiovascular	2 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)
Non-cardiovascular	0	0	2 (0.2)	0	1 (0.1)
Undetermined	0	0	1 (0.1)[g]	0	0
Not yet adjudicated			1 (0.1)[f]	1 (0)[e]	1 (0.1)[d]

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; OLE = open-label extension; SoC = standard of care
a Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348,
20120356. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product..
b Includes the following studies: 20110110, 20120138
c Includes the following studies: 20110110, 20120138
Some cases from the phase 2 and phase 3 lipid lowering clinical studies had lipid values present in the adjudication package
d Malignant lung neoplasm
e Gastric cancer in the evolocumab plus SoC group in a participant who received placebo in the parent study and evolocumab plus SoC in year 1
f Pneumonia in the SoC alone group in a participant who received placebo in the parent study and SoC alone in year 1
g Found dead at home. Autopsy: cause of death: unascertained

7.3.2 Nonfatal Serious Adverse Events

In the integrated parent studies, serious adverse events (SAEs) were reported by 95 (3.0%) participants in the EvoMab Q2W/QM group, 36 (2.4%) participants in the Any Placebo group, and 43 (2.1%) participants in the Any Control groups. The incidences in the evolocumab 140 mg Q2W group (36, 2.9%) and 420 mg QM group (59, 3.0%) were numerically greater than the corresponding placebo group [2.0% (12) for placebo Q2W and 2.6% (24) for placebo QM]. The incidence of SAEs in the ezetimibe comparator group was 7 (1.3%). The most common SAEs (any evolocumab and any control groups, respectively) were myocardial infarction (0.1% and 0%), angina pectoris (0.1% in both groups), and pneumonia (0.1% and 0%). Of note, although the numbers are small, there is a numeric increase in the evolocumab group in the incidence of cardiac disorders (particularly angina and myocardial infarction), pancreatitis, appendicitis, pneumonia and back pain—as denoted by gray highlight in table below.

Table 70: Serious Adverse Events During the Integrated Parent Trials by System Organ Class and Preferred Term: Selected to Include Most Frequent PTs in EvoMab Groups

	CONTROL			EVOLOCUMAB			
SYSTEM ORGAN CLASS Preferred Term	Placebo Q2W (N = 586) n (%)	Placebo QM (N = 940) n (%)	Ezetimibe (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1956) n (%)	420 mg QM + Ezetimibe (N = 30) n (%)
No. Subjects Reporting Adverse Events	12 (2.0)	24 (2.6)	7 (1.3)	7 (1.3)	36 (2.9)	59 (3.0)	0
BLOOD AND LYMPHATIC SYSTEM	0	0	0	0	1 (0.1)	0	0
Anaemia	0	0	0	0	1 (0.1)	0	0
CARDIAC DISORDERS	2 (0.3)	3 (0.3)	0	3 (0.4)	10 (0.8)	11 (0.6)	0
Angina Pectoris	0	2 (0.2)	0	0	1 (0.1)	3 (0.2)	0
Angina Unstable	0	0	0	1 (0.1)	0	2 (0.1)	0
Myocardial Infarction	0	0	0	1 (0.1)	2 (0.2)	2 (0.1)	0
Palpitations	0	0	0	0	0	2 (0.1)	0
Ventricular Extrasystoles	0	0	0	0	0	2 (0.1)	0
Acute Myocardial Infarction	1 (0.2)	0	0	0	2 (0.2)	1 (0.1)	0
Atrial Fibrillation	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)	0
Cardiac Failure	0	0	0	0	1 (0.1)	1 (0.1)	0
Coronary Artery Disease	1 (0.2)	0	0	0	1 (0.1)	1 (0.1)	0
Acute Coronary Syndrome	0	0	0	0	1 (0.1)	0	0
Cardiac Failure Congestive	0	0	0	0	1 (0.1)	0	0
Sinus Bradycardia	0	1 (0.1)	0	0	0	0	0
Tachycardia	0	0	0	0	1 (0.1)	0	0
Ventricular Fibrillation	0	0	0	0	1 (0.1)	0	0
EAR AND LABYRINTH	0	0	0	0	0	3 (0.2)	0

Vertigo Positional	0	0	0	0	0	2 (0.1)	0
Exostosis Of External Ear Canal	0	0	0	0	0	1 (0.1)	0
GASTROINTESTINAL DISORDERS	3 (0.5)	1 (0.1)	2 (0.4)	1 (0.1)	2 (0.2)	4 (0.2)	0
Pancreatitis Acute	0	0	0	1 (0.1)	0	2 (0.1)	0
Gastritis	0	0	0	0	0	1 (0.1)	0
Haemorrhoids	0	0	0	0	0	1 (0.1)	0
Abdominal Pain Upper	0	0	0	0	1 (0.1)	0	0
Gastrointestinal Haemorrhage	1 (0.2)	1 (0.1)	0	0	0	0	0
Gastrointestinal Motility Disorder	0	0	1 (0.2)	0	0	0	0
Gastrooesophageal Reflux Disease	0	0	0	0	1 (0.1)	0	0
Hiatus Hernia	1 (0.2)	0	0	0	0	0	0
Inguinal Hernia	1 (0.2)	0	1 (0.2)	0	0	0	0
HEPATOBILIARY DISORDERS	1 (0.2)	1 (0.1)	0	0	1 (0.1)	3(0.2)	0
Biliary Tract Disorder	0	0	0	0	0	1 (0.1)	0
Cholecystitis	0	0	0	0	1 (0.1)	1 (0.1)	0
Cholelithiasis	0	0	0	0	1 (0.1)	1 (0.1)	0
Cholecystitis Acute	1 (0.2)	0	0	0	0	0	0
Drug-Induced Liver Injury	0	1 (0.1)	0	0	0	0	0
INFECTIONS/INFESTATIONS	3 (0.5)	2 (0.2)	1 (0.2)	1 (0.1)	6 (0.5)	5 (0.3)	0
Appendicitis	0	0	0	0	1 (0.1)	2 (0.1)	0
Pneumonia	0	0	0	1 (0.1)	1 (0.1)	2 (0.1)	0
Postoperative Wound Infection	0	0	0	0	0	1 (0.1)	0
Skin Infection	0	0	0	0	0	1 (0.1)	0
Campylobacter Infection	0	0	0	0	1 (0.1)	0	0
Cellulitis	0	0	0	1 (0.1)	1 (0.1)	0	0

Gastroenteritis	1 (0.2)	0	0	0	0	0	0
Herpes Simplex	1 (0.2)	0	0	0	0	0	0
Meningoencephalitis							
Infected Bites	0	0	0	0	1 (0.1)	0	0
Kidney Infection	0	0	1 (0.2)	0	0	0	0
Pneumonia Mycoplasmal	0	1 (0.1)	0	0	0	0	0
Pyelonephritis Acute	0	0	0	0	1 (0.1)	0	0
Urinary Tract Infection	1 (0.2)	0	0	0	0	0	0
Urinary Tract Infection Bacterial	0	1 (0.1)	0	0	0	0	0
INVESTIGATIONS	0	2 (0.2)	1 (0.2)	0	2 (0.2)	3 (0.2)	0
Alanine Aminotransferase Increased	0	0	0	0	0	1 (0.1)	0
Aspartate Aminotransferase Increased	0	0	0	0	0	1 (0.1)	0
Blood Creatine Phosphokinase Increased	0	1 (0.1)	0	0	0	1 (0.1)	0
Colonoscopy Abnormal	0	0	0	0	0	1 (0.1)	0
Endoscopy Gastrointestinal Abnormal	0	0	0	0	0	1 (0.1)	0
Hepatic Enzyme Increased	0	1 (0.1)	0	0	2 (0.2)	0	0
Troponin Increased	0	0	1 (0.2)	0	0	0	0
MUSCULOSKELETAL DISORDERS	0	2 (0.2)	0	1 (0.1)	2 (0.2)	6 (0.3)	0
Back Pain	0	0	0	0	1 (0.1)	2 (0.1)	0
Arthralgia	0	0	0	0	0	1 (0.1)	0
Intervertebral Disc Protrusion	0	0	0	0	0	1 (0.1)	0
Osteoarthritis	0	0	0	0	0	1 (0.1)	0
Spinal Pain	0	0	0	0	0	1 (0.1)	0
Myalgia	0	1 (0.1)	0	0	0	0	0
Rotator Cuff Syndrome	0	0	0	0	1 (0.1)	0	0

Spinal Osteoarthritis	0	1 (0.1)	0	0	0	0	0
Spondylolisthesis	0	0	0	1 (0.1)	0	0	0
NERVOUS SYSTEM DISORDERS	3 (0.5)	2 (0.2)	0	3 (0.4)	4 (0.3)	4 (0.2)	0
Cerebrovascular Accident	1 (0.2)	0	0	0	1 (0.1)	1 (0.1)	0
Epilepsy	0	0	0	0	0	1 (0.1)	0
Migraine With Aura	0	0	0	0	0	1 (0.1)	0
Syncope	1 (0.2)	0	0	1 (0.1)	0	1 (0.1)	0
Coma	0	0	0	0	1 (0.1)	0	0
Convulsion	0	1 (0.1)	0	0	0	0	0
Grand Mal Convulsion	1 (0.2)	0	0	0	0	0	0
Ischaemic Stroke	0	0	0	0	1 (0.1)	0	0
Neurological Symptom	0	0	0	0	1 (0.1)	0	0
Peripheral Sensory Neuropathy	0	1 (0.1)	0	0	0	0	0
Transient Ischemic Attack	0	0	0	2 (0.3)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.2)	3 (0.3)	0	1 (0.1)	3 (0.2)	4 (0.2)	0
Pulmonary Embolism	0	1 (0.1)	0	1 (0.1)	0	2 (0.1)	0
Asthma	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0
Pleurisy	0	0	0	0	0	1 (0.1)	0
Chronic Obstructive Pulmonary Disease	1 (0.2)	1 (0.1)	0	0	0	0	0
Pleural Effusion	0	0	0	0	1 (0.1)	0	0
Pulmonary Oedema	0	0	0	0	1 (0.1)	0	0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab (AMG 145); QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous. Coded using MedDRA version 17.0.

When evaluating only the four 12-week phase 3 trials, no serious adverse event (by preferred term) occurred in more than 3 participants in any treatment group. Serious adverse events that occurred in 2 or more participants in the evolocumab group were acute myocardial infarction (3, 0.2% versus 1, 0.1% in the any control group), angina pectoris (2, 0.1% versus 0), acute pancreatitis (2, 0.1% versus 0), and increased hepatic enzyme (2, 0.1% versus 0). In the any control group, inguinal hernia occurred in 2 (0.2%) participants and 0 participants in the evolocumab group.

In the year 1 SoC-controlled period, 153 (5.4%) in the evolocumab plus SoC group and 82 (5.8%) participants in the SoC alone group reported an SAE. The most common SAEs (evolocumab plus SoC and SoC alone groups, respectively) were osteoarthritis (0.3% and 0.1%), angina pectoris (0.2% and 0.1%), and myocardial infarction (0.2% and 0.2%).

In the year 2+ OLE period, 76 (8.0%) participants reported a serious adverse event. Of note, a comparison of incidences of adverse events in the different treatment periods is problematic due to differences in exposure of IP. The most common SAEs were non-cardiac chest pain (0.4%), pneumonia (0.4%), and angina pectoris (0.3%).

HoFH
No serious adverse events were reported in part A or part B of Study 20110233.

For trial 20110271, seven (7.3%) participants with HoFH reported a serious adverse event (angina pectoris, aortic stenosis, aortic valve disease, chest pain, coronary artery disease, coronary artery occlusion, hematuria[59] and non-cardiac chest pain). Six of the 7 participants were in the 20110233 parent trial. No serious adverse event was reported in > 1 participant.

7.3.3 Dropouts and/or Discontinuations

In the integrated parent studies, the incidence of adverse events leading to permanent study drug discontinuation was slightly higher in the EvoMab group as compared to the placebo group for both dosing frequencies: 29 (2.3%) participants in the EvoMab 140mg Q2W group vs. 10 (1.7%) participants in the placebo Q2W group, and 42 (2.1%) participants in the EvoMab 420mg QM group vs. 14 (1.5%) participants in the placebo QM group. In the ezetimibe comparator group, the incidence of

59 This case involves a 22-year old white male with a remote history of a single episode of hematuria after LDL-apheresis when he was 7 or 8 years old. His pre-study urinalysis was positive for trace protein and negative for blood. He had an on-study episode of gross hematuria while anticoagulated with heparin during LDL-apheresis. The hematuria resolved without treatment; there was no impact on renal function. Anti-evolocumab antibody testing was negative at all times, including a measurement approximately 3 weeks after the event.

adverse events leading to discontinuation was 24 (4.3%). The only adverse events leading to discontinuation of IP (any evolocumab and any control groups, respectively) occurring in ≥ 0.2% participants were myalgia (11, 0.3% and 10, 0.5%), nausea (6, 0.2% and 3, 0.1%), and dizziness (1, 0% and 4, 0.2%).

The following table summarizes discontinuations in the combined groups of any placebo, any control (includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo participants), to-be-marketed doses of evolocumab and any evolocumab (includes all participants who received any EvoMab dose in the analysis set). The discontinuations are small in number and, for the most part, balanced among the groups.

Table 71: Adverse Events Leading to Discontinuation of Investigational Product during the Parent Studies by System Organ Class and Preferred Term (Integrated Parent Analysis Set)

System Organ Class *Preferred Term*	**Control**		**EvoMab**	
	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)	Any EvoMab (N = 3946) n (%)
# of subjects reporting AE that led to d/c of IP	24 (1.6)	48 (2.3)	71 (2.2)	75 (1.9)
Cardiac Disorder	1 (0.1)	1 (<0.1)	4 (0.1)	4 (0.1)
Cardiac Failure	0	0	2 (0.1)	2 (0.1)
Myocardial Infarction (MI)	0	0	2 (0.1)	2 (0.1)
Supraventricular Extrasystoles	0	0	1 (<0.1)	1 (<0.1)
Ventricular Fibrillation	0	0	1 (<0.1)	1 (<0.1)
Acute MI	1 (0.1)	1 (<0.1)	0	0
Ear & Labyrinth Dis.	0	1 (0.0)	2 (0.1)	2 (0.1)
Eye Disorders	0	0	2 (0.1)	2 (0.1)
Eye irritation	0	0	1 (<0.1)	1 (<0.1)
Vision blurred	0	0	1 (<0.1)	1 (<0.1)
Gastrointestinal Dis.	2 (0.1)	7 (0.3)	13 (0.4)	13 (0.3)
Nausea	1 (0.1)	3 (0.1)	6 (0.2)	6 (0.2)
Abdominal Pain	0	2 (0.1)	2 (0.1)	2 (0.1)
Abdominal Pain Upper	0	1 (<0.1)	2 (0.1)	2 (0.1)
General Disorders	1 (0.1)	4 (0.2)	10 (0.3)	10 (0.3)
Fatigue	1 (0.1)	3 (0.1)	3 (0.1)	3 (0.1)
Hepatobiliary Dis.	1 (0.1)	1 (<0.1)	1 (<0.1)	2 (0.1)
Immune System Dis.	0	0	1 (<0.1)	1 (<0.1)
Infections/Infestation	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Investigations	5 (0.3)	5 (0.2)	5 (0.2)	6 (0.2)

CPK increased	1 (0.1)	1 (<0.1)	4 (0.1)	4 (0.1)
Metabolism/Nutrition	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Musculoskeletal and Connective Tissue	7 (0.5)	18 (0.9)	24 (0.7)	26 (0.7)
Myalgia	4 (0.3)	10 (0.5)	11 (0.3)	12 (0.3)
Pain in Extremity	1 (0.1)	1 (<0.1)	4 (0.1)	4 (0.1)
Neoplasms	0	0	5 (0.2)	5 (0.1)
Nervous System Dis	4 (0.3)	9 (0.4)	12 (0.4)	12 (0.3)
Headache	1 (0.1)	3 (0.1)	3 (0.1)	3 (0.1)
Psychiatric Disorder	2 (0.1)	3 (0.1)	4 (0.1)	4 (0.1)
Renal/Urinary Dis.	0	0	3 (0.1)	3 (0.1)
Reproductive System & Breast Dis	0	0	1 (<0.1)	1 (<0.1)
Respiratory Disorder	0	1 (<0.1)	3 (0.1)	3 (0.1)
Skin/Subcutaneous Tissue Disorders	1 (0.1)	8 (0.4)	4 (0.1)	4 (0.1)
Vascular Disorders	0	2 (0.1)	0	0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Eze=ezetimibe; IP=investigational product; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; CPK= creatine phosphokinase; Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product. Coded using MedDRA version 17.0.
Source Data: modified from ISS Table 14-6.5.2

When looking at discontinuations for the four Phase 3 trials, the discontinuations were highest in the Ezetimibe group and were similar in the placebo and EvoMab groups. However, it was the statin-intolerant trial 20110116 that contributed the greatest percentage of adverse events and AEs that led to IP discontinuation, regardless of assignment to ezetimibe or EvoMab (see Table 64: Summary of Subject Incidence of Adverse Events in the Phase 3 Trials). This likely contributed to the imbalance in the ezetimibe group. There were no notable increases in adverse events (either by system organ class or preferred term) in the EvoMab group as compared to the placebo group.

Table 72: Adverse Events Leading to Discontinuation of Investigational Product for the Four Phase 3 Trials: 20110114, 20110115, 20110116 and 20110117

	Control			**EvoMab**	
	Placebo SC Q2W (N =411) n (%)	Placebo SC QM (N = 410) n (%)	Ezetimibe QD (N = 477) n (%)	140 mg Q2W (N=921) n (%)	420 mg QM (N=927) n (%)
# of subjects reporting AEs	9 (2.2)	9 (2.2)	22 (4.6)	23 (2.5)	22 (2.4)

Includes the following studies: 20110114, 20110115, 20110116, 20110117.

	Control			EvoMab	
	Placebo SC Q2W (N =411) n (%)	Placebo SC QM (N = 410) n (%)	Ezetimibe QD (N = 477) n (%)	140 mg Q2W (N=921) n (%)	420 mg QM (N=927) n (%)
Data cutoff date 01APR2014. N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; QD = once a day; Q2W = every 2 weeks; QM =monthly; SC = subcutaneous. Coded using MedDRA version 17.0. and confirmed with JMP					

In the year 1 SoC-controlled period, 58 (2.0%) participants in the evolocumab plus SoC group reported an adverse event leading to discontinuation of EvoMab. Of note, the SoC alone group could not report an adverse event leading to discontinuation of investigational product because they did not receive an investigational product. The only adverse events leading to discontinuation of IP occurring in ≥ 0.2% participants in the evolocumab plus SoC group was myalgia (7, 0.2%).

In the year 2+ OLE period, 10 (1.0%) subjects reported an adverse event leading to discontinuation of IP. The preferred terms, incidence was 1 (0.1) for each PT, were hypogonadism, dyspepsia, fatigue, malaise, blood testosterone decreased, weight increased, arthralgia, esophageal carcinoma, anxiety, angioedema, drug eruption and pruritus. Some of the cases are summarized below:

- Subject 15466024006 enrolled in study 20110110 was a 47 year old female. Subject received the first dose of 420 mg EvoMab on November, 2012 and last dose on March, 2013. In March, 2013 (20 days after the last dose of EvoMab), the subject experienced angioedema leading to withdrawal of EvoMab. The event resolved on the same day. The relevant medical history included food allergy. The relevant concomitant medication included diphenhydramine, methylprednisolone acetate, dexamethasone, epinephrine, fexofenadine hydrochloride, famotidine, montelukast sodium, cetirizine hydrochloride, and prednisone. The investigator reported the event unrelated to EvoMab.

- Subject 15466024021 enrolled in study 20110110 was a 44 year old male diagnosed with hypercholesterolemia. Subject received the first dose of 420 mg EvoMab on December, 2012 and last dose on June, 2013. In March, 2013 (3 months after the first dose of EvoMab), the subject experienced blood testosterone decreased. In June, 2013 (18 days prior to the last dose of EvoMab), the subject experienced hypogonadism. Both events led to withdrawal of EvoMab. The event blood testosterone decreased resolved on December, 2013. The event hypogonadism was continuing. Relevant medical history included prostatitis. The relevant concomitant medication included tadalafil. In June, 2013 the subject discontinued EvoMab. The investigator reported the events as unrelated to EvoMab.

- Subject 15516046015 enrolled in study 20110110 was a 44 year old male. Subject received the first dose of 420 mg EvoMab in December, 2011 and last dose in August, 2013. On August, 2013 (1 day after the last dose of EvoMab), the subject experienced malaise leading to withdrawal of EvoMab. The event was continuing. There was no relevant medical history.

There was no relevant concomitant medication. In August, 2013 the subject discontinued EvoMab. The investigator reported the event related to AMG 145.

- Subject 15529003004 enrolled in study 20110110 was a 60 year old male. Subject received the first and last dose of 420 mg EvoMab in March, 2013. On the same day of the last dose of EvoMab, the subject experienced pruritus leading to withdrawal of EvoMab. The event resolved the next day. There was no relevant medical history. The relevant concomitant medication included loratadine. In March, 2013 the subject discontinued EvoMab and the investigator reported the event related to EvoMab.

- Subject 15466062001 enrolled in study 20110110 was a 54 year old male. Subject received the first dose of 140 mg EvoMab in January, 2013 and last dose date is unknown. On March, 2014 (approximately 1 year and 2 months after first dose), the subject experienced anxiety. The next day, the subject experienced dyspepsia. Both events led to the withdrawal of EvoMab. The subject received alprazolam for the treatment of anxiety and antacids for the treatment of dyspepsia. The event dyspepsia resolved one month later, April, 2014. The event anxiety resolved ~ 6 weeks later in April 2014. Relevant medical history included anxiety, chronic anxiety and indigestion. There was no relevant concomitant medication. The investigator reported both events as related to EvoMab.

- Subject 1556603005 enrolled in study 20110110 was a 59 year old male. Subject received the first dose of 420 mg EvoMab on February 2012 and last dose on January 2014. On February 2014 (29 days after the last dose of EvoMab), the subject experienced an event of drug eruption leading to withdrawal of EvoMab. The subject received prednisone, clobetasol, hydroxyzine, and cephalexin for the treatment of rash. The event was continuing. There was no relevant medical history. There was no relevant concomitant medication. On January 2014 the subject discontinued EvoMab. The investigator assessed the event as unrelated to AMG 145.

HoFH
No participant in part A or part B of trial 20110233 discontinued study treatment due to an adverse event.

In trial 20110271, 1 (2.4%) HoFH participant discontinued study treatment due to an adverse event of rash. The rash improved after evolocumab withdrawal, although intermittent flares without evolocumab exposure continued to occur. Because of the temporal association of the rash and evolocumab administration, the investigator deemed that there was a reasonable possibility that the adverse event of severe skin rash was related to evolocumab. As of the 01 April 2014 data cutoff date, evolocumab had not been restarted.

7.3.4 Significant Adverse Events

Adjudicated Cardiovascular Events and Noncoronary Revascularizations:
Primary Hyperlipidemia and Mixed Dyslipidemia Trials

During the adjudication process, the applicant states that there were no discordant results between adjudicators and no instances when the CEC chairperson had to determine the final adjudication result.

In the integrated parent studies, the incidence of participants with positively adjudicated cardiovascular events was low across the groups but slightly greater in the any evolocumab group (25, 0.6%) compared with any control group (9, 0.4%) (see table). The incidences between the evolocumab 140 mg Q2W (0.8%) group (0.7% for corresponding placebo) and 420 mg QM (0.6%) group (0.3% for corresponding placebo) were similar and slightly greater than the associated placebo groups. The incidence of positively adjudicated cardiovascular events in the ezetimibe comparator group was 0.4%. Six deaths (4 [0.1%] in the any evolocumab group and 2 [0.1%] in the any control group) were positively adjudicated to be cardiovascular deaths; thus, the incidence of cardiovascular deaths was the same between the two treatment groups. Myocardial infarction was reported in 8 (0.2%) participants in the any evolocumab group and 2 (0.1%) participants in the any control group (1 event in the any control group was fatal). Stroke was reported in 3 (0.1%) participants in the any evolocumab group and 3 (0.1%) participants in the any control group (the hemorrhagic stroke event in the any control group was fatal). Three participants had positively adjudicated cardiovascular events of heart failure, and all were in the evolocumab group.

1. Subject 15566018006: 59-year old white male with a history of coronary arterydisease, ischemic cardiomyopathy, myocardial infarction, coronary artery bypass grafting, congestive cardiac failure, decreased ejection fraction, hypertension, cerebrovascular accident, chronic obstructive pulmonary disease, chronic renal failure, hypokalemia, type 2 diabetes, and tobacco and alcohol use. Relevant concomitant medications included nitroglycerin, carvedilol, amlodipine, lisinopril, hydralazine, furosemide, clopidogrel, potassium, acetylsalicylic acid, and insulin. In the parent study the subject was randomized to evolocumab 140 mg Q2W. Approximately 3 weeks after the first dose of evolocumab, the subject presented with shortness of breath, chest discomfort, and 2+ pitting edema in his legs. The subject reportedly was noncompliant with his medications for 1 week prior to symptom onset. A chest x-ray was consistent with congestive heart failure. Serial troponins peaked at 0.1 ng/mL; there were no ischemic changes on electrocardiogram (ECG). The subject was hospitalized and treated with nitroglycerin, furosemide, and oxygen, and was started on isosorbide. The subject's symptoms resolved and he was discharged the following day. No action was taken with evolocumab.

2. Subject 11528001022: 77-year old Asian female with a history of ischemic heart disease, percutaneous transluminal coronary angioplasty with stent placement, and hypertension. Concomitant medications included losartan, atenolol, atorvastatin, and acetylsalicylic acid. Approximately 3 months after the first dose of evolocumab 420 mg QM in Study 20110115, the subject had chest discomfort and palpitations for 1 week. Heart rate was 76 bpm and an ECG showed premature ventricular complexes. She was treated with furosemide 20 mg and her symptoms improved. Cardiac catheterization revealed right coronary artery stent stenosis 40% to 50% and no obvious stenosis in the left main, left anterior descending, and left circumflex arteries. Chest x-ray was clear. There was no elevated jugular venous pressure, no hepatosplenomegaly, and no lower extremity edema. An echocardiogram showed mild aortic regurgitation, normal left ventricular systolic function, and mild decrease in left ventricular diastolic function (no previous echocardiogram was noted in the discharge summary or medical history). B-type natriuretic peptide was elevated at 592 pg/mL and troponin was

normal. The subject was discharged after 3 days with no change to her medications. Discharge diagnoses included ischemic heart disease, congestive heart failure NYHA class II, hypertension, and premature ventricular beats. Evolocumab was continued.

3. Subject 11551706003: 59-year old white male with a history of atherosclerotic coronary artery disease, angina pectoris, congestive heart failure, coronary artery bypass graft, pacemaker placement, hypertension, carotid artery disease, stroke, transient ischemic attack, peripheral artery disease, and type 2 diabetes mellitus. Relevant concomitant medications included metoprolol, bisoprolol, isosorbide, carvedilol, amlodipine, captopril, clopidogrel, acetylsalicylic acid, and atorvastatin. In the parent study the subject was randomized to evolocumab 140 mg Q2W. Five days after the first dose of evolocumab, the subject presented with shortness of breath and non-radiating chest pain. An ECG showed an acute inferolateral wall myocardial infarction (MI). The subject was hospitalized and treated with nitroglycerin, furosemide, and morphine. One week later, while still in hospital, the subject had a second acute MI with acute left ventricular failure and pulmonary edema. He had ventricular fibrillation (which was successfully defibrillated) and corresponding cerebral anoxia with loss of consciousness. The ventricular fibrillation and loss of consciousness resolved the same day. The MI and pulmonary edema resolved 1 week later and the subject was discharged. The subject discontinued from study therapy and study participation.

In the year 1 SoC-controlled period, a slightly smaller percentage of participants had positively adjudicated cardiovascular events in the evolocumab plus SoC group (22 [0.8%]) compared with the SoC alone group (19 [1.3%]) (see table). There were three deaths (3 [0.1%] in the evolocumab plus SoC group, of which all were CV deaths, and 4 [0.3%] in the SoC alone group, of which one was adjudicated as a CV death. As shown in the table, myocardial infarction, coronary revascularization, cerebrovascular event and heart failure event occurred in a numerically smaller percentage of participants in the evolocumab plus SoC group as compared to the SoC alone group.

While the number of adjudicated events is too small to make any reliable conclusions regarding CV risk reduction, across the two study periods with control groups, the incidence of participants with positively adjudicated events, including deaths, was similar in the evolocumab group as compared to the control group. One limitation of the open label phase of these trials is that nonfatal events could be subject to reporting bias, by either patients or investigators.

Table 73: Participant Incidence of Positively Adjudicated Cardiovascular Events and Noncoronary Revascularizations

	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)
	Any Control (N = 2080) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 655) n (%)	EvoMab + SoC (N = 1314) n (%)	EvoMab + SoC (N = 954) n (%)
Number of participants with any positively adjudicated clinical event	9 (0.4)	25 (0.6)	19 (1.3)	22 (0.8)	12 (1.3)

	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)
	Any Control (N = 2080) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 655) n (%)	EvoMab + SoC (N = 1314) n (%)	EvoMab + SoC (N = 954) n (%)
Death	2 (0.1)	4 (0.1)	4 (0.3)	3 (0.1)	2 (0.2)
Cardiovascular	2 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Non-cardiovascular	0	0	2 (0.1)	0	1 (0.1)
Undetermined	0	0	1 (0.1)	0	0
Myocardial infarction	2 (0.1)	8 (0.2)	5 (0.4)	6 (0.2)	3 (0.3)
Fatal	1 (0.0)	0	0	0	0
Non-fatal	1 (0.0)	8 (0.2)	5 (0.4)	6 (0.2)	3 (0.3)
Hospitalization for unstable angina	0	2 (0.1)	2 (0.1)	2 (0.1)	1 (0.1)
Coronary Revascularization	5 (0.2)	11 (0.3)	8 (0.6)	11 (0.4)	7 (0.7)
Cerebrovascular Event	3 (0.1)	5 (0.1)	5 (0.4)	3 (0.1)	3 (0.3)
Transient ischemic attack	0	2 (0.1)	4 (0.3)	1 (0.0)	1 (0.1)
Stroke (fatal and non-fatal)	3 (0.1)	3 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)
Fatal Stroke	1 (0.0)	0	0	0	0
Ischemic	0	0	0	0	0
Ischemic with hemorrhagic conversion	0	0	0	0	0
Hemorrhagic stroke	1 (0.0)	0	0	0	0
Type Undetermined	0	0	0	0	0
Non-Fatal Stroke	2 (0.1)	3 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)
Ischemic	2 (0.1)	3 (0.1)	0	1 (0.0)	2 (0.2)
Ischemic with hemorrhagic conversion	0	0	0	0	0
Hemorrhagic stroke	0	0	1 (0.1)	1 (0.0)	0
Type Undetermined	0	0	0	0	0
Heart failure event	0	3 (0.1)	1 (0.1)	0	1 (0.1)
Non-coronary revascularization	1 (0.0)	1 (0.0)	3 (0.2)	5 (0.2)	2 (0.2)

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; OLE = open-label extension; SoC = standard of care
a Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product. Some cases from the phase 2 and phase 3 lipid lowering clinical studies had lipid values present in the adjudication package which may have led to unblinding
b Includes the following studies: 20110110, 20120138
c Includes the following studies: 20110110, 20120138
Source: Modified from Summary Clinical Safety, Table 43

HoFH Trials

In Trials 20110233 and 20110271, no participant experienced a positively adjudicated cardiovascular event or a non-coronary revascularization.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Primary Hyperlipidemia Trials

Cardiovascular Disorders

In the integrated parent studies, adverse events for the Cardiac Disorders system organ class were reported in 77 (2.4%) participants in the evolocumab group (140 mg Q2W or 420 mg QM) and 29 (1.4%) participants in the any control group. The most common adverse events in the evolocumab group and any control group were palpitations (0.6% and 0.3%), angina pectoris (0.3% and 0.2%), and ventricular extrasystoles (0.3% and 0.1%). Serious cardiac adverse events were reported in 21 (0.7%) participants in the evolocumab group and 5 (0.2%) participants in the any control group. The most common serious cardiac events in the evolocumab group and any control group were myocardial infarction (0.1% and 0%), angina pectoris (0.1% and 0.1%), and acute myocardial infarction (0.1% and 0%).

In the integrated parent studies, 131 (4.1%) participants in the evolocumab group (Q2W or QM) and 74 (3.6%) participants in the any control group reported an adverse event potentially associated with prolongation of cardiac repolarization or proarrhythmia as identified by preferred term. No events of torsades de pointes or ventricular tachycardia were reported. However, there was a case of “paroxysm of ventricular fibrillation” reported in the setting of an acute MI (20110115-11551706003); refer to narrative #3 in previous section (7.3.4: Significant Adverse Events). Syncope was reported in 12 (0.4%) participants in the evolocumab group (serious in 2 cases) and 6 (0.3%) participants in the any control group (serious in 1 case).

In the year 1 SoC-controlled period, 69 (2.4%) participants and 41 (2.9%) participants reported an adverse event in the evolocumab plus SoC group and SoC alone group, respectively. The most common adverse event in the evolocumab plus SoC group and SoC alone group was angina pectoris (0.6% and 0.7%). For serious cardiac events, 25 (0.9%) participants and 19 (1.3%) participants reported an event in the evolocumab plus SoC group and SoC alone group, respectively. In the year 1 SoC-controlled period, 118 (4.2%) participants in the evolocumab plus SoC group and 49 (3.5%) participants in the SoC group reported an adverse event potentially associated with prolongation of cardiac repolarization or proarrhythmia.

In the year 2+ OLE period, 47 (4.9%) participants reported an adverse event, and the most common adverse event was angina pectoris (1.3%). Sixteen (1.7%) participants reported a serious cardiac adverse event.

In the integrated parent trials, adverse events for the Vascular Disorders system organ class were reported in 96 (2.4%) participants in the any evolocumab group and 55 (2.6%) participants in the any control group. The most frequently reported adverse events in the any evolocumab group and any control group were hypertension (1.4% and 1.3%), flushing (0.2% and <0.1%), and hot flush (0.2% and 0.4%). In the year 1 SoC-controlled period, 145 (5.1%) participants and 49 (3.5%) participants reported an adverse event in the evolocumab plus SoC group and SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were hypertension (3.1% and 2.7%) and hypotension (0.3% and 0%).

Gastrointestinal Disorders

In the integrated parent studies, adverse events for the Gastrointestinal Disorders system organ class were reported in 306 (9.6%) participants in the Q2W or QM evolocumab group and 208 (10.0%) participants in the any control group. The most common adverse events in the evolocumab group and any control group were nausea (2.1% and 1.8%), diarrhea (2.0% and 2.4%), and constipation (1.0% and 0.8%).

In the year 1 SoC-controlled period, 327 (11.5%) participants and 126 (8.9%) participants reported an adverse event in the evolocumab plus SoC and SoC alone groups, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were diarrhea (2.2% and 1.5%), nausea (1.6% and 0.9%), and vomiting (1.2% and 0.6%). In the year 2+ OLE period, 160 (16.8%) participants reported an adverse event, and the most common adverse events were diarrhea (3.5%), nausea (2.3%), and dyspepsia (1.8%).

Pancreatitis
Evolocumab increases hepatic uptake of LDL particles from the circulation due to increased LDLR expression on the surface of hepatocytes, with an increase in the delivery of lipid components of LDL, such as cholesterol, to the liver.

One potential issue is whether this mode of action could lead to increased metabolism and excretion of cholesterol metabolites resulting in changes in bile lithogenicity and associated increased gallstone risk. This could potentially have an impact on the development of gallstone pancreatitis. The applicant contends that three mechanisms, reduction in endogenous cholesterol biosynthesis, excretion directly into the bile as free cholesterol (via ABCG5/G8 transporters), and conversion of cholesterol into bile acids (regulated by CYP7A1) and excretion into bile, have been shown to compensate for increased hepatic LDLR activity in PCSK9 knockout mice, where liver triglyceride, cholesterol, and bile acid content was equivalent to wild-type mice[60] and following treatment with a statin.[61]

60 Rashid S, Curtis DE, Garuti R, Anderson N, Bashmakov Y, Ho YK, Hammer RE, Moon

In cynomolgus monkeys treated with evolocumab, gallbladder hypertrophy/hyperplasia (mild) was observed in 1 out of 3 female monkeys at 134 times the maximum recommended human dose of 420 mg Q2W with six weeks of once-weekly dosing (of note, a mild finding in only a single animal is generally considered to be a spontaneous/incidental lesion). No effects were observed at a similarly high exposure multiple at six months of dosing in cynomolgus monkeys or at three months with rosuvastatin in cynomolgus monkeys. No effects on liver or on gallstone formation were observed in hamsters with evolocumab, although alkaline phosphatase was slightly increased in male hamsters at 28 days at 20 times the maximum recommended human dose of 420 mg Q2W. Alkaline phosphatase was not affected at longer durations of dosing in hamsters at any dose. There were no drug-related pancreas lesions observed with evolocumab in any species.

Overall, 6 participants reported 7 events of pancreatitis (reported as pancreatitis or acute pancreatitis) as of the BLA data cutoff date of 01 April 2014. At the 120-Day Safety Update with a data cut-off date of 01 July 2014, there were 7 participants with 8 events of pancreatitis. Six events occurred while the participants were receiving evolocumab or evolocumab plus SoC (3 events in the parent studies, 2 events in the year 1 SoC-controlled period, and 1 event in the year 2+ OLE period), and 2 events occurred while the subjects were receiving SoC alone (both during the year 1 SoC-controlled period). No cases of chronic pancreatitis were reported. All events were reported as serious requiring hospitalization. None of the 8 events were fatal.

A summary of these cases follows:

- Three participants (Subjects 11466042002, 15966006002, and 11521014006) were withdrawn from investigational product due to the event.

- All 7 participants recovered from the 8 events. Among the participants who had an event while taking EvoMab, 3 resolved despite continuing to receive EvoMab, 2 resolved within a month of the last dose of EvoMab, and 1 resolved 3.5 month after the last dose. For the 2 participants who had an event while on SoC alone, both resolved while continuing to receive SoC.

- One participant (15916004001) reported two adverse events of pancreatitis. The first event of acute pancreatitis occurred approximately 19 days after receiving the first dose of evolocumab (280 mg QM) in the parent study. No etiology was determined and the event resolved after 9 days. Six months later, this same participant reported a second event (as gallstone pancreatitis) while

Y, Horton JD. Decreased plasma cholesterol and hypersensitivity to statins in mice lacking PCSK9. PNAS 2005; 102(15):5374-5379
61 Parker RA, Garcia R, Ryan CS, Liu X, Shipkova P, Livanov V, Patel P, Ho SP. Bile acid and sterol metabolism with combined HMG-CoA reductase and PCSK9 suppression. Journal of Lipid Research. 2013; 54:2400-2409

on SoC alone in the extension study. A cholecystectomy was done, the participant continued on SoC, and the event resolved.

- For 1 event of acute pancreatitis the investigator reported that there was a reasonable possibility the event was related to study drug. The participant (11466042002) was hospitalized with abdominal pain 20 days after the second dose of evolocumab 420 mg QM in the parent study. Amylase was reported as 103 IU/L on an undocumented date. The subject's condition improved overnight with intravenous fluids and bowel rest. A computerized tomogram was reported as negative with slight dilatation of ducts noted. The investigator reported that pancreatitis was a single episode that was mild. The participant's history of cholecystectomy was reported as a risk factor for the reported event. The participant's concomitant medication, valproate semisodium, had recently been increased. This was subsequently discontinued because of a black box warning for pancreatitis. This episode of pancreatitis resolved approximately 4 months later. The participant discontinued investigational product due to the event.

- Of the other 5 participants, 2 had concurrent alcohol use, 2 had diabetes, 1 had gallstones, 1 had a scheduled endoscopic procedure and puncture of a pancreatic cyst, and 5 had concomitant medications associated with pancreatitis.

Table 74: Summary of Pancreatitis Serious Adverse Events

Subject # Study	Age Sex	Treatment at time of Event (Parent treatment) Grade	Serious	Preferred Term/ Verbatim Term Comment	Time to onset from 1st dose from last dose Related	Outcome Discontinued	Medical History Concurrent Medications
Pancreatitis acute Cases in the Parent Studies							
15916004001 20090159	66	Evolocumab 280 mg QM		Pancreatitis acute/Grade 3	19 days 19 days	Resolved in 10 days	Cholecystitis, diabetes mellitus, right shoulder tendonitis, prostatitis, duodenal ulcer, allergic rhinitis, gastroesophageal reflux disease, non-cardiac chest pain, left testicle cyst and decreased hearing
	M	3	Yes	Resolved on evolocumab; diagnosed with gallbladder adenomyomatosis; confounded by history of cholecystitis and diabetes mellitus; confounding concomitant medications ramipril, dexamethasone, paracetamol/codeine	No	No	ezetimibe, metformin, ramipril, rabeprazole sodium, paracetamol/codeine, ciprofloxacin/dexamethasone
11466042002 20110114	62	Evolocumab 420 mg QM + oral placebo		Pancreatitis acute/Grade 3	47 days 20 days	Resolved in 113 days	Cholecystectomy, hypertension, GERD, depression, obstructive sleep apnea, mitral regurgitation, generalised osteoarthrosis, bladder suspension, irritable bowel syndrome; consumed alcohol (2 to 3 glasses of wine daily) chronically
	F	3	Yes	Resolved after withdrawal; confounding factors history of cholecystectomy, chronic alcohol use, irritable bowel syndrome; confounding concomitant medication valproate semisodium (black box warning for pancreatitis)	Yes	Yes	irbesartan, hydrochlorothiazide, guaifenesin, sertraline, bupropion hydrochloride, lorazepam, fexofenadine hydrochloride, omeprazole, valproate semisodium
11756003010 20110117	51	Evolocumab 420 mg QM		Pancreatitis acute/Grade 3	75 days 14 days	Resolved in 4 days	Recurrent tonsillitis, reactive arthritis, moderate alcohol use
	M	3	Yes	Resolved on evomab; confounding factors alcohol use and rosuvastatin	No	No	ezetimibe and rosuvastatin

Subject # Study	Age Sex	Treatment at time of Event (Parent treatment) Grade	Serious	Preferred Term/ Verbatim Term Comment	Time to onset from 1st dose from last dose Related	Outcome Discontinued	Medical History Concurrent Medications
Pancreatitis Cases in the SoC-controlled Period							
15916004001 20110110 (second event)	66	SoC only (Parent: Evolocumab 280 mg QM)		Pancreatitis/Grade 2	180 days 93 days	Resolved in 85 days	Chronic cholecystitis, diabetes mellitus, right shoulder tendonitis, prostatitis, duodenal ulcer, allergic rhinitis, gastroesophageal reflux disease, non-cardiac chest pain, left testicle cyst and decreased hearing
	M	2	Yes	Diagnosed as gallstone pancreatitis; cholecystectomy performed Resolved on SoC confounded by history of cholecystitis and diabetes mellitus; confounding concomitant medications: ramipril, dexamethasone, and paracetamol/codeine	No	No	ezetimibe, metformin, ramipril, rabeprazole sodium, paracetamol/codeine, ciprofloxacin/dexamethasone, triamcinolone acetonide
15966006002 20110110	71	Evolocumab 420 mg QM + SoC (Parent: Evolocumab 280 mg QM)		Pancreatitis/Grade 3	173 days 5 days	Resolved in 13 days	Type 2 diabetes mellitus (uncontrolled)
	M	3	Yes	Resolved within 3 weeks of last QM dose of evolocumab Confounding factors: simvastatin, lisinopril, losartan, and uncontrolled diabetes mellitus; during the event fasting blood glucose was 912 mg/dL and 482 mg/dL	No	Yes	simvastatin, insulin aspart, insulin glargine, glimepiride, lisinopril, terazosin, losartan/hydrochlorothiazide

Subject # Study	Age / Sex	Treatment at time of Event (Parent treatment) Grade	Serious	Preferred Term/ Verbatim Term / Comment	Time to onset from 1st dose from last dose / Related	Outcome / Discontinued	Medical History / Concurrent Medications
Pancreatitis acute Cases in the SoC-controlled Period							
11521014006 20120138	59	Evolocumab 140 mg Q2W (Parent: Evolocumab 140 mg Q2W + SoC		Pancreatitis acute/Grade 3	193 days 10 days	Resolved in 10 days	Hypertension, smoking, occasional alcohol use, laparoscopic surgeries for inguinal hernia, cortical cysts in both kidneys.
	M	3	Yes	Resolved within 3 weeks of Q2W last dose Confounding factors uncontrolled diabetes: fasting blood glucose levels were 212 mg/dL during event, confounding concomitant medications indapamide, perindopril, rosuvastatin and prior exposure to fenofibrate and simvastatin	No	Yes	amlodipine, metoprolol, indapamide, perindopril, and atorvastatin; fenofibrate March 2009 to March 2013; atorvastatin March 2009 to May 2013; simvastatin May to September 2013; atorvastatin May 2013 to pancreatitis event December 2013
11613005012[b] 20120138	68	SoC only (Parent: Evolocumab 420 mg QM)		Pancreatitis acute/Grade 3	331 days 241 days	Resolved in 8 days	Predisposing factor associated with the event was an endoscopic procedure and puncture of the cyst
	M	3	Yes	Resolved on SoC Confounding factor endoscopic procedure and puncture of pancreatic cyst; prior confounding concomitant medications clarithromycin and doxycycline	No	No	ezetimibe; 3 courses of antibiotics to treat bronchitis one month prior to pancreatic cyst puncture procedure: amoxicillin / clavulanate; clarithromycin; doxycycline

Subject # Study	Age / Sex	Treatment at time of Event (Parent treatment) Grade	Serious	Preferred Term/ Verbatim Term / Comment	Time to onset from 1st dose from last dose / Related	Outcome / Discontinued	Medical History / Concurrent Medications
Pancreatitis Case in the year 2+ Period							
15566032029 20110110	78	Evolocumab 350 mg QM (Parent: Evolocumab 420 mg QM + SoC)		Pancreatitis/Grade 2	856 days 14 days	Resolved in 4 days	Ultrasound of abdomen showed sludge and small stones within gall bladder lumen
	F	2	Yes	Resolved on evolocumab Confounding concomitant medications simvastatin and amlodipine	No	No	ezetimibe/simvastatin; escitalopram oxalate, metoprolol, ramelteon, hydrochlorothiazide, rabeprazole sodium, solifenacin succinate, olmesartan, acetylsalicylic acid, medoxomil/amlodipine/hydrochlorothiazide

F = Female; M = Male; Q2W = every 2 weeks; QM = monthly; SoC = Standard of care.
a Period 1 = Parent study; Period 2 = year 1 SoC-controlled period; Period 3 =year 2+ open label extension.
b This case had a data cutoff of 01 July 2014. All others had a data cutoff date of 01 April 2014.
Source: Table 2 from Feb 2015 Clinical Information Request Response

Thus, the incidence of pancreatitis in the clinical development program was low overall but numerically greater in the evolocumab group in the parent studies. Cases were confounded by histories of gallstones, cholecystitis or diabetes; concomitant medications associated with pancreatitis such as valproate therapy; and alcohol use.

Hepatobiliary Disorders
In the integrated parent trials, adverse events for the Hepatobiliary Disorders system organ class were reported in 13 (0.3%) participants in the any evolocumab group and

9 (0.4%) participants in the any control group. The most common adverse events in the any evolocumab group and any control group were cholelithiasis (0.1% and 0.2%), hepatic steatosis (0.1% and < 0.1%), and biliary colic (0.1% and 0%).

In the integrated parent studies, serious adverse events for the Hepatobiliary Disorders system organ class were reported in 4 (0.1%) participants in the any evolocumab group (AE preferred terms: cholecystitis, cholelithiasis and biliary tract disorder) and 2 (0.1%) participants in the any control group (AE preferred terms: acute cholecystitis and drug-induced liver injury).

In the year 1 SoC-controlled period, 15 (0.5%) participants and 8 (0.6%) participants reported an adverse event for the Hepatobiliary Disorders system organ class in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were hepatic steatosis (0.2% in both groups), cholelithiasis (0.1% and 0.2%), and hepatic function abnormal (0.1% and 0%).

In the year 1 SoC-controlled period, 3 (0.1%) participants and 1 (0.1%) participant reported a serious adverse event in the evolocumab plus SoC group [AE preferred terms: cholelithiasis, hepatic function abnormal and hepatotoxicity (both cases described below)] and SoC alone group (AE preferred terms: bile duct stone and chronic cholecystitis), respectively. In the year 2+ OLE period, 5 (0.5%) participants reported a serious adverse event (AE preferred terms: biliary dyskinesia, cholecystitis, cholecystitis acute, cholelithiasis and hepatic lesion).

SAE of hepatotoxicity:

> Subject 15466039016 was a 38-year-old white woman participating in Study 20110110 who experienced hepatotoxicity (reported term: liver toxicity). The subject's medical history included hypercholesterolemia, hypertension, gastritis and obesity. The subject received the first dose of evolocumab in Study 20110110 in October 2011. Baseline values obtained on August 2011 revealed slightly elevated ALT 70 U/L/AST 42 U/L, and normal total bilirubin 0.2 mg/dL. In January 2012, laboratory tests revealed ALT 48 U/L and AST 27 U/L. In April 2012, the subject had symptoms of nausea, mild epigastric pain after eating, vomiting, upper abdominal distention, gas, and poor appetite. In April 2012, laboratory tests showed: ALT 147 U/L (4.3xULN) and AST 90 U/L (2.7xULN). Clinical laboratory investigations in May showed positive test for Helicobacter pylori was positive. Treatment medication included combination of amoxicillin trihydrate, clarithromycin, and lansoprazole. The subject started feeling better and liver function tests improved after one week of therapy. The subject's last dose of evolocumab prior to the event of hepatotoxicity was in April 2012 after which the evolocumab was withheld and again started in June 2012. Evolocumab was continued. As of the data cutoff date of 01 April 2014, the last dose of evolocumab was in May 2013. The event of hepatotoxicity was reported to have resolved in July 2012. In April 2013, liver function tests were normal. Abnormal liver tests not likely related to evolocumab. Helicobacter pylori infection likely contributed to the elevated transaminases and dyspepsia. This case is discussed in greater detail in Section 9.8.

SAE of hepatic function abnormality:

Subject 11565005001 was a 66-year-old white woman participating in Study 20120138 who developed abnormal hepatic function (reported term: liver function abnormality). The subject's medical history included primary hyperlipidemia, unexplained jaundice event in 2007, and recurrent urinary tract infections. Concomitant medications included candesartan, nitrofurantoin in chronic (6 months before the event) use for recurrent urinary infections, ramipril, gabapentin, diclofenac, omeprazole, codeine, paracetamol, salbutamol, budesonide, pseudoephedrine, fexofenadine, and mometasone. She received the first dose of evolocumab in Study 20120138 on 09 October 2013. On 09 December 2013, the subject experienced dyspepsia. Ten days later, the subject developed liver function abnormality with ALT 794 U/L (23xULN), AST 562 U/L (17xULN), and alkaline phosphatase 158 U/L. Evolocumab and simvastatin were discontinued. On 22 January 2014, the subject underwent endoscopy and gastroscopy due to dysphagia, nausea and/or vomiting, which showed a normal upper gastrointestinal tract. On 30 January 2014, laboratory values included immunoglobulin A of 5.2 g/L, iron of 37 µmol/L, total bilirubin of 230 µmol/L, ALT of 636 U/L, AST of 833 U/L, ALP of 266 U/L, transferrin saturation of 64%, albumin of 28 g/L, and alpha fetoprotein of 39 Ku/L. On 07 February 2014, the subject underwent a liver biopsy. The features were those of acute hepatitis with confluent necrosis and focal bridging necrosis with exclusion of viral and autoimmune etiology. The clinical diagnosis was drug-induced acute hepatitis. In April 2014, liver function tests were normalized with values of ALT 21 U/L, AST 27 U/L, albumin 33 g/L, alkaline phosphatase 108 U/L, and total bilirubin 20 µmol/L. Evolocumab and simvastatin continued to be withheld. The subject's last dose of evolocumab prior to the event was on 04 December 2013. As of the data cutoff date of 01 April 2014, evolocumab was still being withheld and the subject was continuing in the study. The investigator reported that there was a reasonable possibility that the event of abnormal liver function was related to evolocumab. The investigator noted that medications such as simvastatin, nitrofurantoin, diclofenac and ramipril may have contributed to the liver dysfunction. This reviewer concurs. This case is discussed in greater detail in Section 9.8.

Narratives of select hepatic-related SAEs are described in Section 9.9 A Selection of Narratives of Hepatic-related Serious Adverse Events

A narrow search strategy [a sub-SMQ of a MedDRA 17.0 Hepatic disorder (SMQ)] was used to evaluate hepatic safety risks with evolocumab therapy. The incidence of reported adverse events related to transaminase elevations and potential hepatic disorders was low in the integrated parent studies (any evolocumab: 0.9%; any control 0.8%), the year 1 SoC-controlled period (evolocumab plus SoC: 1.1%; SoC alone: 1.2%), and the year 2+ OLE period (1.4%).

Laboratory analyses of liver-related tests are presented in the following tables. The participant incidence of transaminase and bilirubin abnormalities was low and similar in the parent and extension trials for both the control and EvoMab groups.

In the integrated parent studies, 13 (0.4%) participants in the evolocumab group (140 mg Q2W or 420 mg QM) and 20 (1.0%) participants in the any control group had ALT or AST > 3 x ULN at any postbaseline visit. No participant had both (ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR > 1.5) at any study visit. Of note, more participants in the control group had baseline AST/ALT elevations than in the EvoMab group which affected the number of postbaseline abnormalities. However, among participants with normal baseline transaminases, 6 (0.2%) participants in the any evolocumab group and 4 (0.2%) participants in the any control group had ALT or AST > 3 x ULN at any postbaseline visit.

Table 75: Participant Incidence of Liver Related Test Abnormality (Integrated Parent Analysis Set)

	CONTROL			EVOLOCUMAB				TOTAL	
	Pbo Q2W (N= 586) n (%)	Pbo QM (N =940) n (%)	Eze. (N = 554) n (%)	Other EvoMab dose (N = 715) n (%)	140 mg Q2W (N =1245) n (%)	420 mg QM (N =1956) n (%)	420 mg QM+Eze. (N = 30) n (%)	Any Control (N=2080) n (%)	EvoMab 140 Q2W or 420 mg QM (N = 3201) n (%)
Baseline									
ALT or AST > 3 x ULN	3 (0.5)	3 (0.3)	5 (0.9)	1 (0.1)	1 (0.1)	3 (0.2)	0	11 (0.5)	4 (0.1)
ALT or AST > 5 x ULN	3 (0.5)	1 (0.1)	1 (0.2)	0	0	1 (0.1)	0	5 (0.2)	1 (0.0)
Total bilirubin > 2 x ULN	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	1 (0.0)	2 (0.1)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR>1.5)	0	0	0	0	0	0	0	0	0
Any Postbaseline Visit	579	928	548	712	1227	1924	30	2055	3151
ALT or AST > 3 x ULN	6 (1.0)	9 (1.0)	5 (0.9)	4 (0.6)	5 (0.4)	8 (0.4)	0	20 (1.0)	13 (0.4)
ALT or AST > 5 x ULN	3 (0.5)	4 (0.4)	0	1 (0.1)	1 (0.1)	4 (0.2)	0	7 (0.3)	5 (0.2)
Total bilirubin > 2 x ULN	0	2 (0.2)	1 (0.2)	1 (0.1)	0	5 (0.3)	0	3 (0.1)	5 (0.2)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR>1.5)	0	0	0	0	0	0	0	0	0

	CONTROL			EVOLOCUMAB				TOTAL	
	Pbo Q2W (N= 586) n (%)	Pbo QM (N =940) n (%)	Eze. (N = 554) n (%)	Other EvoMab dose (N = 715) n (%)	140 mg Q2W (N =1245) n (%)	420 mg QM (N =1956) n (%)	420 mg QM+Eze. (N = 30) n (%)	Any Control (N=2080) n (%)	EvoMab 140 Q2W or 420 mg QM (N = 3201) n (%)
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR=international normalized ratio. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab ncludes any subject with EvoMab as a component of investigational product. Source: Modified from ISS Tables 14-7.3.1 and 14-7.3.2									

In the year 1 SoC-controlled period, 27 (1.0%) participants in the evolocumab plus SoC group and 17 (1.2%) participants in the SoC alone group had ALT or AST > 3 x ULN at any postbaseline visit. Nine (0.3%) participants in the evolocumab plus SoC group and 3 (0.2%) participants in the SoC alone group had ALT or AST > 5 x ULN at any postbaseline visit. Eight (0.3%) participants in the evolocumab plus SoC group and 2 (0.1%) participants in the SoC alone group had total bilirubin > 2 x ULN at any postbaseline visit. Three (0.1%) participants in the evolocumab plus SoC group of the year 1 SoC-controlled period had transaminase levels 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5:

- Case 15466045017: the LFT abnormalities occurred 3 days after the participant admitted himself to rehabilitation for alcohol detoxification.
- Case 11565005001: The participant (who had a medical history of unexplained jaundice and chronic kidney disease, stage 3) had significant elevations in ALT, AST and total bilirubin. The participant was being treated for a urinary tract infection with nitrofurantoin. Nitrofurantoin was suspected as a possible cause of the LFT abnormalities per the investigator, as well as simvastatin, diclofenac, ramipril, and evolocumab.[62] Liver biopsy in this participant was consistent with drug-induced hepatitis. LFTs normalized after suspending nitrofurantoin, evolocumab, simvastatin and other medications. See detailed description in previous section on hepatobiliary disorders adverse events and in Section 9.9 A Selection of Narratives of Hepatic-related Serious Adverse Events.
- Case 23134087003: the participant's bilirubin was normal; the participant was also taking warfarin. Additionally, this participant's transaminases declined despite continuation of evolocumab treatment.

62 Reviewer note, nitrofurantoin can cause drug induced liver disease and can cause either an acute or a chronic hepatitis-like syndrome that can be severe and lead to liver failure or cirrhosis http://livertox.nih.gov/Nitrofurantoin.htm, accessed 2/3/2015

Among participants with normal baseline transaminases in the year 1 SoC-controlled period, 15 (0.6%) participants in the evolocumab plus SoC group and 7 (0.6%) participants in the SoC alone group had ALT or AST > 3 x ULN at any postbaseline visit. Six (0.2%) participants in the evolocumab plus SoC group and 2 (0.2%) participants in the SoC alone group had ALT or AST > 5 x ULN at any postbaseline visit.

In the year 2+ OLE period, 13 (1.4%) participants had ALT or AST > 3 x ULN at any postbaseline visit. Two (0.2%) participants had ALT or AST > 5 x ULN at any postbaseline visit. Two (0.2%) participants had total bilirubin > 2 x ULN at any postbaseline visit. No participant had both ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5 at any study visit. Among participants with normal baseline LFTs, 9 (1.1%) subjects had ALT or AST > 3 x ULN at any postbaseline visit.

HoFH Trials
In part A of Trial 20110233, no participant had ALT or AST > 3 x ULN, total bilirubin > 2 x ULN, or INR > 1.5. In part B of Trial 20110233, 2 (6.1%) participants in the evolocumab group and 1 (6.3%) participant in the placebo group had ALT or AST > 3 x ULN postbaseline. All 3 participants had ALT or AST > ULN at baseline and none discontinued IP. All of the ALT and AST elevations resolved to < 3 x ULN at a subsequent assessment. No participant had both ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5 at any study visit.

In Trial 20110271, 4 (5.6%) participants had ALT or AST > 3 x ULN at any postbaseline visit, and 2 of these participants had ALT or AST > 5 x ULN at any postbaseline visit. One participant had total bilirubin > 2 x ULN both at baseline and at OLE Week 12. No participant had both ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5 at any study visit. After the AST/ALT elevation, the 4 participants continued evolocumab treatment, and no dosage adjustments for concomitant statin treatment were reported. For 2 of the participants, the ALT/AST elevations resolved to < 3 x ULN at a subsequent assessment; the other 2 did not have a subsequent assessment of ALT or AST before the data cutoff date.

Injection Site Reactions

Broad and narrow search strategies were used to assess multiple preferred terms associated with possible injection site reaction. Of note, participants assigned to SoC alone in the extension studies did not receive any placebo injections. In the narrow searches, the incidence of injection site reactions was low and similar between treatment groups in the integrated parent studies (any evolocumab: 3.3%; any control 3.0%), the year 1 SoC-controlled period (evolocumab plus SoC: 3.7%; SoC alone did not receive injections), and the year 2+ OLE period (3.1%).

In total, there were 265 participants on evolocumab who reported 586 injection site reactions (high-level term). The most common injection site reaction adverse events were injection site erythema, injection site pain, and injection site bruising. Six participants received pain medication, steroids, or antihistamines as treatment for the event. Eighty-eight of the 265 participants (33%) reported recurring injection site reactions. Nine participants discontinued evolocumab due to injection site reactions, and of these, 5 had recurring events and 4 had single events and then withdrew.

Anti-evolocumab Antibody Formation
From the 14 integrated phase 2 and phase 3 studies supporting the indication in patients with primary hyperlipidemia and mixed dyslipidemia, including the open-label extension studies, 0.1% (7 out of 4846) of subjects developed binding antibodies *after at least one dose of evolocumab*. Four out of these 7 subjects were transiently positive (negative at the last time point tested for a subject) and none of the subjects developed neutralizing antibodies.

From the 2 studies supporting the indication in patients with HoFH (20110233 and 20110271), none of the 96 subjects (80 HoFH) developed anti-evolocumab antibodies.

Binding antibodies in the baseline sample (pre-existing antibodies) were detected in 0.1% (5 out of 4662) of subjects from the phase 2 and phase 3 integrated parent studies. The applicant states that positive results from these baseline samples may be due to the presence of pre-existing antibodies capable of binding to evolocumab.

In subjects <u>not</u> treated with evolocumab from the phase 2 and phase 3 integrated parent studies, 0.3% (2 out of 769) of subjects tested positive for the development of binding antibodies. The applicant believes that this is due to low level pre-existing antibodies that were detected intermittently at different time points due to borderline positive results.

Across the entire evolocumab clinical program, as of the study cutoff date, 15 participants (from all participants tested and including pre-existing antibodies) tested positive for binding antibodies. Again, no neutralizing antibodies were detected in any participant. The table below presents the adverse events that correlate temporally with a positive binding antibody result in the 10 participants that had a positive result for binding antibodies <u>after Day 1</u>. No serious adverse events were temporally associated with a positive binding antibody result. There does not appear to be a temporal correlation between the development of binding antibodies and specific adverse events such as hypersensitivity. The applicant was asked to provide antibody titer information for these subjects but provided the signal-to-noise (S/N) value information as an alternative as this reportedly provides a relative level of the anti-evolocumab binding antibody in the sample. A positive result is defined as a screen S/N > 1.16 and sample % depletion > the depletion cut point. The Office of

Biotechnology Products is also reviewing the signal-to-noise (S/N) value as an alternative to reporting anti-evolocumab binding antibody titers.

Table 76: Adverse Events Occurring in Participants in Conjunction with a Positive Binding Antibody Result

Subject ID	Study Period[a]	Treatment	Positive Result [b] (Visit Day)	Additional Results	Reported AEs	S/N[c]
109572-07052	Parent Study Yr 1 SoC-Controlled	EvoMab 420 mg QM EvoMab + SoC	day 87 day 253 OLE day 83	(parent) days 177 and 365 (EOS visit) and OLE day 165 were negative	day 193 grade 1 folliculitis day 255 & 277 grade 1/2 influenza day 325 grade 1 back pain day 330 grade 1 sinusitis	1.40
115516-90003*	Parent Study	EvoMab 420 mg QM	day 1 day 92	(parent) no further results after day 92	day 14 grade 1 rhinitis, grade 1 laryngitis	4.08
154130-12005	Parent Study Year 1 SoC-Contr OLE All-IP	EvoMab 105 mg Q2W in Parent; EvoMab + SoC	day 29	parent day 99 to OLE day 364 were negative	day 26 grade 1 abdominal pain	1.98
154660-39020	Parent Study Year 1 SoC-Contro OLE All-IP	Placebo SC QM EvoMab + SoC	day 86	OLE: day 28 to day 708 were negative	none	1.76
158660-03017	Parent Study Year 1 SoC-Contr. OLE All-IP	EvoMab 420 mg QM SoC only EvoMab + SoC	day 29	OLE: day 85 to day 795 were negative	none	1.20
154660-70002	Parent Study Yr 1 SoC-Controlled OLE All-IP	EvoMab 70 mg Q2W SoC only EvoMab + SoC	day 27	OLE: day 84 to day 1120 were negative	none	1.61
231340-30001	Parent Study	Placebo EvoMab + SoC	day 36 day 85 day 337	OLE days 169, 253 and 365 were negative	day 36 grade 1 contusion day 85 grade 2 worsening diabetes mellitus	1.48 1.46 1.60

Subject ID	Study Period[a]	Treatment	Positive Result [b] (Visit Day)	Additional Results	Reported AEs	S/N[c]
	Yr 1 SoC-Controlled					
231340-79012	Parent Study Yr 1 SoC-Controlled	Placebo SC QM EvoMab + SoC	day 86 day 1	OLE: day 29 to day 372 were negative	day 44 grade 1 myalgia	1.33
115660-30021	Parent Study Yr 1 SoC-Controlled	EvoMab 140 mg Q2W EvoMab + SoC	OLE day 92	(OLE) day 85 and day162 were negative	day 75 grade 1 influenza day 77 grade 1 back pain day 85 grade 1 malaise	1.59
115660-41001	Parent Study Yr 1 SoC - Controlled	EvoMab 420 mg QM EvoMab + SoC	day 183	No further results after OLE day 183	None	1.24

AE = adverse event; EvoMab = evolocumab; OLE = open label extension; Q2W = once every 2 weeks; QM = once monthly; SC = subcutaneously; SoC = standard of care
The method used for adverse events listed included all adverse events occurring before and after the positive binding antibody result. These adverse events occurred before the positive antibody result (or at the beginning of study) through the date of the next negative finding.
*This subject was antibody positive at baseline (Day 1), demonstrating the presence of pre-existing, cross-reactive antibodies prior to dosing.
a Study period during which anti-evolocumab antibody results (positive or negative) were reported.
b Antibody time point is reported in weeks.
c S/N = Signal to Noise of samples binding antibody-positive.
Source: Modified from Summary of Clinical Safety, Table 55 and Table 9 from Feb 2015 Information Request Response

In the 120-day Safety Update (data cutoff 01 July 2014), the cumulative incidence of anti-evolocumab binding antibody development after receiving at least 1 dose of evolocumab in the integrated phase 2 and phase 3 studies was 0.3% (13 of 4915 participants), compared with 0.1% (7 of 4846 participants) in the BLA. No neutralizing antibodies were detected in any participant.

Hypersensitivity

Using the SMQ narrow search strategy with multiple preferred terms possibly associated with hypersensitivity, the incidence of potential hypersensitivity events was low overall but slightly higher in the evolocumab group compared to placebo or to any control: in the integrated parent trials (evolocumab: 3.2%; any placebo: 2.4%; any control 2.4%), the year 1 SoC-controlled period (evolocumab plus SoC: 4.4%; SoC alone: 3.3%), and the year 2+ OLE period (5.7%). Nine events of drug hypersensitivity were reported by 8 participants: one in the any evolocumab group and 1 in the any control group were in the integrated parent studies; 3 in the evolocumab plus SoC group and 1 in the SoC alone group were in the year 1 SoC-controlled period; and 2 were in the year 2+ OLE period. One event was a serious adverse event and occurred when a participant was administered moxifloxacin hydrochloride for bronchitis and experienced an anaphylactic reaction. Of the 6 evolocumab treated participants, 4 reported drug hypersensitivity caused by antibiotic administration, and 1 reported the event as caused by prednisone administration. The other participant (11622001013, from trial 20110116 on EvoMab 140 mg Q2W) reported 2 adverse events of drug hypersensitivity on the same day. This participant was a 68 year old male with a medical history of hay fever, hiatal hernia, and esophagitis (treated with omeprazole). Sixteen days after the first dose and 1 day after the last dose of evolocumab prior to the event, the participant reported swelling of the throat and sore throat. The participant received 2 additional doses of evolocumab over the next 4 weeks. The participant's concomitant medications included bisoprolol, bendroflumethiazide, potassium chloride, acetylsalicylic acid, cetirizine, and budesonide. These 2 adverse events led to the withdrawal of evolocumab. Both events were reported resolved the day following the last dose of evolocumab. The investigator assessed the event as related to EvoMab and unrelated to placebo PO and placebo PO was continued.

Infections and Infestations

In the integrated parent studies, adverse events for the Infections and Infestations system organ class were reported in 828 (21.0%) participants in the any evolocumab group and 397 (19.1%) participants in the any control group. The most common adverse events in the any evolocumab group and the any control group were nasopharyngitis (5.9% and 4.8%), upper respiratory tract infection (3.2% and 2.7%), and influenza (2.1% and 2.0%).

In the year 1 SoC-controlled period, 815 (28.8%) participants and 388 (27.3%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab

plus SoC group and the SoC alone group were nasopharyngitis (8.5% and 7.9%), upper respiratory infection (4.2% and 4.0%), and influenza (3.0% and 2.6%).

Hepatitis C

Because the potential for increased HCV infectivity in evolocumab-treated participants is a theoretical possibility, participants believed to be at increased risk for hepatitis C were screened and monitored for HCV infection. Of the 94 participants identified at risk for HCV and tested for HCV antibody, 9 had confirmed positive antibody tests. In those 9 participants, AST/ALT were all < 2 x ULN. Two of these 9 participants had detectable HCV RNA. The other 7 participants remained HCV RNA undetectable throughout the study, and AST/ALT remained stable. A total of 3 participants had measurable HCV RNA on day 1 or subsequent visits. Two of the 3 participants were in the evolocumab group of Trial 20110115 (1 participant also had detectable viral load in the 20120138 extension study). One of these 2 participants reported an adverse event (worsening exertional angina), and in both participants transaminase levels remained < 2 x ULN. The third participant (10966402015) is discussed in the next paragraph.

Analyses were also performed to assess potential cases of hepatitis C. Broad and narrow Standardized MedDRA Queries (SMQs) or Amgen search strategies were used to assess multiple preferred terms associated with potential hepatitis C. In the narrow searches, the incidence of potential hepatitis C was low: 0% in the parent studies; in the year 1 SoC-controlled period (evolocumab plus SoC: 0%; SoC alone: 1, 0.1%) and the year 2+ OLE period (1, 0.1%). The 2 events are discussed below:

- An adverse event of hepatitis C was reported in a 59-year-old woman (10966402015) who received evolocumab 420 mg QM in the 20110109 parent trial and SoC alone in the 20120138 extension study. This adverse event was reported on day 235 (end-of-study-visit) as non-serious and evolocumab was withheld. This participant had mildly elevated ALT (59 U/L) from day 1 of the 20110109 parent study; the ALT increased to 89 U/L at Week 52. During the 20120138 extension study, a hepatitis panel was performed and an adverse event of hepatitis C was reported in response to the detectable viral load at day 235 (end-of-study visit). On Day 289, AST=40 IU/L, ALT=60 IU/L, Total bilirubin =9.0 µmol/L and hep C viral load= 565605 IU/L. Childhood blood transfusion was the suspected source of hepatitis C infection in this participant.

- An adverse event of hepatitis C antibody positive was reported in a 79-year-old woman (15566064002) who received placebo in the 20101155 parent trial and SoC alone in the 20120138 extension study. This event was discovered during routine testing before blood donation during the extension study. Additional testing revealed non-reactive hepatitis C serology, and was considered a false positive.

Metabolism and Nutrition Disorders

In the integrated parent studies, adverse events for the Metabolism and Nutrition Disorders system organ class were reported in 74 (2.3%) participants in the evolocumab group and 37 (1.8%) participants in the any control. The most common adverse events in the evolocumab group and the any control group were gout (0.4% and 0.1%), decreased appetite (0.3% and 0.1%), and diabetes mellitus (0.2% and 0.3%).

In the year 1 SoC-controlled period, 103 (3.6%) and 44 (3.1%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were diabetes mellitus (1.0% and 0.4%), gout (0.6% and 0.4%), and type 2 diabetes mellitus (0.5% and 0.4%). In the year 2+ OLE period, 37 (3.9%) subjects reported an adverse event, and the most common adverse events were diabetes mellitus (0.7%) and type 2 diabetes mellitus (0.7%).

Diabetes Mellitus
Because diabetes related adverse events have been reported with statins, broad and narrow SMQs or Amgen search strategies were used to assess safety risks with evolocumab therapy. In addition, there has been some recent interest and supportive data in the literature suggesting that the LDL receptor may play a role in the risk of developing type 2 diabetes.[63, 64] PCSK9 and LDLR are also expressed in insulin-producing pancreatic islet β cells and there has been some animal data in the literature suggesting that this may have an affect on the function of these cells. Mbikay et. al. showed that, compared to control mice, PCSK9-null male mice over 4 months of age carried more LDLR and less insulin in their pancreas. These PCSK9-null male mice were hypoinsulinemic, hyperglycemic and glucose-intolerant; their islets exhibited signs of malformation, apoptosis and inflammation. The authors suggest cholesterol accumulation in the islets of PCSK9-deficient mice could be a cause of these abnormalities, considering experimental evidence of the toxic effect of accumulation of this sterol in β cells.[65,66] The authors conclude that these observations suggest that PCSK9 may be necessary for the normal function of pancreatic islets.[67]

63 Besseling J, Kastelein JJ, Defesche JC, Hutten BA, Hovingh GK. Association Between Familial Hypercholesterolemia and Prevalence of Type 2 Diabetes Mellitus JAMA. 2015;313(10):1029-1036.
64 Preiss D, Sattar N. Does the LDL Receptor Play a Role in the Risk of Developing Type 2 Diabetes? JAMA. 2015;313(10):1016-1017.
65 Ishikawa M, Iwasaki Y, Yatoh S, Kato T, Kumadaki S, et. al. Cholesterol accumulation and diabetes in pancreatic beta-cell-specific SREBP-2 transgenic mice: a new model for lipotoxicity. J. Lipid Res. 2008; 49: 2524–2534.
66 Brunham LR, Kruit JK, Pape TD, Timmins JM, Reuwer AQ, et. al. Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. Nat. Med. 2007; 13: 340–347.
67 Mbikay M, Sirois F, Mayne J, Wang GS, Chen A, Dewpura T, et al. PCSK9-deficient mice exhibit impaired glucose tolerance and pancreatic islet abnormalities. FEBS Lett. 2010;584:701-6.

Using the hyperglycaemia-new onset diabetes mellitus SMQ (narrow search) to identify potential cases, the incidence of potential diabetes events was low in the integrated parent studies (any evolocumab: 0.9%; any control 0.8%), the year 1 SoC-controlled period (evolocumab plus SoC: 2.1%; SoC alone: 1.6%), and the year 2+ OLE period (1.8%).

Changes in HbA1c in the integrated parent and the extension studies were similar across treatment groups within the analysis periods. In the integrated parent studies, the mean change from baseline HbA1c ranged from 0.01% at Week 12 (N=2834) to 0.02% at Week 52 (N=535) in the any evolocumab group and from 0.04% at Week 12 (N=1732) to 0% at Week 52 (N=273) in the any control group. In the year 1 SoC-controlled period, the mean change from baseline HbA1c ranged from 0.03% at Week 12 (N=2203) to 0.02% at Week 52 (N=243) in the evolocumab plus SoC group and ranged from 0.07% at Week 12 (N=1068) to 0.11% at Week 52 (N=96) in the SoC alone group.

To further explore the potential for diabetes, the incidence of new onset diabetes and diabetes-related adverse events was evaluated among all patients, patients with baseline impaired fasting glucose and patients with baseline normoglycemia. The subject incidence of new onset diabetes mellitus was assessed in the integrated parent studies and the year 1 SoC-controlled period of the long-term extension studies for the following fasting blood glucose (FBG) subgroups of subjects without diabetes mellitus.

- subjects who were normoglycemic at parent study baseline (ie, FBG < 100 mg/dL at the latest time point measured prior to or on parent study day 1)
- subjects who had baseline impaired fasting glucose (IFG) at parent study baseline (ie, FBG of 100 to < 126 mg/dL at the latest time point measured prior to or on parent study day 1)
- combination of the above groups

The presence of diabetes at the parent study baseline was determined using the following criteria recommended by the Division: 1) reported medical history of diabetes mellitus, 2) diabetes medication use at baseline, and 3) FBG ≥ 126 mg/dL at baseline. The applicant added a fourth criterion, HbA1c ≥ 6.5% at baseline, to the FBG criterion for the presence of diabetes at baseline for consistency with current ADA recommendations.[68] In addition, subjects included in the analyses for the year 1 SoC-controlled period did not have new onset diabetes mellitus during the parent study.

68 American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Suppl. 1):S8-S16.

New onset diabetes mellitus was defined using laboratory, adverse event, and concomitant medication data for the integrated parent studies and in the year 1 SoC-controlled period of the long-term extension studies as follows in the 4-component definition:

- local or central laboratory data: at least 2 consecutive post-baseline FBG measurements ≥ 126 mg/dL
- local or central laboratory data: a post-baseline HbA1c ≥ 6.5% (measured approximately every 12 weeks)
- adverse event reporting data: adverse events consistent with new onset diabetes mellitus selected from the New Onset Diabetes Mellitus Narrow Standardized MedDRA Query (SMQ)
- concomitant medications data: initiation of any anti-diabetic medications at any time during the study. Relevant concomitant medications were defined as any drug in the World Health Organization Drug Anatomical Therapeutic Chemical (WHODrug ATC) Index pharmacological/therapeutic subgroup A10 Drugs Used in Diabetes. The medications in this index were considered anti-diabetes medications without regard for the indication.

Analyses were also prepared, consistent with the Division's request (3-component definition) not including the HbA1c criterion for baseline and new onset diabetes mellitus. Per the 3-component definition at baseline, subjects with 1) reported medical history of diabetes mellitus, 2) diabetes medication use at baseline, and 3) FBG ≥ 126 mg/dL at baseline were considered diabetic. If not diabetic at baseline, subjects who met any of the above bulleted criteria for new onset diabetes mellitus, excluding the HbA1c criterion, were considered to have new onset diabetes mellitus per the 3-component definition.

New Onset Diabetes Mellitus: Integrated Parent Studies

The table below describes the subjects without diabetes at baseline. A small percentage of these subjects, which was greater in the group with baseline IFG and slightly increased in the EvoMab group, had baseline HbA1c ≥ 6.5%.

Table 77: Summary of Baseline HbA1c in Subjects without Diabetes Mellitus (Integrated Parent Analysis Set)

	Any Placebo n (%)	Any Control n (%)	EvoMab 140 mg Q2W or 420 mg QM n (%)	Any EvoMab n (%)
Subjects Without Baseline Diabetes Mellitus	1343	1822	2753	3389
Baseline normoglycemia (FBG < 100 mg/dL) - N	901	1235	1778	2166
baseline HbA1c ≥ 6.5%	1 (0.1)	1 (0.1)	5 (0.3)	5 (0.2)
Baseline IFG (100 <= FBG < 126 mg/dL) - N	428	570	943	1177

baseline HbA1c ≥ 6.5%	5 (1.2)	6 (1.1)	15 (1.6)	18 (1.5)
Baseline FBG < 126 mg/dL (normoglycemia or IFG) - N	1329	1805	2721	3343
baseline HbA1c ≥ 6.5%	6 (0.5)	7 (0.4)	20 (0.7)	23 (0.7)

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
Subjects without baseline diabetes mellitus = no diabetes recorded in medical history and no diabetic medication use at baseline.
FBG = fasting blood glucose; HbA1c = hemoglobin A1c; EvoMab = Evolocumab.
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects.
Any EvoMab includes any subject with EvoMab as a component of investigational product
Source: modified from Table 3 from Feb 2015 FDA Information Request Response

Using either the 4-component or the 3-component definition of new onset diabetes mellitus and diabetes mellitus at baseline, no notable differences were observed between treatment groups in the median change from baseline in FBG or HbA1c over time for each baseline FBG subgroup. Using the 4-component definition of new onset diabetes mellitus and no diabetes mellitus at baseline, all post-dose HbA1c medians were ≤ 5.8% for both groups. In subjects with baseline IFG, the post-dose median FBG was ≤ 106 mg/dL for both treatments at each study visit.

Using the 3-component definition, rather than the 4-component definition, of new onset diabetes mellitus, fewer subjects were identified as having new onset diabetes mellitus during the studies. The overall results between the EvoMab and control groups were similar to the 4-component analysis but both are presented below for comparison. Using the 3-component definition analysis, in the group with IFG (defined as 100 ≤ FBG < 126 mg/dL), there was a small increase in post baseline new onset diabetes in the EvoMab group (29, 3.1% in EvoMab vs 11, 2.6% in Placebo vs 11, 1.9% in Any Control).

Table 78: Incidence of New Onset Diabetes Mellitus Without Incorporating HbA1c ≥ 6.5% (Integrated Parent Analysis Set)

Subjects With	Any Placebo (N=1343) n (%)	Any Control (N=1822) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N=2753) n (%)	Any EvoMab (N=3389) n (%)
Baseline normoglycemia (FBG < 100 mg/dL)	901 (67.1)	1235 (67.8)	1778 (64.6)	2166 (63.9)
Post baseline new onset diabetes	0	1 (0.1)	2 (0.1)	2 (0.1)
Diabetes AE	0	0	0	0
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	0	0	1 (0.1)	1 (0.0)
Concomitant medications used for diabetes	0	1 (0.1)	1 (0.1)	1 (0.0)
Baseline IFG (100 ≤ FBG < 126 mg/dL)	428 (31.9)	570 (31.3)	943 (34.3)	1177 (34.7)
Post baseline new onset diabetes	11 (2.6)	11 (1.9)	29 (3.1)	35 (3.0)

Diabetes AE	3 (0.7)	3 (0.5)	4 (0.4)	4 (0.3)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	11 (2.6)	11 (1.9)	22 (2.3)	28 (2.4)
Concomitant medications used for diabetes	3 (0.7)	3 (0.5)	6 (0.6)	6 (0.5)
Baseline FBG < 126 mg/dL (normoglycemia or IFG)	1329 (99.0)	1805 (99.1)	2721 (98.8)	3343 (98.6)
Post baseline new onset diabetes	11 (0.8)	12 (0.7)	31 (1.1)	37 (1.1)
Diabetes AE	3 (0.2)	3 (0.2)	4 (0.1)	4 (0.1)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	11 (0.8)	11 (0.6)	23 (0.8)	29 (0.9)
Concomitant medications used for diabetes	3 (0.2)	4 (0.2)	7 (0.3)	7 (0.2)

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
Subjects without baseline diabetes mellitus = no diabetes recorded in medical history and no diabetic medication use at baseline. FBG = fasting blood glucose; HbA1c = hemoglobin A1c; EvoMab = Evolocumab. N = number of subjects randomized in the integrated parent analysis set without diabetes mellitus (defined as no diabetes recorded in medical history and no diabetic medication use at baseline);
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects.
Any EvoMab includes any subject with EvoMab as a component of investigational product
Source: modified from Table 5 from Feb 2015 FDA Information Request Response

Using the 4-component definition of new onset diabetes, the subject incidence of new onset diabetes mellitus in the integrated parent studies was similar in subjects with either normoglycemia or IFG who received any evolocumab (1.9%) or any control (1.7%). Not surprisingly, more subjects with baseline IFG (53 subjects [4.6%] any evolocumab, 23 subjects [4.1%] any control) had new onset diabetes mellitus compared with subjects with baseline normoglycemia (11 [0.5%] any evolocumab, 7 [0.6%] any control) (see table below). In the group with IFG (defined as 100 ≤ FBG < 126 mg/dL), there was a slight increase in ≥2 consecutive post-baseline FBG ≥ 126 mg/dL (20, 2.2% in EvoMab vs 8, 1.9% in Placebo vs 8, 1.4% in Any Control). This finding was not seen for diabetes AEs, concomitant medications used for diabetes or post baseline HbA1c ≥ 6.5%. Overall, no notable differences were found in the incidence of new onset of diabetes between the evolocumab and control groups. In the table below, unlike in the previous table using the 3-component definition of new onset diabetes, participants who had HbA1c ≥6.5% at baseline were excluded. For example, there were a total of 2753 participants in the EvoMab 140 mg Q2W/420 mg QM group in the previous table. This number of participants has been reduced to a total of 2730 participants due to the additional requirement that their baseline HbA1c had to be <6.5%.

Table 79: Incidence of New Onset Diabetes Mellitus Incorporating HbA1c ≥ 6.5% (Integrated Parent Analysis Set)

Subjects With	Any Placebo (N=1335) n (%)	Any Control (N=1813) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N=2730) n (%)	Any EvoMab (N=3363) n (%)
Baseline normoglycemia (FBG < 100 mg/dL)	900	1234	1773	2161

	(67.4)	(68.1)	(64.9)	(64.3)
Post baseline new onset diabetes	6 (0.7)	7 (0.6)	11 (0.6)	11 (0.5)
Diabetes AE	0	0	0	0
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	0	0	1 (0.1)	1 (0.0)
Concomitant medications used for diabetes	0	1 (0.1)	1 (0.1)	1 (0.0)
Any post baseline HbA1c ≥ 6.5%	6 (0.7)	6 (0.5)	10 (0.6)	10 (0.5)
Baseline IFG (100 ≤ FBG < 126 mg/dL)	423 (31.7)	564 (31.1)	928 (34.0)	1159 (34.5)
Post baseline new onset diabetes	23 (5.4)	23 (4.1)	42 (4.5)	53 (4.6)
Diabetes AE	3 (0.7)	3 (0.5)	2 (0.2)	2 (0.2)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	8 (1.9)	8 (1.4)	20 (2.2)	26 (2.2)
Concomitant medications used for diabetes	3 (0.7)	3 (0.5)	3 (0.3)	3 (0.3)
Any post baseline HbA1c ≥ 6.5%	18 (4.3)	18 (3.2)	24 (2.6)	31 (2.7)
Baseline FBG < 126 mg/dL (normoglycemia or IFG)	1323 (99.1)	1798 (99.2)	2701 (98.9)	3320 (98.7)
Post baseline new onset diabetes	29 (2.2)	30 (1.7)	53 (2.0)	64 (1.9)
Diabetes AE	3 (0.2)	3 (0.2)	2 (0.1)	2 (0.1)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	8 (0.6)	8 (0.4)	21 (0.8)	27 (0.8)
Concomitant medications used for diabetes	3 (0.2)	4 (0.2)	4 (0.1)	4 (0.1)
Any post baseline HbA1c ≥ 6.5%	24 (1.8)	24 (1.3)	34 (1.3)	41 (1.2)

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
FBG = fasting blood glucose; HbA1c = hemoglobin A1c; EvoMab = Evolocumab. N = number of subjects randomized in the integrated parent analysis set without diabetes mellitus (defined as no diabetes recorded in medical history, no diabetic medication use at baseline, and baseline HbA1c < 6.5%);
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects.
Any EvoMab includes any subject with EvoMab as a component of investigational product
Source: modified from Table 4 from Feb 2015 FDA Information Request Response

The table below presents analyses of the integrated parent studies (12-week studies presented separately from the 52-week study) using the 4-component definition of new onset diabetes mellitus. The HRs ranged from 0.3 to 1.8 and the 95% CIs associated with each HR included 1 for all FBG subgroups.

Table 80: Subgroup Analyses of Incidence of New Onset Diabetes Mellitus Incorporating HbA1c ≥ 6.5% (Integrated Parent Analysis Set)

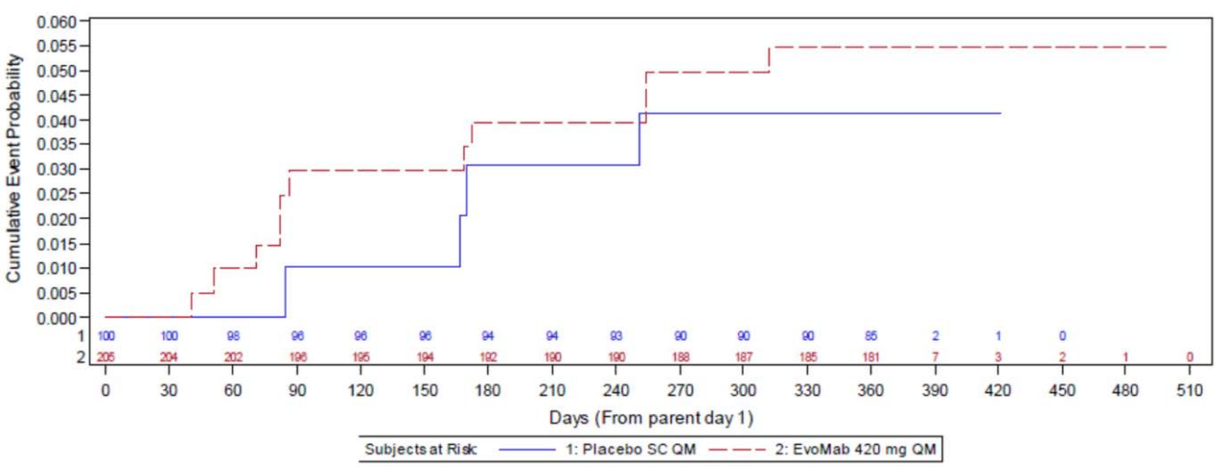
	Control N Events - n (%)	EvoMab N Events – n (%)	Hazard Ratio[a] (CI)
Integrated parent analysis set excluding Study 20110109 (52-week)	Any Control	Any EvoMab	
Baseline normoglycemia	1074 4 (0.4)	1833 2 (0.1)	0.31 (0.06, 1.67)
Baseline IFG	465 9 (1.9)	965 33 (3.4)	1.83 (0.88, 3.83)
Baseline normoglycemia or IFG	1539	2798	1.53

	13 (0.8)	35 (1.3)	(0.81, 2.89)
Study 20110109 (52-week duration)	Placebo SC QM	EvoMab 420 mg QM	
Baseline normoglycemia	160 3 (1.9)	328 9 (2.7)	1.46 (0.40, 5.40)
Baseline IFG	99 14 (14.1)	194 20 (10.3)	0.70 (0.35, 1.39)
Baseline normoglycemia or IFG	259 17 (6.6)	522 29 (5.6)	0.85 (0.47, 1.54)

CI = Confidence Interval; EvoMab = Evolocumab (AMG 145); HbA1c = hemoglobin A1c; IFG = impaired fasting glucose; QM = once monthly; IFG N = number of subjects in the analysis set with IFG at baseline (defined as glucose ≥ 100 mg/dL and ≤ 125 mg/dL, no diabetes recorded in medical history, no diabetic medication use at baseline, baseline HbA1c < 6.5% at [parent] study baseline). Normoglycemic: N = defined as glucose < 100 mg/dL, no diabetes recorded in medical history, no diabetic medication use, and baseline HbA1c < 6.5% at [parent] study baseline).
a The hazard ratio estimate is obtained from a Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer event free survival for evolocumab relative to control or placebo.
Source: modified from Table 6 from Feb 2015 FDA Information Request Response

Time-to-event analyses, including Kaplan-Meier (KM) curves, were conducted for new onset diabetes events, with the time to the event defined as the earliest among the following: time to the adverse event onset date, time to initiation of the first anti-diabetic medication during the study, HbA1c ≥ 6.5% (4-component analyses only), or the first of 2 consecutive FBG measurements ≥ 126 mg/dL. Study 20110109, which had a treatment duration of 1 year, was analyzed separately from the other parent studies, which had treatment durations of approximately 12 weeks. A time-to-event analysis (3-component definition) for new onset diabetes events in the impaired fasting glucose group is shown below.

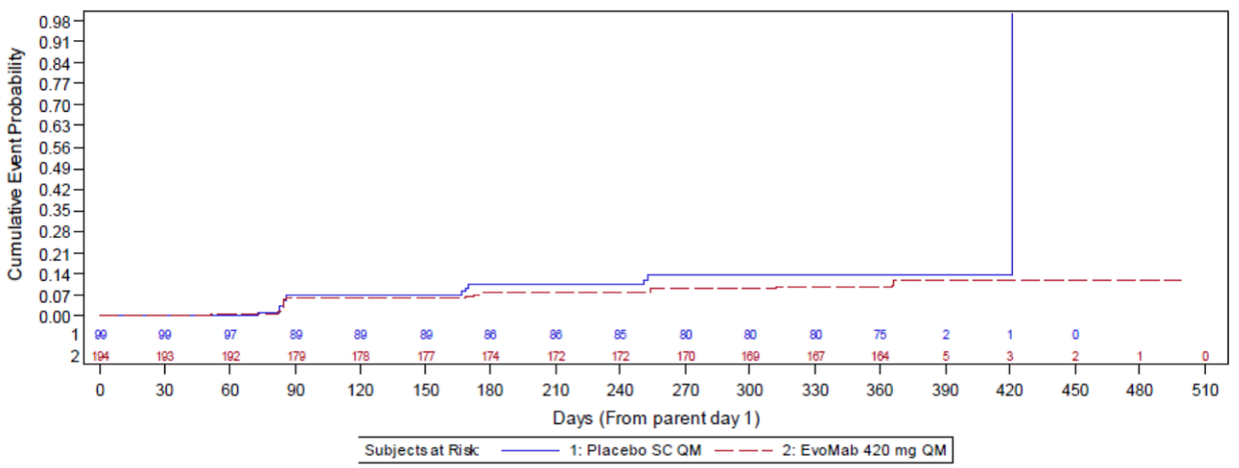
Figure 11: Cumulative Incidence Estimates for New-Onset Diabetes (3-component definition) During Study 20110109: Subjects with Impaired Fasting Glucose and No Diabetes Mellitus at Baseline



EvoMab = Evolocumab; QM = monthly; SC = subcutaneous; IP = investigational product.
New-onset diabetes event is defined as any of the following that happened during parent studies: new-onset diabetes AE, ≥ 2 consecutive post-baseline FBG ≥ 126 mg/dL, or started new anti-diabetic medications.
Estimates are obtained using Kaplan-Meier methods.
Source: Figure 150209q9-6.3.8.from Feb 2015 FDA Information Request Response

A time-to-event analysis using the 4-component definition for new onset diabetes events in Study 20110109 in the impaired fasting glucose group is shown below. This analysis does not show the increase in cumulative incidence that was seen with the 3-component analysis.

Figure 12: Cumulative Incidence Estimates for New-Onset Diabetes (4-component definition) During Study 20110109: Subjects With Impaired Fasting Glucose and no Diabetes Mellitus at Baseline



EvoMab = Evolocumab; QM = monthly; SC = subcutaneous; IP = investigational product.
New-onset diabetes event is to defined as any of the following that happened during parent studies: new-onset diabetes AE, ≥ 2 consecutive post-baseline FBG ≥ 126 mg/dL, started new anti-diabetic medications or at least one post-baseline HbA1c ≥ 6.5%,
Estimates are obtained using Kaplan-Meier methods.
Source: Figure 150209q9-6.4.8.from Feb 2015 FDA Information Request Response

New Onset Diabetes Mellitus: Integrated Year 1 SoC-controlled Period of the Open-label Long-Term Extension Studies

A slightly higher incidence of HbA1c ≥ 6.5% was observed at baseline in subjects randomized to evolocumab plus SoC compared with SoC alone (see table below).

Table 81: Summary of Baseline HbA1c in Subjects without Diabetes Mellitus (Integrated Extension SoC-controlled Period Analysis Set)

	SoC n (%)	EvoMab+SoC n (%)
Subjects Without Baseline Diabetes Mellitus	1257	2550

Baseline normoglycemia (FBG < 100 mg/dL) - N	834	1647
baseline HbA1c ≥ 6.5%	0 (0.0)	4 (0.2)
Baseline IFG (100 <= FBG < 126 mg/dL) - N	412	876
baseline HbA1c ≥ 6.5%	1 (0.2)	14 (1.6)
Baseline FBG < 126 mg/dL (normoglycemia or IFG) - N	1246	2523
baseline HbA1c ≥ 6.5%	1 (0.1)	18 (0.7)

Includes the following studies: 20110110, 20120138.
Subjects without baseline diabetes mellitus = no diabetes recorded in medical history, no diabetic medication use at parent study baseline, and no new onset of diabetes during the parent study. FBG = fasting blood glucose; HbA1c = hemoglobin A1c; IFGT = impaired fasting glucose; EvoMab = Evolocumab; SoC = Standard of Care.
Source: modified from Table 8 from Feb 2015 FDA Information Request Response

Using the 3- or 4-component definition of new onset diabetes mellitus and diabetes mellitus at baseline, no notable differences were observed between treatment groups in the median change from baseline in HbA1c or FBG over time for each baseline FBG subgroup. In the 4-component definition, all post-dose HbA1c medians were ≤ 5.8% for evolocumab plus SoC and ≤ 5.7% for SoC alone. In subjects with baseline IFG, the median post-dose FBG was ≤ 106 mg/dL for evolocumab plus SoC and ≤ 104 mg/dL for SoC alone.

During the year 1 SoC-controlled period and using the 3-component definition of new onset diabetes mellitus, the subject incidence of new onset diabetes mellitus during the year 1 SoC-controlled period was slightly higher in subjects with either normoglycemia or IFG at parent study baseline[69] who received evolocumab plus SoC (1.5%) compared with those who received SoC alone (1.0%) (see table). As expected, more subjects with baseline IFG (29 subjects [3.3%] evolocumab plus SoC, 10 subjects [2.4%] SoC alone) had new onset diabetes mellitus compared with subjects with baseline normoglycemia (9 [0.5%] evolocumab plus SoC, 3 [0.4%] SoC alone). Of note, in the year 1 SoC-controlled period, the SoC and EvoMab+SoC groups were not treated identically as the EvoMab+SoC group had more clinic visits; this may have been a factor in the increased incidence of adverse events in the EvoMab+SoC group.

Table 82: Incidence of New Onset Diabetes Mellitus Without Incorporating HbA1c ≥ 6.5% (Integrated Extension SoC-controlled Period Analysis Set)

Subjects With	SoC (N=1257) n (%)	EvoMab + SoC (N=2550) n (%)
Baseline normoglycemia (FBG < 100 mg/dL)	834 (66.3)	1647 (64.6)
Post baseline new onset diabetes	3 (0.4)	9 (0.5)

69 Subjects included in the analyses for the year 1 SoC-controlled period did not have new onset diabetes mellitus during the parent study.

Diabetes AE	2 (0.2)	3 (0.2)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	0	5 (0.3)
Concomitant medications used for diabetes	1 (0.1)	2 (0.1)
Baseline IFG (100 ≤ FBG < 126 mg/dL)	412 (32.8)	876 (34.4)
Post baseline new onset diabetes	10 (2.4)	29 (3.3)
Diabetes AE	3 (0.7)	11 (1.3)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	8 (1.9)	17 (1.9)
Concomitant medications used for diabetes	1 (0.2)	10 (1.1)
Baseline FBG < 126 mg/dL (normoglycemia or IFG)	1246 (99.1)	2523 (98.9)
Post baseline new onset diabetes	13 (1.0)	38 (1.5)
Diabetes AE	5 (0.4)	14 (0.6)
≥2 consecutive post-baseline FBG ≥ 126 mg/dL	8 (0.6)	22 (0.9)
Concomitant medications used for diabetes	2 (0.2)	12 (0.5)

Includes the following studies: 20110110, 20120138.
Data cutoff date 01JUL2014.
AE = adverse event; FBG = fasting blood glucose; HbA1c = haemoglobin A1c; IFG = impaired fasting glucose; N = number of subjects randomized in the integrated extension SoC-controlled period analysis set without diabetes (defined as no diabetes recorded in medical history, no diabetic medication use at parent study baseline and no new onset of diabetes during the parent study); EvoMab = Evolocumab (AMG 145); SoC = Standard of Care
Source: modified from Table 10 from Feb 2015 FDA Information Request Response

Using the 4-component definition of new onset diabetes mellitus, the subject incidence of new onset diabetes mellitus was similar in subjects with either normoglycemia or IFG at parent study baseline who received evolocumab plus SoC (2.9%) compared with those who received SoC alone (2.7%). More subjects with baseline IFG (53 subject [6.3%] evolocumab plus SoC, 21 subjects [5.2%] SoC alone) had new onset diabetes mellitus compared with subjects with baseline normoglycemia (18 [1.1%] evolocumab plus SoC, 12 [1.4%] SoC alone).
Using the 3-component definition of new onset diabetes mellitus during the year 1 SoC-controlled period, HRs ranged from 1.4 to 1.5 and 95% CIs each included 1.Using the 4-component definition of new onset diabetes mellitus, the HRs varied and ranged from 0.8 to 1.2; wider 95% CIs associated with each HR included 1 for all FBG subgroups (see table).

Table 83: Subgroup Analyses of Incidence of New Onset Diabetes Mellitus (Integrated Extension SoC-controlled Period Analysis Set)

	SoC N Events - n (%)	EvoMab + SoC N Events – n (%)	Hazard Ratio[a] (CI)
Incorporating HbA1c ≥ 6.5%			
Baseline normoglycemia	831 12 (1.4)	1633 18 (1.1)	0.76 (0.37, 1.58)
Baseline IFG	403 21 (5.2)	845 53 (6.3)	1.23 (0.74, 2.04)

Baseline normoglycemia or IFG	1234 33 (2.7)	2478 71 (2.9)	1.08 (0.71, 1.63)
Without incorporating HbA1c ≥ 6.5%			
Baseline normoglycemia	834 3 (0.4)	1647 9 (0.5)	1.52 (0.41, 5.63)
Baseline IFG	412 10 (2.4)	876 29 (3.3)	1.39 (0.68, 2.85)
Baseline normoglycemia or IFG	1246 13 (1.0)	2523 38 (1.5)	1.45 (0.77, 2.73)

Data cutoff date 01JUL2014.
CI = Confidence Interval; EvoMab = Evolocumab (AMG 145); HbA1c = hemoglobin A1c; IFG = impaired fasting glucose; SoC = standard of care
N = number of subjects in the analysis set with normoglycemia at baseline (defined as glucose < 100 mg/dL, no diabetes recorded in medical history, no diabetic medication use, no new onset of diabetes during the parent study, and, for analyses incorporating HbA1c only, baseline HbA1c < 6.5% at parent study baseline).
a The hazard ratio estimate is obtained from a Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer event free survival for evolocumab + SoC relative to SoC alone.
Source: modified from Table 11 from Feb 2015 FDA Information Request Response

In conclusion, new onset diabetes mellitus, HbA1c, FBG concentrations, and diabetes-related adverse events were assessed for the parent studies (6026 subjects total) and the year 1 SoC-controlled period of the long-term extension studies (4465 subjects total). The following findings were observed:

- There were small differences in baseline characteristics of evolocumab and control groups in both study periods, with a slightly higher incidence of IFG and baseline HbA1c ≥ 6.5% in subjects randomized to evolocumab.
- In the integrated parent studies, using the 3-component definition of new onset diabetes mellitus, in the group with IFG (defined as 100 ≤ FBG < 126 mg/dL), there was a small increase in post baseline new onset diabetes in the EvoMab group (29, 3.1% in EvoMab vs 11, 2.6% in Placebo vs 11, 1.9% in Any Control). This was not seen using the 4-component definition (42, 4.5% in EvoMab vs 23, 5.4% in Placebo vs 23, 4.1% in Any Control).
- In the baseline impaired fasting glucose group, cumulative incidence estimates for new-onset diabetes in Study 20110109 were increased in the EvoMab group as compared to the placebo group using the 3-component definition; this was not seen using the 4-component definition.
- During the year 1 SoC-controlled period and using the 3-component definition of new onset diabetes mellitus, the subject incidence of new onset diabetes mellitus was slightly higher in subjects with either normoglycemia or IFG at parent study baseline who received evolocumab plus SoC (1.5%) compared with those who received SoC alone (1.0%). This finding was primarily due to more subjects with baseline IFG in the evolocumab plus SoC group (29 subjects, 3.3%) as compared to the SoC alone group (10 subjects, 2.4%) who developed new onset diabetes mellitus. This was also seen in the 4-component definition in subjects with baseline IFG: 53 subjects (6.3%) in the evolocumab plus SoC developed new onset diabetes as compared to 21 subjects (5.2%) in the SoC alone group.

A potential signal for new onset diabetes with evolocumab use, particularly with subjects with baseline impaired fasting glucose, is possible from these analyses. This potential for an increased incidence of new onset diabetes should be explored in the on-going CVOT (FOURIER).Of note, with statins, we believe that the modest diabetogenic effect is outweighed by the CV event reduction, which has been shown in CV outcomes trials in patients with diabetes.

Musculoskeletal and Connective Tissue Disorders

In the integrated parent trials, adverse events for the Musculoskeletal and Connective Tissue Disorders system organ class were reported in 466 (14.6%) participants in the evolocumab group (140mg Q2W or 420 mg QM) and 284 (13.7%) participants in the any control group. The most common adverse events in the evolocumab group and any control group were back pain (3.1% and 2.7%), myalgia (2.2% and 2.6%), and arthralgia (2.2% and 2.2%). In the year 1 SoC-controlled period, 541 (19.1%) participants and 216 (15.2%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were arthralgia (3.4% and 2.5%), back pain (3.1% and 2.5%), myalgia (2.5% and 2.4%), and pain in extremity (2.5% and 1.5%). In the year 2+ OLE period, 268 (28.1%) participants reported an adverse event. The most common adverse events were arthralgia (6.7%), back pain (6.6%), and pain in extremity (4.6%).

Because muscle-related adverse events have been reported with approved lipid-lowering therapies, broad and narrow MedDRA SMQ search strategies were used to assess safety risks with evolocumab therapy. Using the rhabdomyolysis-myopathy SMQ (narrow search) strategy, only 1 event was found in the phase 2 and 3 trials (a case of myopathy occurring in the year 1 SoC-controlled period in a participant receiving SoC only).

In the integrated parent studies, serious adverse events for the Musculoskeletal and Connective Tissue Disorders system organ class were reported in 9 (0.2%) participants in the any evolocumab group and 2 (0.1%) participants in the any control group. Back pain was the only serious adverse event in this system organ class to be reported in > 1 participant during the parent studies (3 participants in the any evolocumab group). In the year 1 SoC-controlled period, 19 (0.7%) participants and 5 (0.4%) participants reported a serious adverse event in the evolocumab plus SoC group and SoC alone group, respectively. Osteoarthritis was the only serious adverse event in this system organ class to be reported in > 1 participant [9 (0.3%) participants in the evolocumab+SoC group and 2 (0.1%) participants in SoC only]. In the year 2+ OLE period, 7 (0.6%) reported a serious adverse event.

The following three cases report episodes of rhabdomyolysis and/or CK> 10 x ULN in healthy individuals in the Phase 1 trials suggests that evolocumab can contribute to muscle symptoms/CK increase when used as monotherapy without the potential confounding use of concomitant statin therapy.

In the phase 1 Study 20120133 (a PK equivalence study with PFS and AI/pen), a non-serious case of rhabdomyolysis was reported in a 26-year-old black male (healthy volunteer, 13366003015). This participant had elevated CK levels at screening (510 IU/L) (this value was within the protocol pre-specified CK limits of 3 x ULN) and at baseline (428 IU/L), and slightly elevated creatinine levels at screening and baseline (119.3 µmol/L [1.3 mg/dL] both times). He received 2 doses of evolocumab 140 mg separated by approximately 8 weeks. On the day of the second and final dose of evolocumab, his CK was 327 IU/L and creatinine was 120.2 µmol/L. At the end-of-study visit (56 days after the second dose), the adverse event of rhabdomyolysis was reported, at which time, his CK levels were 3058 IU/L (> 15 x ULN). His CK levels peaked (12440 IU/L,> 62 x ULN) 3 days later. Approximately 2 weeks after the peak CK, the adverse event was reported to be resolved, and the CK levels had decreased to 453 IU/L. The rhabdomyolysis adverse event did not require hospitalization and was not associated with myopathy. No other adverse events were reported for this participant.

In another phase 1 study, there were two healthy individuals on evolocumab monotherapy who developed CK> 10xULN. Study 20110121 was a phase 1, single center study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab after single subcutaneous (SC) administration in healthy Japanese subjects. Japanese subjects were randomized 6:2 to receive evolocumab or matching placebo SC at 70, 210, or 420 mg and 1 cohort of Caucasian subjects was randomized 6:2 to receive evolocumab or matching placebo SC at 210 mg. Two subjects experienced creatine kinase (CK) shifts to > 10 x ULN:

- Subject 12166001025 (Caucasian, evolocumab 210 mg) had elevated CK value of 750 U/L on day 22 that reached 10248 U/L (51 x ULN) on day 24 (unscheduled visit) and was 4286 U/L (21 x ULN) on day 29. At day 36, his CK level neared normal levels, at 205 U/L, and was within normal range at subsequent visits. His CK level returned to baseline 21 days after the start of the adverse event. Creatinine remained within normal range throughout. This subject had an associated activity of walking at a car show, which this reviewer believes is unlikely to have precipitated such a CK rise. The CK elevation in Subject 12166001025 was considered a treatment related adverse event.

- Subject 12166001065 (Japanese, evolocumab 420 mg) had a slightly elevated CK value of 219 U/L (1.1 x ULN) on day 71 that reached 3486 U/L (17.4 x ULN) at day 85 and was within normal limits (162 U/L) 1 week later. Creatinine

remained within normal range throughout. This subject had an associated activity of bicycle riding.

Serious adverse events of increased blood creatine phosphokinase were reported in 1 evolocumab monotherapy participant (10931202010) and 1 placebo participant (11742008006). For the participant on evolocumab, the serious adverse event (with a CK peak 2138 U/L from baseline 137 U/L at the time of reporting) was considered to be related to hypothyroidism; this case is discussed in more detail in Section 5.3.1 Trial 20110109: DESCARTES.

Creatine Kinase Laboratories
In the integrated parent studies, 27 (0.7%) participants in the any evolocumab group and 14 (0.7%) participants in the any control group had CK > 5 x ULN at any postbaseline visit. For CK > 10 x ULN, the incidence was also the same between the groups: 9 (0.2%) participants in the any evolocumab group and 5 (0.2%) participants in any control group.

In the year 1 SoC-controlled period, 14 (0.5%) participants in the evolocumab plus SoC group and 17 (1.2%) participants in the SoC alone group had CK > 5 x ULN at any postbaseline visit. For CK > 10 x ULN, the incidence was also low and similar between the groups: 5 (0.2%) in the evolocumab plus SoC group and 8 (0.6%) in the SoC alone group.

Analyses of CK abnormalities were done by therapeutic settings (monotherapy, combination therapy and statin intolerant). The participant incidence of CK abnormalities was low and similar between the groups.

An analysis was done by Amgen to identify participants who had normal baseline CK levels, a post baseline CK elevation > 5 x ULN, and a concurrent muscle-related adverse event, in order to search for clinically meaningful muscle events. There were 51 participants with CK elevation > 5 x ULN (normal at baseline) and 613 participants with an adverse event from the HLGT “Muscle Disorders.” Of those identified participants, 6 had both a muscle adverse event and an elevated CK. Four of these 6 participants were on evolocumab treatment (2 myalgia, 1 muscle spasms, and 1 myositis) and 2 were on SoC (2 muscle spasms). Of the 4 cases occurring during treatment with evolocumab, evolocumab was continued in all but 1 participant, who was participating in the statin intolerance trial (20090159). In 5 of the 6 cases for which post peak CK values were available, serum CK improved. For the other case (on statin only), the final reported CK level was the peak CK. Creatinine was normal for all 6 participants at the time of and post CK elevation. One of the 6 events was reported by the site as likely due to hard physical labor preceding the CK elevation (participant on evolocumab only), and in 2 other cases the adverse event duration did not overlap the CK elevation (1 on evolocumab plus statin and 1 on statin only). Of the other 3 participants, 2 were treated with statins.

In the phase 2 and phase 3 integrated trials, 14 participants during the integrated parent studies [9 (0.2%) in the any evolocumab group and 5 (0.2%) in any control group], 13 during the year 1 SoC-controlled period [5 (0.2%) in the evolocumab plus SoC group and 8 (0.6%) in the SoC alone group], and 6 (0.6%) during the year 2+ OLE period had a postbaseline CK > 10 x ULN. Most of these participants had confounding factors (such as concurrent hypothyroidism, muscle and joint injuries, tendonitis, and concomitant statin therapy) that may have contributed to the events. Some of the participant narratives for CK > 10 ULN are included below:

- Subject 15856001005, a 25-year-old male, was enrolled in Year 2+ OLE study 20110110, IP evolocumab QM 420 mg (rolled over from Parent study 20090158, IP placebo, and Year 1 SoC-controlled study 20110110, IP SoC only). Baseline (BL) blood creatine phosphokinase (CK) levels for this subject were within normal limits (WNL). The parent study BL CK was136 U/L on 16 January 2012, and BL CK for the year 2+ OLE was 124 U/L on 13 April 2013. During the Year 1 SoC-controlled study, the subject was on SoC only and continued to have blood lab values monitored in 4 to 12 week intervals. The subject's CK levels were WNL during the Year 1 SoC-controlled study. The first dose of evolocumab in the year 2+ OLE was on 8 May 2013 (week 68 of the entire study). Approximately 20 weeks later, on 30 September 2013 (week 88), this subject's CK increased to 2853 U/L (14.3 x ULN). This was accompanied by an increase in AST (97 U/L) 2.5X upper limit of normal (ULN) and ALT above ULN (57 U/L). Creatinine was 0.8 mg/dL (WNL). Ten days later on, the CK level had decreased to 425 U/L (2.1 x ULN), and on the next visit, 20 December 2013 the CK level was WNL (141 U/L). ALT (28 U/L), AST (24 U/L), and creatinine (0.1 mg/dL) were all WNL on this date. On the follow up visit 14 March 2014 (week 100) the CK was WNL (100 U/L). There was no pertinent medical history, however twice during the study the subject reported musculoskeletal pain, in hip (March 3013) and in feet (May 2013). Pertinent concomitant medication included atorvastatin 80 mg and acetaminophen with phenylpropanolamine for flu-like symptoms that occurred during the period of increased CK. The subject continued treatment with evolocumab.

- Subject 15958001002, a 48-year-old male, was enrolled in Parent study 20090159 (statin-intolerant trial), IP evolocumab QM 350 mg. The subject's BL CK was 75 U/L (WNL) on 15 December 2011, also the date of the first dose. Twelve days after the first dose of evolocumab, the subject's CK increased to 2030 U/L (10.1 x ULN). Creatinine was 0.8 mg/dL (WNL). AST was 60 U/L (1.6 x ULN). An adverse event myositis, grade 4, was reported on 24 December 2011, 9 days after the first dose of evolocumab. On the next follow up visit, 2 January 2012, six days after the peak measurement, CK (132 U/L) and AST (21 U/L) levels returned to WNL and the myositis event resolved. Pertinent concomitant medications included ezetimibe, rosuvastatin 5 mg and acetylsalicylic acid. The subject discontinued rosuvastatin and evolocumab. The investigator assessed the adverse event myositis as related to IP.

- Subject 11466014002, a 59-year-old female, was enrolled in the parent study 20110114, IP evolocumab Q2W 140 mg. The BL CK was 82 U/L (WNL) on 25 February 2013, which was also the first dose date of evolocumab Q2W 140 mg. On 19 April 2013, the subject had surgery for repair of her Achilles tendon. The patient received on [redacted] (b) (6) fentanyl, marcaine, epinephrine, midazolam, propofol, ketorolac, lidocaine, and oxycodone for the surgery to repair the Achilles tendon. Four days later, 2 weeks after the last dose of evolocumab, the subject's CK was 2246 U/L (13.3 x ULN), and this was reported as the adverse event blood creatine phosphokinase increased. On the same day, the adverse event hepatic enzyme increased was reported due to AST 422 U/L (>10x ULN) and ALT 493 U/L (>10x ULN). Creatinine was WNL (0.82 mg/dL). At the follow up visits on 29 April 2013 (week 8) and 29 May 2013 (visit week 12) the CK were 221 U/L (1.3 x ULN) and 73 U/L (WNL) respectively. The hepatic enzymes also dropped on these 2 follow up visits to close to WNL

and by the week 12 visit, CK, AST, and ALT were WNL. An SAE for Hepatic enzyme increased was also recorded for this subject for study 20110114. The adverse events resolved on 29 May 2013. The subject had a medical history of hypothyroidism, enthesopathy, fibromyalgia and muscular weakness, hypertension, aortic aneurism, a renal transplant, depression and gastroesophageal reflux disease. Pertinent concomitant medication included levothyroxine, pregabalin, dexamethasone, acetylsalicylic acid. The subject discontinued treatment with evolocumab.

Nervous System Disorders and Psychiatric Disorders

In the integrated parent trials, adverse events for the Nervous System Disorders system organ class were reported in 246 (7.7%) participants in the evolocumab group (140mg Q2W or 420 mg QM) and 164 (7.9%) participants in the any control group. The most common adverse events in the evolocumab group and the any control group were headache (3.1% and 3.2%), dizziness (1.7% and 1.6%), and paraesthesia (0.6% and 0.4%).

In the year 1 SoC-controlled period, 239 (8.4%) participants and 100 (7.0%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were headache (2.9% and 1.7%), dizziness (1.6% and 1.6%), and paraesthesia (0.6% and 0.5%).

In the year 2+ OLE period, 119 (12.5%) participants reported an adverse event, and the most common adverse events were headache (3.4%), dizziness (2.8%), and hypoaesthesia (1.4%).

During the phase 2 and 3 evolocumab studies (using the 120-day Safety Update 01 July 2014 data cutoff), a total of 5 subjects developed intracranial hemorrhage adverse events; 2 subjects (< 0.1%) were receiving evolocumab (1 event in the year 1 SoC-controlled period and 1 event in the year 2+ OLE period), and 3 subjects (0.1%) were receiving placebo or standard of care (SoC) alone (1 event in the integrated parent studies and 2 events in the year 1 SoC-controlled period) at the time of the event. The incidence of subjects who reported intracranial hemorrhage adverse events in any treatment group was low (5 out of 6026 subjects who were exposed to study treatment). None of the intracranial hemorrhage events was fatal. These 5 events are summarized as follows:

- All of the intracranial hemorrhage events except for the subdural hemorrhage were serious adverse events. The subdural hemorrhage occurred secondary to a serious adverse event of skull fracture.

- Both subjects who were receiving evolocumab plus SoC (Subjects 10916300060 and 15522001013) were withdrawn from investigational product due to the event; in 1 case the withdrawal was at the subject’s request.

- Three of the 5 subjects (10957204025 [SoC alone], 15522001013 [evolocumab plus SoC], 23134023001 [SOC alone]) had LDL-C levels < 40 mg/dL at some time point before the intracranial hemorrhage event. In all 3 subjects, LDL-C < 40 mg/dL occurred intermittently, and only 1 subject experienced consecutive low-LDL-C measurements. The time between the most recent LDL-C < 40 mg/dL and event onset for these subjects ranged from 6.5 to 14 months.

- Confounding factors in the 5 subjects included skull fracture secondary to a fall subsequent to reported alcohol consumption (10966425008), recent coronary revascularization procedure and initiation of clopidogrel therapy (10957204025), event onset while smoking crack cocaine (10916300060), hypertension and identification of right middle cerebral artery aneurysm (23134023001), and hypertension and previous stroke (15522001013)

A safety signal for intracranial hemorrhage with evolocumab use was not identified in this submission.

In the integrated parent studies, adverse events for the Psychiatric Disorders system organ class were reported in 85 (2.2%) participants in the any evolocumab group and 41 (2.0%) participants in the any control group. The most common adverse events in the any evolocumab group and the any control group were insomnia (0.7% and 0.5%), anxiety (0.5% and 0.2%), and depression (0.3% and 0.6%).

In the year 1 SoC-controlled period, 94 (3.3%) participants and 33 (2.3%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were insomnia (1.2% and 0.9%), depression (0.8% and 0.6%), and anxiety (0.8% and 0.4%).

In the year 2+ OLE period, 50 (5.2%) participants reported an adverse event, and the most common adverse events were depression (1.8%), insomnia (1.7%), anxiety (1.4%), libido decreased (0.3%), and sleep disorder (0.3%).

One of the theoretical safety issues is related to cognitive function in patients who achieve very low levels of circulating LDL-cholesterol with PCSK9 therapy. To examine this more thoroughly, a search was done of neurocognitive-related adverse event terms. The following is a list of the High Level Group Terms (HLGT) that was used:

- deliria (including confusion)
- cognitive and attention disorders and disturbances
- dementia and amnestic conditions
- disturbances in thinking and perception
- mental impairment disorders

For the integrated parent studies, 11 participants reported neurocognitive adverse events, and of these, 5 (0.1%) were in the any evolocumab group and 6 (0.3%) were in the any control group. The results are summarized in the table below. One event of delirium in a participant (15566056014) who received evolocumab 140 mg Q2W was considered serious due to a prolongation of hospitalization; this participant had been in a traffic accident and had alcohol withdrawal syndrome. Overall, the number of events was small and no notable differences were evident among the treatment groups.

Table 84: Adverse Events Related to Neurocognitive Function during the Parent Studies by High Level Group Term and Preferred Term (IPAS)

High Level Group Term Preferred Term	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)	Any EvoMab (N = 3946) n (%)
Number of subjects reporting adverse events	3 (0.2)	6 (0.3)	5 (0.2)	5 (0.1)
Deliria (incl confusion)	1 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Delirium	0	0	1 (0.0)	1 (0.0)
Disorientation	1 (0.1)	2 (0.1)	1 (0.0)	1 (0.0)
Mental impairment disorders	2 (0.1)	4 (0.2)	3 (0.1)	3 (0.1)
Amnesia	0	0	2 (0.1)	2 (0.1)
Memory Impairment	1 (0.1)	1 (0.0)	1 (0.0)	1 (0.0)
Cognitive Disorder	0	1 (0.0)	0	0
Dementia With Lewy Bodies	1 (0.1)	1 (0.0)	0	0
Disturbance In Attention	0	1 (0.0)	0	0

N = number of subjects randomized in the integrated parent analysis set (IPAS); EvoMab = Evolocumab; HLGT = High Level Group Term; Q2W = every 2 weeks (subcutaneous) and QM = monthly (subcutaneous).
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
Searched HLGT terms are deliria (incl confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects.
Any EvoMab includes any subject with EvoMab as a component of investigational product.
Coded using MedDRA version 17.0.
Source: Modified from ISS Table 14-6.4.402 and Summary Clinical Safety Table 65.

For the year 1 SoC-controlled period, 16 (0.6%) participants in the evolocumab plus SoC group and 3 (0.2%) in the SoC alone group reported 22 neurocognitive adverse events (see table). The number of events was small but there was slightly more

participants on EvoMab for both the Parent Study and the extended study with neurocognitive adverse events (13, 0.7%) than the other groups.

Table 85: Adverse Events Using HLGT Related to Cognitive Function During the Extension Studies SoC-Controlled Period by High Level Group Term and Preferred Term (IECAS)

	Control in Parent Study		EvoMab in Parent Study		All	
High Level Group Term Preferred Term	SoC (N = 472) n (%)	EvoMab + SoC (N = 943) n (%)	SoC (N = 947) n (%)	EvoMab + SoC (N = 1890) n (%)	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)
Number of subjects reporting adverse events	1 (0.2)	3 (0.3)	2 (0.2)	13 (0.7)	3 (0.2)	16 (0.6)
Deliria (incl confusion)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)
Confusional State	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Disorientation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Mental impairment disorders	1 (0.2)	2 (0.2)	2 (0.2)	12 (0.6)	3 (0.2)	14 (0.5)
Memory Impairment	1 (0.2)	2 (0.2)	1 (0.1)	5 (0.3)	2 (0.1)	7 (0.2)
Amnesia	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)
Dementia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Mental Impairment	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Dementia Alzheimer's Type	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)

N = number of subjects randomized in the integrated extension SoC-controlled period analysis set (IECAS); EvoMab = Evolocumab; HLGT = High Level Group Term; SoC = Standard of Care. Includes the following studies: 20110110, 20120138. Searched HLGT terms are deliria (incl confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.
Coded using MedDRA version 17.0.
Source: Modified from ISS Table 14-6.4.405 and Summary Clinical Safety Table 66.

All events were reported as grade 1 or 2 in severity except for 1 event of grade 3 event of mental impairment that occurred in a participant (15566064005) who had previously reported a grade 1 event of mental impairment. This participant had recurrent events of cyclical decreased mental acuity that were considered by the investigator to be possibly related to evolocumab; the participant had a history of depression and was taking concomitant alprazolam and atorvastatin. The first event of mental impairment (grade 1) occurred on day 117 in the extension study and resolved 187 days later; the second event of mental impairment (grade 3) occurred on day 304 of the extension study and resolved after 18 days.

Thirteen of the 16 participants in the evolocumab plus SoC group had at least 1 risk factor associated with neurocognitive events, such as previous memory loss, history of depression, concurrent statins, benzodiazepine use, gabapentin use, and topiramate use. Treatment with evolocumab was continued without interruption after 14 of the 19 neurocognitive adverse events and was interrupted and restarted after 3 of the 5 remaining events. Of these 3 events, 1 event (memory impairment) was ongoing as of the 01 April 2014 data cutoff date (evolocumab was continued), 1 event (mental impairment) resolved 18 days after the event occurred (evolocumab was withheld), and the remaining event (mental impairment) resolved in 64 days

(evolocumab was continued). Of the 14 events for which evolocumab dosing was not interrupted, 9 events were ongoing as of the data cutoff date, and the remaining 5 events resolved 1 to 187 days after the event occurred.

Analyses of the neurocognitive adverse events were performed for LDL-C subgroups. This is discussed in Section 7.4.1.3 LDL-C Subgroup.

Renal and Urinary Disorders

In the integrated parent trials, adverse events for the Renal and Urinary Disorders system organ class were balanced between the groups: 58 (1.5%) participants in the any evolocumab group and 24 (1.2%) participants in the any control group, of which the most common adverse events in the any evolocumab group and any control group were hematuria (0.3% and 0.3%), nephrolithiasis (0.3% and 0.1%), and pollakiuria (0.2% and 0.1%). However, serious adverse events for this system organ class were reported in 4 (0.1%) participants in the any evolocumab group (glomerulonephritis acute, glomerulonephritis minimal lesion, IgA nephropathy, and renal failure acute) and no participants in the any control group. Narratives for these SAEs are in Section 9.11 A Selection of Narratives of Renal Adverse Events

In the year 1 SoC-controlled period, adverse events were also balanced: 47 (1.7%) participants and 29 (2.0%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were hematuria (0.4% and 0.2%) and nephrolithiasis (0.2% and 0.4%). Six (0.2%) participants reported a serious adverse event in the evolocumab plus SoC group (nephrolithiasis, urinary incontinence, calculus ureteric and renal failure acute) and 1 (0.1%) participant in the SoC alone group (renal failure acute).

A total of 4 participants reported adverse events of proteinuria. In the integrated parent trials, there was one participant in the any evolocumab group and 1 in the any control group—both had proteinuria at baseline. In the year 1 SoC-controlled period, there were 2 participants and both received evolocumab plus SoC. All the proteinuria events were grade 1 or 2, time to onset of the proteinuria events ranged from 1 to 97 days and all continued IP.

Renal-related Laboratories

In the integrated parent trials

- eGFR: The mean change from baseline of eGFR at Week 12 was -0.2 mL/min/1.73 m^2 for both the evolocumab group (140 mg Q2W or 420 mg QM) and the any control group; at Week 52 it was -0.6 mL/min/1.73 m^2 for the

evolocumab group (140 mg Q2W or 420 mg QM) and 1.3 mL/min/1.73 m^2 for the any control group.

- Proteinuria: Of the participants who had no proteinuria at baseline, 159 (5.4%) participants in the evolocumab group (140 mg Q2W or 420 mg QM) and 102 (5.3%) in the any control group had postbaseline proteinuria. Of the participants who had proteinuria at baseline, 82 (39.4%) participants in the evolocumab group (140 mg Q2W or 420 mg QM) and 42 (33.6%) in the any control group had postbaseline proteinuria. Eighty-nine (2.3%), 6 (0.2%), and 1 (< 0.1%) participants had shift in proteinuria from a negative baseline to postbaseline 1+, 2+, and 3+, respectively in the any evolocumab group compared with 44 (2.1%), 4 (0.2%), and 1 (< 0.1%) participants in the any control group.

In the year 1 SoC-controlled period

- eGFR: The mean change from baseline of eGFR at Week 24 (~75% of EvoMab and control group has data at this time point) was -0.5 mL/min/1.73 m2 for the evolocumab + SoC group and -0.4 mL/min/1.73 m2 for the SoC group. The Week 52 data is similar for both groups.

- Proteinuria: Of the participants who had no proteinuria at baseline, 217 (8.4%) participants in the evolocumab plus SoC group and 108 (8.3%) participants in SoC alone group had postbaseline proteinuria in the year 1 SoC-controlled period. One hundred three (3.6%), 15 (0.5%), and 2 (0.1%) participants in the evolocumab plus SoC group had shift in proteinuria from a negative baseline to postbaseline 1+, 2+, and 3+, respectively, compared with 61 (4.3%), 6 (0.4%), 1 (0.1%) participants in the SoC alone group.

Analyses of proteinuria were done by therapeutic settings (see table). The analyses were overall consistent across the monotherapy and combination therapy trials but there were imbalances in the statin-intolerant group during the year 1 SoC-controlled period.

Table 86: Analysis of Subject Incidence of Proteinuria in Subjects With No Baseline Proteinuria Across Therapeutic Settings

	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)
	Any Control n (%)	Any EvoMab n (%)	SoC n (%)	EvoMab + SoC n (%)	EvoMab + SoC n (%)
MONOTHERAPY	N = 480	N = 651	N = 264	N = 485	N = 258
Postbaseline proteinuria	23 (5.1)	31 (5.2)	17 (7.0)	40 (8.9)	1 (0.4)
COMBINATION THERAPY	N = 1466	N = 2965	N = 1028)	N = 2101	N = 585
Postbaseline proteinuria	72 (5.4)	151 (5.6)	85 (9.0)	146 (7.6)	1 (0.2)
STATIN INTOLERANT	N = 134	N = 330	N = 127	N = 247	N = 111
Postbaseline proteinuria	7 (5.8)	16 (5.4)	6 (5.1)	31 (14.0)	0 (0.0)

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; OLE = open-label extension; SoC = standard of care
[a] Included the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product.
[b] Includes the following studies: 20110110, 20120138
[c] Includes the following studies: 20110110, 20120138
Source: Table 88 of Summary of Clinical Safety

Increased Proteinuria in Statin-intolerant Subjects in Year 1 OLE Study
The subjects in the statin-intolerant trials, as compared to the monotherapy and statin combination therapy trials, were older, were more likely to be at high or moderately high CHD risk, and had a higher incidence of diabetes and hypertension. In this population with more CV risk factors, the incidence of proteinuria was balanced in the integrated parent studies in statin-intolerant subjects (16, 5.4% EvoMab vs 7, 5.8% Any Control). However, an increased incidence of proteinuria in statin intolerant participants during the year 1 SoC-controlled period was reported in the evolocumab group (31, 14.0%) as compared to the SoC group (6, 5.1%) (data cutoff date 01 April 2014). Data from the 120-day Safety Update showed a continued imbalance in proteinuria during the year 1 SoC-controlled period for subjects from the statin-intolerant studies (33 [14.6%] subjects receiving evolocumab plus SoC and 7 [5.7%] subjects receiving SoC alone; data cutoff date 01 July 2014. In the open-label extension year 1 SoC-controlled period, urine protein was measured twice through urine dipstick testing in Study 20110110 (at enrollment and week 52) and 4 times in Study 20120138 (at enrollment and at weeks 12, 24, and 48). Unscheduled repeat testing due to positive urine protein results was not routinely performed. Only dipstick urinalyses were obtained and quantitative measurements (e.g., urinary protein/creatinine ratios) were not performed. Of the 33 subjects from the 120-day

safety update with proteinuria on EvoMab, 13 subjects had no subsequent testing after the positive result in the OLE year 1 study. In the 20 evolocumab plus SoC-treated, statin-intolerant subjects for whom repeat testing after a positive result was available, 16 subjects had resolution of the proteinuria (transient events) on subsequent testing in the OLE year 1 study. Two subjects had episodic proteinuria, which initially resolved but had subsequent positive results. Proteinuria persisted in 2 of the 33 subjects. Both subjects had potential confounding factors:

- 1 subject had trace proteinuria at baseline in the parent study. This subject's first positive protein result occurred at the OLE week 0 visit on the same date as initiating evolocumab following placebo in the parent study. The subject had received placebo in the parent study and had a history of chronic kidney disease, hypertension, hepatitis C and HIV
- 1 subject had trace proteinuria at baseline in the parent study and a history of renal cancer, a nephrectomy and hypertension.

During the year 1 SoC-controlled period, for subjects with statin intolerance who had baseline proteinuria (≥ 1+) and a later postbaseline negative or trace result during the study, the incidence was 38% in the evolocumab plus SoC group and 40% in the SoC alone group.

Of the 33 statin-intolerant subjects in the evolocumab plus SoC group, 26 subjects had confounding factors for the development of proteinuria in either their documented medical history or as adverse events. The most common confounding factors among these subjects were a medical history of diabetes and/or hypertension (23/33 subjects had either a history of hypertension or diabetes: 11 had diabetes; 22 had hypertension; 10 had both diabetes and hypertension.). Additional confounding factors included a medical history of microalbuminuria, nephrolithiasis, viral infection (including HIV and hepatitis C) and chronic kidney disease. Four subjects also had adverse events at the time of the proteinuria which may have contributed. These adverse events included a worsening of diabetes, hypertension, recent upper respiratory infection, and recent viral infection. Twenty-nine subjects had 1+ proteinuria and 4 subjects had 2+ proteinuria. All 4 subjects with 2+ proteinuria had confounding factors: 1 of these subjects had diabetes, hypertension and non-steroidal anti-inflammatory drug (NSAID) use, and the remaining 3 subjects had a history of hypertension, one of whom also had a history of diabetes. Two of these 3 subjects resolved on repeat testing; the remaining subject did not have a repeat urine protein test.

Of the 7 subjects in the SoC alone group with negative or trace proteinuria at baseline who experienced proteinuria post baseline, all were 1+. Three cases resolved on repeat testing and 4 cases had no repeat testing in the OLE year 1 study as of 01 July 2014. Four subjects in this group had potential confounding factors which included a history of hypertension, diabetes, nephrolithiasis, or NSAID use.

While the incidence of proteinuria was balanced in the integrated parent studies in subjects with statin-intolerance, there was a small but greater incidence of proteinuria in the statin-intolerant subjects who had no baseline proteinuria in the evolocumab plus SoC group, compared with the SoC alone group. Of note, there were no nonclinical concerns for renal toxicity or proteinuria.

Increased Proteinuria in Diabetic Subjects in Year 1 OLE Study
The incidence of proteinuria in diabetic subjects was numerically smaller in the EvoMab group in the integrated parent studies (29, 6.1% EvoMab vs 21, 9.4% Any Control). In the OLE year 1 SoC-controlled period (data cutoff 01 April 2014), there were 560/4252 (13.2%) subjects overall with type 2 diabetes mellitus at baseline: 359/2833 (12.7%) subjects in the evolocumab plus SoC group and 201/1419 (14.2%) subjects in the SoC alone group. Diabetic patients, with no baseline proteinuria, in the year 1 SoC-controlled period had a greater incidence of proteinuria (43, 13.7%) in the EvoMab group compared to the SoC group (20, 10.8%) and to the entire integrated population on EvoMab (217, 8.4%). As of the data cutoff date 01 July 2014, there were 50 [15.1%] subjects receiving evolocumab plus SoC and 27 [13.6%] subjects receiving SoC alone who developed proteinuria. A summary of these 50 subjects with diabetes mellitus who developed proteinuria in the evolocumab plus SoC group follows:

- 6 out of 50 subjects had a positive urine protein at the year 1, OLE week 0 visit on the same date as evolocumab was initiated following placebo in the parent study.
- 40 of these 50 diabetic subjects had a history of hypertension.
- 40 of the 50 subjects had 1+ proteinuria.
- 10 of the 50 subjects had 2+ proteinuria: All 10 subjects had a history of hypertension. Four of the 10 subjects had an HbA1C ≥ 7% and 3/10 subjects had blood glucose levels ≥ 200 mg/dL, consistent with poor glucose control.
- No subjects had > 2+ proteinuria.
- Of the 50 subjects, 21 had resolution of the proteinuria on subsequent testing in the OLE year 1 study, 17 subjects had no subsequent testing following the positive result in the OLE year 1 study as of the 120-day Safety Update and 2 cases were fluctuating (ie, a positive result which resolved to negative or trace but was followed by a subsequent positive result).
- Proteinuria persisted in 10 of 50 subjects:
    - 9 of the 10 subjects had a history of hypertension; 3 had a HbA1C ≥ 7% and blood glucose levels ≥ 200 mg/dL; 4 had concomitant rosuvastatin use; 2 had concomitant NSAID use; and 1 subject had a medical history of impaired renal function.

- In the remaining subject (Subject 23134022008) with no notable confounding factors, the subject's first positive urine protein result occurred at the OLE week 0 visit on the same date as initiating evolocumab following placebo in the parent study.

Twenty-seven subjects in the SoC alone group developed proteinuria. Of these, 22 subjects had 1+ proteinuria and 5 had 2+ proteinuria. Ten subjects resolved on repeat testing, 8 cases of proteinuria persisted, and 9 subjects had no subsequent testing following the positive result in the year 1 OLE study. Twenty four of the 27 subjects in the SoC alone group had a history of hypertension including the 5 subjects with 2+ proteinuria.

While the incidence of proteinuria was balanced in the integrated parent studies in subjects with diabetes mellitus, there was a small but greater incidence of proteinuria in diabetic subjects who had no baseline proteinuria in the evolocumab plus SoC group, compared with the SoC alone group. Both the EvoMab and SoC alone group had additional confounding factors for the development of proteinuria, such as hypertension and concomitant medications.

Skin and Subcutaneous Tissue Disorders

In the integrated parent studies, adverse events for the Skin and Subcutaneous Tissue Disorders system organ class were reported in 188 (4.8%) participants in the any evolocumab group and 93 (4.5%) in the any control group. The most common adverse events in the evolocumab group and the any control group were rash (0.9% and 0.7%), eczema (0.4% and 0.1%), pruritus (0.4% and 0.8%), and urticaria (0.4% and 0.1%).

In the year 1 SoC-controlled period, 178 (6.3%) and 61 (4.3%) participants reported an adverse event in the evolocumab plus SoC group and the SoC alone groups, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were rash (1.2% and 0.6%), contact dermatitis (0.6% and 0.5%), pruritus (0.5% and 0.1%), urticaria (0.4% and 0.4%), and eczema (0.4% and 0.9%).

For the year 2+ OLE period, 77 (8.1%) participants reported an adverse event, and the most common adverse events were rash (1.5%), pruritus (1.0%), and contact dermatitis (0.9%).

Summary narratives of some of the cases presented in the BLA follow:

- One of the participants who reported a rash adverse event had a skin biopsy consistent with drug eruption. This 62-year-old male participant (15566030005) reported a grade 2 rash, which was patchy and scaly with central erythema on back, abdomen, arms, and leg. The event occurred approximately 20 months after he

received his first dose of evolocumab and 7 days after receiving the most recent dose of evolocumab. He was treated with oral antihistamines, topical steroid cream, and antibiotics. Evolocumab was continued. The rash flared 2 days after the next administration of evolocumab, and persisted during the next 3 administrations of evolocumab. A skin biopsy obtained and reviewed by a dermatopathologist reported focal interface dermatitis and superficial perivascular and interstitial mixed inflammatory infiltrate including numerous eosinophils. The report stated “a drug eruption is the major consideration in the microscopic differential diagnosis. Subacute eczema, especially allergic contact dermatitis, is another possibility.” Evolocumab was discontinued. All anti-evolocumab antibody results were negative. The participant reported that the rash persists and had not resolved as of the data cutoff date.

- A 54-year-old white woman (11760001004, evolocumab 140 mg Q2W group) with a medical history of photosensitivity reaction, generalized pruritus following vitamin D3/calcium, and rash and edema because of allergy to aspartame, developed erythema (reported term: red dots) with associated pruritus during trial 20110117. Approximately 2 months after receiving the first dose of evolocumab, she developed erythema that appeared 5 to 6 hours after the evolocumab injection and persisted for several weeks. After the next injection, erythema and pruritus developed on her neck. The pruritus resolved approximately 9 hours post injection. Approximately 2 months later, a first report of histopathological findings from a skin biopsy indicated the event was possibly drug induced and the differential diagnosis included borreliosis, necrobiosis lipoidica, or scleroderma. Immunofluorescence assessment results indicated possible vasculitis. A second-opinion report of the skin biopsy indicated no evidence of vasculitis or malignancy. This report also indicated that connective tissue disorder was a consideration in the differential diagnosis and that a connective tissue disease-like drug reaction was another possibility. Evolocumab was continued and she completed the study. The event of erythema was reported as resolved approximately 2 weeks after the biopsy.

Five participants (all on evolocumab) reported adverse events of angioedema. Four of the participants each reported 1 event of angioedema. One participant reported multiple events of angioedema.

- Subject 15466024006: reported multiple events of angioedema, had a medical history of fruit allergies and injection site reactions in the parent study. She was treated with oral and IV antihistamines and oral, intramuscular, and IV corticosteroids. She was withdrawn from evolocumab. She had multiple events of angioedema after discontinuing evolocumab.
- Subject 15566030001: (EvoMab 420 mg QM in study 20101155 and 20110110) received a course of amoxicillin for sinusitis approximately 2 weeks prior to the event of angioedema and had moderate adverse event of urticaria during the same time frame as the adverse event of angioedema. The angioedema resolved. EvoMab was continued.
- Subject 11666014003: (EvoMab 420 mg QM in study 20110116 and 20120138) reported both angioedema and allergic urticaria occurring on the same day; seen by an allergist who believed events were due to pantoprazole or aspirin. Both of these medications were discontinued and the angioedema and urticaria resolved.

- Subject 15566032034: angioedema occurred approximately 6 weeks after initiating allopurinol treatment for gout. Allopurinol and evolocumab were withdrawn, and the angioedema resolved.
- Subject 11558003002: (EvoMab 420 mg QM in study 20110115 and 20120138) history of periorbital rash and localized angioedema in the eyes, believed to be related to cosmetic use. Last dose of EvoMab approximately one month after start of AE. This subject's angioedema was reported as ongoing at the end of the study.

A serious adverse event of anaphylactic reaction was reported for one participant in the year 1 SoC-controlled period in the120-day Safety Update. This update provided safety data from the 3 ongoing extension studies up to a data cutoff date of 01 July 2014.

- The participant (35666002009) was a 65-year old man in the evolocumab plus SoC group who had a history of hypertension and allergies to sulfa and quinapril. Concomitant medications included lisinopril, atenolol, and pravastatin. While undergoing tooth extraction approximately 10 months after initiation of evolocumab dosing, he received an intravenous bolus of penicillin; approximately 15 minutes later the subject developed hypotension, lip and tongue swelling, chest tightness, and diffuse erythema. He was diagnosed with an anaphylactic reaction likely related to penicillin and/or angiotensin-converting-enzyme inhibitor and was treated with epinephrine, methylprednisolone, and diphenhydramine. The event resolved within 2 days with no change in evolocumab dose required. He continued evolocumab treatment and did not have anaphylactic reaction reported again.

7.3.5.2 HoFH Trials

The clinically notable incidence of adverse events for Trial 20110233 part B and Trial 20110271 (420 mg Q2W dose) is presented in this section. Updated information from Trial 20110271 is discussed in Section 7.7.1 120-Day Safety Update for BLA: Primary Hyperlipidemia/Mixed Dyslipidemia and HoFH Populations.

No important differences were identified in analyses of adverse events by organ system or syndrome in the HoFH population versus the primary hyperlipidemia population.

Table 87: Adverse Events by System Organ Class in Trial 20110233 Part B (Full Analysis Set)

	Placebo	EvoMab 420 mg QM
System Organ Class *Preferred Term*	Total (N = 16) n (%)	Total (N = 33) n (%)
Number of subjects reporting adverse events	10 (62.5)	12 (36.4)

Cardiac Disorders	1 (6.3)	0
Gastrointestinal Disorders	3 (18.8)	1 (3.0)
General Disorders and Administration Site Conditions	3 (18.8)	2 (6.1)
Infections and Infestations	1 (6.3)	10 (30.3)
Influenza	0 (0.0)	3 (9.1)
Upper Respiratory Tract Infection	1 (6.3)	3 (9.1)
Injury, Poisoning and Procedural Complications	0	1 (3.0)
Investigations	2 (12.5)	1 (3.0)
Musculoskeletal and Connective Tissue Disorders	1 (6.3)	2 (6.1)
Nervous System Disorders	3 (18.8)	0
Reproductive System and Breast Disorders	1 (6.3)	1 (3.0)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (3.0)

N = number of HoFH subjects randomized and dosed in full analysis set; HoFH=Homozygous Familial Hypercholesterolemia; EvoMab=Evolocumab (AMG 145). Coded using MedDRA version 16.1.
Source: modified from Table 14-6.2.1 of CSR for trial 20110233 B

HoFH Trial: Participants Who Received Evolocumab 420 mg Q2W in 120-day Safety Update

As shown in the table below, in the 120-day Safety Update (data cutoff 01 July 2014), the subject incidence of adverse events (82.1%) was numerically greater in the subgroup of 28 HoFH participants who only received 420 mg Q2W dosing, compared with the incidence in participants in the other HoFH and HeFH subgroups by dosing regimen (range of 53.3% to 66.7%). This was also true for the SAEs. Of note, the Q2W only group was the group receiving apheresis and 68% of this group had HoFH compared to 34% in the non-apheresis group. The apheresis group had a higher cardiovascular risk at baseline compared to the non-apheresis group. The apheresis group, due to their apheresis schedule, also had more frequent protocol-specified visits than those participants who started out with QM dosing.

There were more AEs in the HoFH and HeFH 420 mg Q2W group related to injection site reactions (such as erythema, pain, haematoma, bruising) than were reported in the HoFH and HeFH 420 mg QM dose group.

Table 88: Adverse Events in Study 20110271 by Dosing Regimen (QM only, Q2W only, or QM and Q2W)

	20110271: HoFH			20110271: HeFH		
	Q2W Only[a]	QM and Q2W[b]	QM Only[c]	Q2W Only[a]	QM and Q2W[b]	QM Only[c]
Total Number of Participants	28	47	25	15	3	124
Number of participants reporting adverse event (AE) - n (%)						
Adverse events	23 (82.1)	29 (61.7)	16 (64.0)	8 (53.3)	2 (66.7)	70 (56.5)

SAEs	4 (14.3)	6 (12.8)	0	1 (6.7)	0	2 (1.6)
AEs leading to d/c of evolocumab	0	1 (2.1)	0	0	0	1 (0.8)

Data cutoff date 01JUL2014. HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; Q2W = once every 2 weeks; QM = once monthly.
a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.
b Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.
c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM.
Source: Applicant's response to Feb 2015 Information Request.

The SAEs in the HoFH 420 mg Q2W group included AV fistula thrombosis, carotid artery occlusion, haematuria and myocardial ischaemia. The SAEs in the HoFH QM/Q2W group included angina pectoris, aortic stenosis, aortic valve disease, chest pain, coronary artery disease, coronary artery occlusion, and non-cardiac chest pain. There were no SAEs in the HoFH QM group. The SAE in the HeFH Q2W group was angina pectoris. The SAEs in the HeFH QM group included colitis and uterine prolapse. None of these serious adverse events were fatal and most were cardiovascular events, which is consistent with the increased incidence of such events in subjects with HoFH.

AEs that led to evolocumab discontinuation include rash in the HoFH QM/Q2W group and myalgia/muscle spasms/ malaise/pyrexia in one HeFH participant on QM dosing. A description of the rash AE in the HoFH participant in the QM/Q2W group follows:

- Subject 23356001008 was a 50-year-old man with HoFH from South Africa who uptitrated from QM to Q2W dosing at OLE week 12 and then continued Q2W dosing until he discontinued evolocumab at approximately OLE week 30 due to rash. Episodic worsening of the rash, which was treated in 1 instance with chlorpheniramine, was reported while the subject was receiving evolocumab 420 mg QM in Study 20110233 and Study 20110271. The rash was ongoing as of the 01 July 2014 data cutoff; but the company reports that the rash subsequently resolved per correspondence with the investigator. This subject tested negative for anti-evolocumab antibodies both before and after stopping evolocumab; however, serum IgE levels were found to be persistently elevated to 3x upper limit of normal (ULN) up to 6 months after stopping evolocumab.

Experience of Uptitration Group

Per the study protocol, non-apheresis participants could have their dose uptitrated at OLE week 12 from 420 mg QM to 420 mg Q2W if serum unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) was not maximally suppressed (defined by the protocol as a concentration ≥ 100 ng/mL) and apheresis participants could have their dose downtitrated from 420 mg Q2W to 420 mg QM if there was sufficient evidence of LDL-C reduction with Q2W dosing (defined by the protocol as a reduction from baseline ≥ 5%). Titration could also occur at the OLE week 24 visit. As of the

BLA submission (data cutoff 1 April 2014), 31 non-apheresis participants (30 HoFH and 1 HeFH) had their dose uptitrated from 420 mg QM to 420 mg Q2W in OLE Study 20110271. As of the 120-day Safety Update (data cutoff 1 July 2014), this increased to 43 non-apheresis participants (41 HoFH and 2 severe HeFH).

Of the 43 non-apheresis participants in the 120-day Safety Update who had their dose uptitrated from 420 mg QM to 420 mg Q2W, 3 participants subsequently had their dose downtitrated back to 420 mg QM. Investigators indicated that downtitration was primarily based on the comparatively small incremental LDL-C reduction associated with 420 mg Q2W dosing in these 3 participants. A review of adverse events in these 3 participants did not identify any safety issues before downtitration.

For apheresis participants, there were 4 in the BLA and 7 in the 120-day Safety Update who had their dose downtitrated from Q2W dosing to QM dosing. It appears that none of these participants had safety issues contributing to the decision to downtitrate.

This reviewer is concerned that the safety and efficacy data submitted to date to support the 420 mg Q2W dosing regimen, as opposed to the 420 mg QM dosing regimen, is quite limited and is insufficient to make an informed evaluation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Primary Hyperlipidemia/Mixed Dyslipidemia

In the integrated parent trials, which combines the Phase 2 trials (Process 1 drug formulation) and Phase 3 trials (Process 2 to-be-marketed drug formulation), the incidences of adverse events in the evolocumab 140 mg Q2W (43.6%) and the placebo Q2W groups (41.0%) were similar as well as for evolocumab 420 mg QM group (54.0%) and placebo QM groups (54.6%). In the ezetimibe comparator group, the incidence of adverse events was 278 (50.2%). As discussed elsewhere in this document, the higher incidence of adverse events with QM dosing was likely due to an additional ~900 participants reporting adverse events only for QM dosing. For example, the 1-year trial (20110109) only used QM dosing whereas some of the 12-week trials used both Q2W and QM dosing. In addition, there were 2 phase 2 trials (ie, 20090158, 20090159) in participants with HeFH and statin-intolerance, respectively that only had QM dosing. These unique trial populations may have contributed to the difference as well. To address this discrepancy, some analyses were done excluding data from trial 20110109 and analyses were done separately for

phase 2 and phase 3 trials so that a more accurate dose comparison could be made as well as exploring any differences between the Process 1 and Process 2 drug formulation.

The incidence of participants in the integrated, 12-week, parent phase 2 (Process 1 drug formulation only) analysis who experienced at least 1 adverse event was higher in the evolocumab group (58.3%) compared with any control (49.8%). The 3 most common adverse events in the evolocumab group were (evolocumab; any placebo) nasopharyngitis (7.7%; 6.6%), upper respiratory tract infection (5.1%; 3.7%), and back pain (4.5%; 2.3%).

In the integrated, 12-week, parent phase 3 (Process 2 to-be-marketed drug formulation only) analysis, the incidence of participants who experienced at least 1 adverse event was similar between the evolocumab 140 mg every 2 weeks group (43.8%) and the 420 mg once monthly group (43.4%) –this was slightly greater than the two corresponding placebo groups (40.9% and 42.7%, respectively). In the ezetimibe comparator group, the incidence of adverse events was 48.8%. The 3 most common adverse events in the evolocumab group (140 mg Q2W) were nasopharygitis, back pain and arthralgia and for the 420 mg QM group were headache, pain in extremity and nasopharyngitis.

Table 89: Adverse Events by Preferred Term in Descending Order of Frequency Preferred Terms Reported by ≥ 1% of Subjects in Either EvoMab Group [Integrated Parent Analysis Set Phase 3 (Process 2; to-be-marketed formulation) Trials: 20110114, 20110115, 20110116, 20110117]

	Control			**EvoMab**	
Preferred Term	Placebo Q2W (N = 411) n (%)	Placebo QM (N = 410) n (%)	Ezetimibe QD (N = 477) n (%)	140 mg Q2W (N = 921) n (%)	420 mg QM (N = 927) n (%)
# of subjects reporting AEs	168 (40.9)	175 (42.7)	233 (48.8)	403 (43.8)	402 (43.4)
Headache	14 (3.4)	9 (2.2)	19 (4.0)	20 (2.2)	35 (3.8)
Pain In Extremity	4 (1.0)	7 (1.7)	5 (1.0)	14 (1.5)	25 (2.7)
Nasopharyngitis	8 (1.9)	8 (2.0)	13 (2.7)	23 (2.5)	24 (2.6)
Back Pain	6 (1.5)	13 (3.2)	12 (2.5)	23 (2.5)	20 (2.2)
Myalgia	4 (1.0)	10 (2.4)	25 (5.2)	17 (1.8)	20 (2.2)
Muscle Spasms	5 (1.2)	4 (1.0)	11 (2.3)	17 (1.8)	19 (2.0)
Arthralgia	7 (1.7)	6 (1.5)	11 (2.3)	21 (2.3)	18 (1.9)
Nausea	5 (1.2)	5 (1.2)	11 (2.3)	15 (1.6)	18 (1.9)
Dizziness	6 (1.5)	5 (1.2)	9 (1.9)	9 (1.0)	15 (1.6)
Fatigue	3 (0.7)	4 (1.0)	15 (3.1)	14 (1.5)	15 (1.6)
Diarrhoea	8 (1.9)	9 (2.2)	12 (2.5)	16 (1.7)	14 (1.5)
URI	8 (1.9)	5 (1.2)	8 (1.7)	16 (1.7)	14 (1.5)
UTI	4 (1.0)	6 (1.5)	7 (1.5)	14 (1.5)	12 (1.3)

	Control			EvoMab	
Preferred Term	Placebo Q2W (N = 411) n (%)	Placebo QM (N = 410) n (%)	Ezetimibe QD (N = 477) n (%)	140 mg Q2W (N = 921) n (%)	420 mg QM (N = 927) n (%)
Cough	0 (0.0)	1 (0.2)	4 (0.8)	11 (1.2)	11 (1.2)
Contusion	1 (0.2)	2 (0.5)	4 (0.8)	9 (1.0)	9 (1.0)
Inj. Site Bruising	1 (0.2)	4 (1.0)	4 (0.8)	0 (0.0)	9 (1.0)
Inj. Site Pain	1 (0.2)	3 (0.7)	1 (0.2)	5 (0.5)	9 (1.0)
Oedema Periph	2 (0.5)	3 (0.7)	5 (1.0)	4 (0.4)	9 (1.0)
Hypertension	3 (0.7)	6 (1.5)	4 (0.8)	10 (1.1)	8 (0.9)
Constipation	8 (1.9)	1 (0.2)	2 (0.4)	11 (1.2)	6 (0.6)
Abd. Distension	0 (0.0)	1 (0.2)	3 (0.6)	9 (1.0)	5 (0.5)
Influenza	1 (0.2)	2 (0.5)	7 (1.5)	9 (1.0)	4 (0.4)
Bronchitis	2 (0.5)	4 (1.0)	1 (0.2)	12 (1.3)	2 (0.2)

Includes the following studies: 20110114, 20110115, 20110116, 20110117.
Data cutoff date 01APR2014.
N = number of subjects randomized in the integrated parent analysis set excluding subjects taking ezetimibe without subcutaneous placebo; EvoMab = Evolocumab; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous. Coded using MedDRA version 17.0.
Source: Modified from Table 14110601-6.6.11; Response to IR 06Nov2014

The following table combines the placebo groups from the table above (Any Placebo), the placebo groups and the ezetimibe group (Any Control), and both EvoMab groups (Any EvoMab). In these pools, the most common adverse events in the Any EvoMab group where EvoMab > Placebo were (evolocumab; any placebo) headache (3.0%; 2.8%), nasopharyngitis (2.5%; 1.9%), arthralgia (2.1%; 1.6%), pain in extremity (2.1%; 1.3%) and myalgia (2.0%; 1.7%).

Table 90: Adverse Events by Preferred Term in Descending Order of Frequency; Preferred Terms Reported by ≥ 1% of Subjects in Any Treatment Group, Collapsed Groups (Integrated Parent Analysis Set Phase 3 Process 2 Studies: 20110114, 20110115, 20110116, 20110117)

Preferred Term	Any Placebo (N = 821) n (%)	Any Control (N = 1298) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 1848) n (%)
Number of subjects reporting AEs	343 (41.8)	576 (44.4)	805 (43.6)
Headache	23 (2.8)	42 (3.2)	55 (3.0)
Nasopharyngitis	16 (1.9)	29 (2.2)	47 (2.5)
Back Pain	19 (2.3)	31 (2.4)	43 (2.3)
Arthralgia	13 (1.6)	24 (1.8)	39 (2.1)
Pain In Extremity	11 (1.3)	16 (1.2)	39 (2.1)
Myalgia	14 (1.7)	39 (3.0)	37 (2.0)

Diarrhoea	17 (2.1)	29 (2.2)	30 (1.6)
Upper Respiratory Tract Infection	13 (1.6)	21 (1.6)	30 (1.6)
Fatigue	7 (0.9)	22 (1.7)	29 (1.6)
Urinary Tract Infection	10 (1.2)	17 (1.3)	26 (1.4)
Dizziness	11 (1.3)	20 (1.5)	24 (1.3)
Cough	1 (0.1)	5 (0.4)	22 (1.2)
Contusion	3 (0.4)	7 (0.5)	18 (1.0)
Hypertension	9 (1.1)	13 (1.0)	18 (1.0)
Constipation	9 (1.1)	11 (0.8)	17 (0.9)

Includes the following studies: 20110114, 20110115, 20110116, 20110117. Data cutoff date 01APR2014. N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Q2W = every 2 weeks (subcutaneous) and QM = monthly (subcutaneous). Any Control includes subcutaneous placebo and ezetimibe with subcutaneous placebo subjects. Coded using MedDRA version 17.0.
Shaded rows indicate incidence in EvoMab > Placebo
Source: Table 1-6 and 14110601-6.6.12; Response to IR 06Nov2014

In the integrated parent trials, which combines the Phase 2 trials (Process 1 drug formulation) and Phase 3 trials (Process 2 to-be-marketed drug formulation), the most common adverse events (any evolocumab and any control groups, respectively) were nasopharyngitis (5.9% and 4.8%), upper respiratory tract infection (3.2% and 2.7%), headache (3.0% and 3.2%), back pain (3.0% and 2.7%), and myalgia (2.5% and 2.6%) (see table).

Table 91: Adverse Events During the Parent Trials by Preferred Term in Descending Order of Frequency Preferred Terms Reported by ≥ 1% of Participants in Any Treatment Group (Integrated Parent Analysis Set)

Preferred Term	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)	Any EvoMab (N = 3946) n (%)
Number of participants reporting adverse events	753 (49.3)	1031 (49.6)	1599 (50.0)	2016 (51.1)
Nasopharyngitis	77 (5.0)	99 (4.8)	154 (4.8)	231 (5.9)
Upper Respiratory Tract Infection	43 (2.8)	56 (2.7)	103 (3.2)	127 (3.2)
Headache	46 (3.0)	66 (3.2)	98 (3.1)	120 (3.0)
Back Pain	44 (2.9)	57 (2.7)	99 (3.1)	117 (3.0)
Myalgia	28 (1.8)	55 (2.6)	70 (2.2)	98 (2.5)
Arthralgia	33 (2.2)	45 (2.2)	72 (2.2)	91 (2.3)
Influenza	32 (2.1)	41 (2.0)	73 (2.3)	83 (2.1)
Nausea	25 (1.6)	37 (1.8)	68 (2.1)	81 (2.1)
Diarrhoea	36 (2.4)	50 (2.4)	63 (2.0)	79 (2.0)

Includes the following trials: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. N = number of participants randomized in the integrated parent analysis set; EvoMab = Evolocumab. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product. Coded using MedDRA version 17.0. Source: ISS Table 14-6.2.2

For the year 1 SoC-controlled period, the most common adverse events (evolocumab plus SoC and SoC alone groups, respectively) were nasopharyngitis (8.5% and 7.9%), upper respiratory tract infection (4.2% and 4.0%), arthralgia (3.4% and 2.5%), back pain (3.1% and 2.5%), and hypertension (3.1% and 2.7%) (see table).

Table 92: Adverse Events During the Year 1 SoC-Controlled Period by Preferred Term in Descending Order of Frequency Preferred Terms Reported by ≥ 2% of Participants in All Evolocumab plus SoC Group (IECAS)

	Control in Parent Study		EvoMab in Parent Study		All	
Preferred Term	SoC (N = 472) n (%)	EvoMab + SoC (N = 943) n (%)	SoC (N = 947) n (%)	EvoMab + SoC (N = 1890) n (%)	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)
Number of subjects reporting adverse events	265 (56.1)	567 (60.1)	516 (54.5)	1141 (60.4)	781 (55.0)	1708 (60.3)
Nasopharyngitis	39 (8.3)	85 (9.0)	73 (7.7)	157 (8.3)	112 (7.9)	242 (8.5)
Upper Respiratory Tract Infection	17 (3.6)	32 (3.4)	40 (4.2)	87 (4.6)	57 (4.0)	119 (4.2)
Arthralgia	12 (2.5)	24 (2.5)	24 (2.5)	73 (3.9)	36 (2.5)	97 (3.4)
Back Pain	9 (1.9)	20 (2.1)	26 (2.7)	69 (3.7)	35 (2.5)	89 (3.1)
Hypertension	9 (1.9)	31 (3.3)	30 (3.2)	58 (3.1)	39 (2.7)	89 (3.1)
Influenza	14 (3.0)	29 (3.1)	23 (2.4)	55 (2.9)	37 (2.6)	84 (3.0)
Headache	4 (0.8)	22 (2.3)	20 (2.1)	60 (3.2)	24 (1.7)	82 (2.9)
Bronchitis	15 (3.2)	19 (2.0)	28 (3.0)	54 (2.9)	43 (3.0)	73 (2.6)
Cough	9 (1.9)	15 (1.6)	29 (3.1)	56 (3.0)	38 (2.7)	71 (2.5)
Myalgia	11 (2.3)	29 (3.1)	23 (2.4)	42 (2.2)	34 (2.4)	71 (2.5)
Pain In Extremity	5 (1.1)	15 (1.6)	16 (1.7)	56 (3.0)	21 (1.5)	71 (2.5)
Urinary Tract Infection	8 (1.7)	27 (2.9)	17 (1.8)	38 (2.0)	25 (1.8)	65 (2.3)
Diarrhoea	7 (1.5)	19 (2.0)	14 (1.5)	44 (2.3)	21 (1.5)	63 (2.2)
Sinusitis	15 (3.2)	14 (1.5)	22 (2.3)	47 (2.5)	37 (2.6)	61 (2.2)
Fatigue	4 (0.8)	20 (2.1)	8 (0.8)	40 (2.1)	12 (0.8)	60 (2.1)

N = number of subjects randomized in the integrated extension SoC-controlled period analysis set; EvoMab = Evolocumab; SoC = Standard of Care. Includes the following trials: 20110110, 20120138
Coded using MedDRA version 17.0.
Source: Modified from ISS Table 14-6.2.5 and Summary Clinical Safety Table 28

7.4.1.2 HoFH

The common adverse events in the HoFH participants were similar to those seen in the primary hyperlipidemia and mixed dyslipidemia trials in the evolocumab program. Please refer to Table 111: Cumulative Subject Incidences of Adverse Events by System Organ Class in the Evolocumab BLA and 120-day Safety Update Trial 20110271 (HoFH Interim Analysis Set) for additional information.

7.4.1.3 LDL-C Subgroup

Safety in Subjects Who Achieved LDL-C < 40 mg/dL in Primary Hyperlipidemia Trials

A summary of baseline characteristics, by minimum postbaseline achieved LDL-C subgroups (< 25 mg/dL, <40 mg/dL, and ≥ 40 mg/dL), was examined for the integrated parent studies and year 1 SoC-controlled period. Baseline characteristics in the LDL-C subgroups were overall similar to those in the general study population of the integrated parent studies and year 1 SoC-controlled period. Some differences were noted and include:

- With the exception of triglycerides and very low-density lipoprotein cholesterol (VLDL-C), mean and median baseline lipid levels were higher for subjects with a minimum on-study LDL-C ≥ 40 mg/dL compared to subjects with a minimum on-study LDL-C < 25 mg/dL or < 40 mg/dL

- There was more baseline statin use, and more use of moderate- and high-intensity (vs. low-intensity) statins, among patients who achieved LDL-C < 25 mg/dL or < 40 mg/dL

- There was a slightly greater percentage of subjects with coronary artery disease, diabetes or hypertension among those who achieved LDL-C < 25 mg/dL or < 40 mg/dL

- There was a slightly greater percentage of subjects in the NCEP CHD high risk or moderately high risk categories who achieved LDL-C < 25 mg/dL or < 40 mg/dL

Regardless of LDL-C level achieved during the study, in the integrated parent studies, the majority of subjects (≥ 94%) completed IP. Likewise, for year 1 of the OLE period, ≥ 91% of subjects either completed or are continuing IP (>36% of subjects completed IP and >51% are continuing IP).

Analyses of adverse events were performed by LDL-C subgroup (see table), although it is important to note that these are not randomized comparisons. As very few participants on placebo or ezetimibe achieved low LDL C, it is difficult to make meaningful comparisons between the control and EvoMab groups. However, since randomized comparisons are not possible in this analysis, it does allow for a comparison of adverse events in the EvoMab low-LDL group versus EvoMab higher LDL group. In the integrated parent studies, adverse events were reported in 826 (51.3%) participants in the any evolocumab group who achieved LDL-C < 25 mg/dL and 1308 (51.0%) participants in the any evolocumab group who achieved LDL-C < 40 mg/dL compared with 696 (52.0%) participants in the any evolocumab group with LDL-C ≥ 40 mg/dL and 1018 (50.0%) participants in the any control group with LDL-C ≥ 40 mg/dL. There were no remarkable findings in the different subgroups regarding common adverse events. In the integrated parent trial analysis, there does not appear

to be a signal for diabetes or eye disorder AEs by achieved LDL-C subgroup. In this analysis, no safety signal was identified for neurocognitive adverse events with evolocumab regardless of LDL-C level. Of note, most of the trials in this group are short-term (12 week duration), except for the one-year placebo controlled trial, which limits the likelihood of finding an adverse effect from prolonged low LDL-C levels.

Table 93: Adverse Events by Achieved LDL-C Subgroup in Integrated Parent Studies

	LDL-C < 25 mg/dL		LDL-C < 40 mg/dL		LDL C ≥ 40 mg/dL	
Controlled Blinded Studies						
N	Any EvoMab N=1609	Any Control N=6	Any EvoMab N=2565	Control N=30	Any EvoMab N=1339	Control N=2038
Median exposure, months	3.2		3.2		3.0	3.2
All AEs	826 (51.3%)	4 (66.7%)	1308 (51.0%)	12 (40.0%)	696 (52.0%)	1018 (50.0%)
SAEs	47 (2.9%)	1 (16.7%)	70 (2.7%)	2 (6.7%)	35 (2.6%)	41 (2.0%)
Most common AEs						
nasopharyngitis	6.5%	33.3%	6.6%	10.0%	4.6%	4.7%
upper respiratory tract infection	4.0%	0%	3.6%	0%	2.6%	2.7%
back pain	3.5%	0%	3.2%	0%	2.5%	2.8%
arthralgia	2.7%	0%	2.4%	0%	2.2%	2.2%
influenza	2.6%	0%	2.3%	0%	1.9%	2.0%
headache	2.6%	0%	2.7%	0%	3.6%	3.2%
cough	2.3%	0%	2.5%	0%	1.1%	1.3%
myalgia	2.2%	0%	1.9%	0%	3.6%	2.7%
diarrhea	2.1%	0%	2.0%	3.3%	2.0%	2.0%
dizziness	2.1%	0%	1.7%	0%	1.5%	1.7%
nausea	1.9%	0%	1.9%	0%	2.4%	1.8%
fatigue	1.6%	0%	1.6%	0%	2.0%	2.4%
Other AEs of interest						
Diabetes Mellitus	6, 0.4%	0%	8, 0.3%	0%	4, 0.3%	6, 0.3%
Type 2 DM	5, 0.3%	0%	6, 0.2%	0%	1, 0.1%	4, 0.2%
Hyperglycaemia	2, 0.1%	0%	2, 0.1%	0%	3, 0.2%	2, 0.1%
Eye Disorders SOC	25, 1.6%	0%	37, 1.4%	1, 3.3%	23, 1.7%	29, 1.4%
Cataract	4, 0.2%	0%	4, 0.2%	0%	1, 0.1%	1, 0%
Vision blurred	1, 0.1%	0%	2, 0.2%	1, 3.3%	4, 0.3%	1, 0%
Vitreous floaters	1, 0.1%	0%	3, 0.1%	0%	0%	2, 0.1%
Conjunctival haemmorrhage	2, 0.1%	0%	2, 0.1%	0%	0%	2, 0.1%
Conjunctivitis	2, 0.1%	0%	2, 0.1%	0%	1, 0.1%	0%

Allergic						
Lacrimation increased	2, 0.1%	0%	2, 0.1%	0%	0%	0%
Select Nervous System Disorders AEs						
Nervous System Disorders SOC	115, 7.1%	0	181, 7.1%	0	112, 8.4%	164, 8.0%
amnesia	1, 0.1%	0	1, <0.1%	0	1, 0.1%	0
cognitive disorder	0	0	0	0	0	1, <0.1%
Disturbance in attention	0	0	0	0	0	1, <0.1%
memory impairment	0	0	0	0	1, 0.1%	1, <0.1%
paraesthesia	11, 0.7%	0	15, 0.6%	0	7, 0.5%	8, 0.4%
hypoaesthesia	3, 0.2%	0	7, 0.3%	0	5, 0.4%	9, 0.4%
Neuropathy peripheral	1, 0.1%	0	1, <0.1%		0	1, <0.1%
Select Psychiatric Disorders AEs						
Psychiatric Disorders SOC	31, 1.9%	0	50, 1.9%	0	34, 2.5%	41, 2.0%
insomnia	12, 0.7%	0	17, 0.7%	0	11, 0.8%	10, 0.5%
disorientation	0	0	0	0	1, 0.1%	2, 0.1%

Source: Summary of Clinical Safety, Appendix Table 7 and ISS table 14-6.3.110, 14-6.3.116 and 14-6.3.122

In the Year 1 Controlled Period of the extension trials, there were no notable differences in the incidence of common adverse events across the LDL-C subgroups. There does not appear to be a signal for eye disorder AEs by LDL subgroup. There is a numeric increase in AEs of diabetes, in the two lower LDL subgroups. In the nervous system and psychiatric disorders AE preferred terms, shown in the table below, the incidence among the groups is low and similar. It is important to note that the safety information and adverse event data from this year 1 SoC-controlled period reflects a median exposure of 7.4 months of controlled but open-label data.

Table 94: Adverse Events by Achieved LDL-C Subgroup in the Year 1 Controlled Period of the Extension Trials

	LDL-C < 25 mg/dL		**LDL-C <40 mg/dL**		**LDL C ≥ 40 mg/dL**	
Year 1 SoC-controlled Period						
Preferred Terms	EvoMab+ SoC: N=666	SoC alone: N=4	EvoMab +SoC: N=1369	SoC alone: N=12	EvoMab +SoC: N=1427	SoC alone: N=1380
Median exposure, months	8.3		8.2		7.2	7.4
All AEs	394 (59.2%)	0%	814 (59.5%)	4 (33.3%)	882 (61.8%)	774 (56.1%)
SAEs	34 (5.1%)	0 (0%)	68 (5.0%)	0 (0%)	85 (6.0%)	80 (5.8%)
Most common AEs (EvoMab+SoC and SoC alone)						
nasopharyngitis	10.2%	0%	9.2%	8.3%	8.1%	8.0%
upper respiratory tract infection	4.4%	0%	3.9%	0%	4.6%	4.1%
back pain	4.2%	0%	3.7%	0%	2.7%	2.5%
arthralgia	3.8%	0%	4.2%	0%	2.7%	2.6%
hypertension	3.5%	0%	3.7%	0%	2.7%	2.8%
diarrhoea	3.3%	0%	2.6%	0%	2.0%	1.5%
cough	3.3%	0%	2.5%	0%	2.5%	2.8%
influenza	2.0%	0%	2.2%	0%	3.8%	2.7%
headache	2.7%	0%	2.7%	0%	3.2%	1.7%
Other AEs of interest (EvoMab+SoC and SoC alone)						
Diabetes	11, 1.7%	0%	20, 1.5%	0%	9, 0.6%	5, 0.4%
Type 2 DM	4, 0.6%	0%	5, 0.4%	0%	8, 0.6%	5, 0.4%
Hyperglycaemia	4, 0.6%	0%	6, 0.4%	0%	1, 0.1%	3, 0.2%
Eye Disorders SOC	15, 2.3%	0%	42, 3.1%	0%	35, 2.5%	28, 2.0%
Cataract	4, 0.6%	0%	11, 0.8%	0%	11, 0.8%	11, 0.8%
Dry Eye	3, 0.5%	0%	8, 0.6%	0%	3, 0.2%	0%
Conjunctivitis allergic	1, 0.2%	0%	4, 0.3%	0%	2, 0.1%	0%
Asthenopia	1, 0.2%	0%	1, 0.1	0%	0%	0%
Select Nervous System Disorders AEs						
Nervous System Disorders SOC	52, 7.8%	0	116, 8.5%	0	122, 8.5%	100, 7.2%
amnesia	1, 0.2%	0	2, 0.1%	0	0	1, 0.1%
memory impairment	0	0	4, 0.3%	0	3, 0.2%	2, 0.1%
mental impairment	0	0	1, 0.1%	0	1, 0.1%	0
hypoaesthesia	5, 0.8%	0	6, 0.4%	0	8, 0.6%	5, 0.4%

neuropathy peripheral	1, 0.2%	0	5, 0.4%	0	0	2, 0.1%
paraesthesia	1, 0.2%	0	6, 0.4%	0	11, 0.8%	7, 0.5%
toxic neuropathy	0	0	0	0	1, 0.1%	0
dementia	0	0	0	0	2, 0.1%	0
Dementia Alzheimer's type	0	0	0	0	1, 0.1%	0
Select Psychiatric Disorders AEs						
Psychiatric Disorders SOC	19, 2.9%	0	52, 3.8%	0	42, 2.9%	33, 2.4%
insomnia	8, 1.2%	0	16, 1.2%	0	17, 1.2%	13, 0.9%
depression	5, 0.8%	0	15, 1.1%	0	9, 0.6%	9, 0.7%
disorientation	0	0	1, 0.1%	0	0	0
confusional state	0	0	1, 0.1%	0	0	0
mental status changes	0	0	1, 0.1%	0	0	0

Source: Summary of Clinical Safety, Appendix Table 7, ISS Tables 14-6.3.113, 14-6.3.119 and 14-6.3.125

Shown below is a listing of participants in the Year 1 SoC-Controlled period, who had neurocognitive events and an LDL-C < 40 mg/dL in the parent study or the extension study, showing that many of these cases are confounded by other conditions or medications that could also affect cognitive function. Many of these participants also had an LDL > 40 mg/dL just prior to the event. A review of the patient narratives confirms that it is challenging to definitely attribute the neurocognitive adverse event to evolocumab vs another drug or pre-existing condition. These evaluations also lack any prospective neurocognitive testing. This potential neurocognitive safety concern is being prospectively evaluated with neurocognitive testing in a subset of the population in the on-going CVOT (FOURIER).

Table 95: Subjects with Low LDL-C and Neurocognitive Adverse Events During the Year 1 SoC-Controlled Period

Subject #	Age / Sex	Treatment/ Schedule: Parent Grade	Treatment/ Schedule: Ext Serious	Preferred Term/ Verbatim Term / Comment	Time to Onset[a] / Related	Outcome / Discon	Medical History / Concurrent Medications	LDL-C (mg/dL): Pre AE / Post AE	LDL-C (mg/dL): Study Nadir[b]
15529011003	68	EvoMab 350 mg QM	EvoMab 420 mg QM	Memory impairment/ forgetful	160 days	Ongoing	Arthralgia	57	18
		2	N	Alzheimer's dementia concurrently reported; concomitant statin	N	N	Aspirin, bisoprolol, fluvastatin, nitroglycerine	66	
	F	EvoMab 350 mg QM	EvoMab 420 mg QM	Dementia Alzheimer's type/ Alzheimer dementia	160 days	Ongoing	Arthralgia	57	18
		2	N	Concomitant statin	N	N	Aspirin, bisoprolol, fluvastatin, nitroglycerine	66	
15466036017	56	EvoMab 420 mg QM	EvoMab 420 mg QM	Memory impairment/ increased forgetfulness	214 to 244 days[c]	Ongoing	Depression, GERD, arthritis	58	36
	F	1	N	Depression	N	N	Phenylephrine, vitamin D, aspirin, naproxen, ranitidine	52	

15466046011	52	EvoMab 420 mg QM	EvoMab 420 mg QM	Memory impairment/ forgetfulness	56 days	Ongoing	Obesity , arthritis, renal calculi	59	29
	M	1	N	Evolocumab temporarily withheld due to this event.	N	N[d]	Various NSAIDs	45	
15466061012	38	Placebo	EvoMab 420 mg QM	Memory impairment/ memory impairment	31 days	Resolved in 90 days	Back pain, migraine, GERD	49	39
		1	N	Reported as related to topiramate regimen	N	N	Pantoprazole, acyclovir, cyclobenzaprin, topiramate, gabapentin	48	
	F	Placebo	EvoMab 420 mg QM	Memory impairment/ memory impairment	270 days	Resolved in 43 days	Back pain, migraine, GERD	52	39
		1	N	Reported as related to topiramate regimen	N	N	Pantoprazole, acyclovir, cyclobenzaprin, topiramate, gabapentin	39	
10966434002	46	EvoMab 420 mg QM	EvoMab 420 mg QM	Memory impairment/ occasional forgetfulness	30 days	Ongoing	Ovarian cyst, anxiety	32	14
	F	1	N	Anxiety; alprazolam	N	N	Alprazolam, fish oil	58	
15566064005	61	EvoMab 280 mg QM	EvoMab 420 mg QM	Mental impairment/ intermittent decreased mental acuity – cyclic with onset 72 hours following IP, lasting 2 weeks	117 days	Resolved in 187 days	Emphysema, malignant melanoma, anxiety, depression, anemia, arthritis	44	34
		1	N	Anxiety; depression; concomitant statin and alprazolam	Y	N	Atorvastatin, alprazolam, cyanocobalamin, ferrous sulfate, ibuprofen	74	
	M	EvoMab 280 mg QM	EvoMab 480 mg QM	Mental impairment/ worsened cyclic decreased mental acuity	304 days	Resolved in 18 days	Emphysema, malignant melanoma, anxiety, depression, anemia, arthritis	74	34
		3	N	Anxiety; depression; concomitant statin and alprazolam. Evolocumab temporarily withheld due to this event.	Y	N[d]	Atorvastatin, alprazolam, cyanocobalamin, ferrous sulfate, ibuprofen	42	
15566064001	55	EvoMab 105 mg Q2W	EvoMab 420 mg QM	Disorientation/ intermittent disorientation while driving car lasting seconds to 1-2 minutes	111 days	Ongoing	Arthritis, lethargy, sleep disorder, dyspepsia, myalgia, erectile dysfunction, hypersensitivity	35	29
	M	1	N	Sleep disorder; simvastatin	N	N	Aspirin, simvastatin, loratidine, ibuprofen, sildenafil	36	
15966018001	64	EvoMab 280 mg QM	EvoMab 420 mg QM	Amnesia/ amnesia	274 days	Ongoing	Bipolar disorder, depression, fatigue, insomnia, GERD, diabetes mellitus, chronic sinusitis, obesity, osteoarthritis, and drug hypersensitivity	38	28
	F	1	N	Bipolar disorder; depression; eszopiclone; lorazepam; temazepam; lamotrigine; methylphenidate; nefazodone; quetiapine	N	N	Aripiprazole, aspirin, eszopiclone, lorazepam, temazepam, lamotrigine, methyphenidate, nefazodone, quetiapine, metformin, pioglitazone, olmesartan, fish oil, vitamin supplements	60	
15566053008	60	EvoMab 350 mg QM	EvoMab 420 mg QM	Amnesia/ worsening memory loss	195 days	Ongoing	Hypertension, memory loss, GERD, peripheral neuropathy, spinal cord neoplasm, bone neoplasm, hypersensitivity	22	4
	M	1	N	History of memory loss; concomitant simvastatin; gabapentin	N	N	Aspirin, acetaminophen, simvastatin, hydrochlorothiazide, losartan, metoprolol, gabapentin, ranitidine	25	
11513004002	70	EvoMab 140mg Q2W	EvoMab 140mg Q2W	Memory impairment/ worsening of decreases in memory	47 days	onging	Decrease in memory, hypertension	102	28
	F	1	N	Decrease in memory ; concomitant statin	N	N	Atenolol, tibolone, atorvastatin	28	
11511009023	80	Placebo	EvoMab 140mg Q2W	Memory impairment/ memory impairment	36 days	ongoing	Depression, osteoarthritis	100	32
	F	1	N	Depression; concomitant statin	N	Y	Aspirin, fluoxetine, rosuvastatin	61	

34866017008	72	EvoMab 140mg Q2W	EvoMab 140mg Q2W	Dementia/ dementia	79 days	ongoing	Mild memory loss, depression, anemia, anxiety, asthma, insomnia, fibromyalgia, diabetic peripheral neuropathy, esophageal stricture, coronary artery disease, obesity, peripheral edema, dyspnea, osteoporosis	28	44
	F	2	N	Mild memory loss; depression; concomitant statin	N	N	Sertraline, triamterine/hydrochlorothiazide, sitagliptin, glyceryl trinitrate, clopidogrel, duloxetine, dicycloverine,simvastatin	44	
11666014004	71	Placebo	EvoMab 140mg Q2W	Confusional state/ confusion	249 days	Resolved in 1 day	Atopic dermatitis, fatigue, gastroesophageal reflux, gout, malaise, intracranial hemorrhage (resolved), palpitation, seizure disorder	40	32
	M	1	N	Reported vertigo concomitantly	N	N	Aspirin, allopurinol, clonidine, metoprolol	NA	

AE = adverse event; Disc = discontinued; EvoMab = evolocumab; Ext = extension study; F = female; GERD = gastroesophageal reflux disease; IP = investigational product; LDL-C = low-density lipoprotein cholesterol; M = male; N = no; NSAID = nonsteroidal anti-inflammatory drug; Q2W = every 2 weeks; QM = once a month; Rel = related; Ser = serious; y = yes.
a Time to onset was calculated based on the first dose in the extension study.
b LDL-C nadir includes LDL-C values from the parent study and the extension study.
c Partial study date of July 2012 listed in the case report form.
d Evolocumab temporarily withheld as a result of this adverse event.
Includes Studies 20120138 and 20110110. Data cutoff dates were 01 April 2014 for study 20120138 and Study 20110110. Source: Modified from Appendix Table 8. Summary of Clinical Safety

A selection of narratives for participants who experienced neurocognitive events is in Section 9.10 A Selection of Narratives of Neurocognitive Adverse Events

No participants in the year 2+ OLE period reported a neurocognitive adverse event.

7.4.1.4 Device Related Adverse Events

The autoinjector pen (AI/pen) was used in the phase 3 parent trials (20110114, 20110115, 20110116, and 20110117). Across the integrated phase 3 trials, fewer than 3% of participants reported a device related adverse event after administration using the AI/pen. The overall incidence of device related adverse events was similar across treatment groups (see table); however, the EvoMab QM dosing had a slightly higher incidence of adverse events than the EvoMab Q2W dosing. Device related adverse events reported in ≥ 0.5% of participants in any treatment group were injection site bruising, injection site erythema, and injection site pain. Most device related adverse events were grade 1 in severity; 5 (0.2%) participants reported a grade 2 device related adverse event. Most device-related adverse events were consistent with injection site reactions. There were 5 AI/Pen failures that were all associated with 1 cause code (“syringe broken during/after use”). In these cases, glass breakage was either contained within the AI/Pen or resulted in glass cone/needle detachment.

Table 96: Device related Adverse Events During the Phase 3 Parent Studies by Preferred Term in Descending Order of Frequency (AI/pen Studies 20110114, 20110115, 20110116, 20110117) (IPAS)

Preferred Terms	Placebo SC Q2W AI/Pen (N = 651) n (%)	Placebo SC QM AI/Pen (N = 647) n (%)	EvoMab 140 mg Q2W AI/Pen (N = 921) n (%)	EvoMab 420 mg QM AI/Pen (N = 927) n (%)
Number of subjects reporting adverse events	5 (0.8)	17 (2.6)	14 (1.5)	26 (2.8)
Injection Site Bruising	1 (0.2)	5 (0.8)	0	6 (0.6)
Contusion	0	1 (0.2)	0	4 (0.4)
Injection Site Erythema	1 (0.2)	3 (0.5)	1 (0.1)	3 (0.3)
Injection Site Pain	1 (0.2)	3 (0.5)	4 (0.4)	3 (0.3)
Injection Site Haematoma	0	0	1 (0.1)	2 (0.2)
Injection Site Haemorrhage	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.2)
Injection Site Reaction	0	0	1 (0.1)	2 (0.2)
Application Site Bruise	0	0	0	1 (0.1)
Cellulitis	0	0	0	1 (0.1)
Injection Site Discharge	0	0	0	1 (0.1)
Injection Site Induration	0	0	1 (0.1)	1 (0.1)
Injection Site Inflammation	0	1 (0.2)	0	1 (0.1)
Injection Site Swelling	0	0	1 (0.1)	1 (0.1)
Pain In Extremity	0	0	0	1 (0.1)
Rash	0	0	0	1 (0.1)
Rash Erythematous	0	0	0	1 (0.1)

N = number of subjects randomized in the integrated parent analysis set (IPAS); AI/pen = autoinjector/pen; QM = once monthly; Q2W = every 2 weeks; SC = subcutaneous. Includes the following studies: 20110114, 20110115, 20110116, 20110117. Coded using MedDRA version 17.0. Source: Modified from Table 36: Summary of Clinical Safety

During the year 1 SoC-controlled period, 37 (1.9%) participants reported a device related adverse event. All 37 participants were in the evolocumab group because subjects assigned to SoC alone did not receive any placebo injections. An additional 5 participants experienced device related adverse events in Study 20120138 when including all randomized subjects. During the year 2+ OLE period, 17 participants received evolocumab via AI/pen in Study 20120138, and no device related adverse events were reported.

Two phase 3 evolocumab device clinical home-use studies were performed to assess the administration of evolocumab by participants using the 3 different devices [pre-filled syringe (PFS), AI/pen, auto mini-doser (AMD)] when the product was

administered by participants or caregivers in non-clinic settings. Study 20120348 evaluated AI/pen vs PFS, and Study 20120356 evaluated AI/pen vs AMD.

In Study 20120348, no device related adverse events were reported. In Study 20120356, in the AMD group, where 82 participants received a total dose of 420 mg evolocumab via a single 3.5 mL injection administered over approximately 9 minutes, 1 (1.2%) participant experienced 2 non-serious adverse events of injection site reaction that were considered related to the device by the investigator. In the AI/pen group, where 82 participants received a total dose of 420 mg evolocumab via 3 separate 1.0 mL injections, 1 participant (1.2%) experienced an adverse event of injection site hematoma, and 1 participant (1.2%) experienced an event of pain in extremity, and both events were non-serious and considered related to the device by the investigator.

Two phase 1 clinical studies were performed to evaluate the PK equivalence and safety of the PFS, AI/pen, and AMD devices. Study 20120133 compared the AI/pen to the PFS, while Study 20110168 compared the AMD to the AI/pen. In Study 20120133, 3 (3.1%) participants reported a total of 3 non-serious device related adverse events: 2 events of injection site hemorrhage and 1 event of injection site pain. All 3 events were associated with the AI/pen and resolved without intervention.

In Study 20110168, device related adverse events were reported in a total of 109 (37.7%) participants: 39 (26.9%) participants in the 3xAI/Pen group and 70 (48.6) participants in the AMD group. None of these events were serious. Complete delivery of the device was defined as: the entire window on AI/pen turning yellow, or the AMD device light turning solid green, no observed fluid leakage during delivery, and window on device showing complete delivery. Complete delivery of evolocumab was observed for 430/435 (98.9%) of the AI/pens used and for 134/144 (93.1%) AMDs used.

7.4.2 Laboratory Findings

Liver-related laboratory tests are discussed in Section 7.3.5.1 Primary Hyperlipidemia Trials, under Hepatobiliary Disorders.

7.4.2.1 Renal Tests

Renal-related laboratory tests are discussed in Section 7.3.5.1 Primary Hyperlipidemia Trials, under Renal and Urinary Disorders.

7.4.2.2. Creatine Kinase

Information on CK abnormalities can be found in Section 7.3.5.1 Musculoskeletal and Connective Tissue Disorders.

7.4.2.3. HbA1c

Information on new onset diabetes and glucose abnormalities can be found in Section 7.3.5.1 Metabolism and Nutrition Disorders/*Diabetes Mellitus*.

7.4.3 Vital Signs

Changes from baseline for systolic and diastolic blood pressure and heart rate did not reveal clinically important differences among treatment groups.

Approximately half (51.4%) of the participants in the integrated parent studies had hypertension at baseline. In the integrated parent studies, the mean change from baseline to each study time point in systolic and diastolic blood pressure ranged from -1.1 to 0.6 mmHg (systolic) and -0.8 to 0.2 mmHg (diastolic) in the any evolocumab group and -1.0 to 1.0 mmHg (systolic) and -0.8 to 0.1 mmHg (diastolic) in the any control group. In the year 1 SoC-controlled period, the mean change from baseline to each study time point in systolic and diastolic blood pressure ranged from -0.9 to 2.1 mmHg (systolic) and -1.5 to 0.8 mmHg (diastolic) in the evolocumab plus SoC group and -0.4 to 2.0 mmHg (systolic) and 0.2 to 0.9 mmHg (diastolic) in the SoC alone group. In the year 2+ OLE period, the mean change from baseline to each study time point up to week 124 in systolic and diastolic blood pressure ranged from -1.5 to 4.9 mmHg (systolic) and -0.9 to 2.7 mmHg (diastolic).

The mean change from baseline to each study time point in heart rate ranged from 0.5 to 1.9 beats per minute (bpm) (any evolocumab group) and -0.4 to 2.3 bpm (any control group) in the integrated parent studies, from 1.5 to 3.2 bpm (evolocumab plus SoC group) and 0.9 to 1.9 bpm (SoC alone group) in the year 1 SoC-controlled period, and from 0.7 to 3.3 bpm in the year 2+ OLE period.

While no safety signal was identified regarding changes from baseline for systolic and diastolic blood pressure and heart rate among treatment groups, hypertension adverse events occurred slightly more often in the EvoMab group during the longer treatment period in the open-label, Year 1 SoC-controlled studies: 89 (3.1%) Any EvoMab vs 39 (2.7%) Any control. The participants in the EvoMab+SoC group had more frequent clinical contact and vital sign assessment than the SoC only group, which may have led to some element of reporting bias. In the 120-day Safety Update (data cutoff 01 July 2014), the incidence of hypertension AEs was not increased in the EvoMab group (3.5% evolocumab plus SoC and 3.8% SoC alone). An increase in hypertension AEs was also seen in the 52-week placebo-controlled trial 20110109: (19, 3.2% EvoMab vs 7, 2.3% placebo). This imbalance was not seen in the four phase 3 trials (13, 1.1% EvoMab vs 7, 1.2% control), but these trials were only 12 weeks in duration.

7.4.4 Electrocardiograms (ECGs)

QRS prolongation beyond specified thresholds was infrequent in all treatment groups. Of participants who had baseline values < 100 msec, no participant in the evolocumab groups and 1 (0.1%) in the placebo QM group had a maximum postbaseline QRS interval change ≥ 50%. Of participants who had baseline values that were ≥ 100 msec, 1 (0.5%) in the evolocumab 140 mg Q2W group, 1 (0.4%) in the evolocumab 420 mg QM group, and no participant in the control groups had a maximum postbaseline QRS interval change ≥ 25%.

In the integrated parent studies, the incidence of new ECG abnormalities reported after baseline was similar among participants treated with evolocumab and those treated with any control: 229 (6.3%) in any evolocumab group and 132 (6.3%) in any control group. The most frequently reported events were sinus bradycardia, which was reported in 152 (4.2%) participants in the any evolocumab group and 91 (4.4%) participants in the any control group, and prolonged QTc, which was reported in 14 (0.4%) participants in the any evolocumab group and 8 (0.4%) in the any control group.

The DCRP QT Interdisciplinary Review Team reviewed the applicant's integrated cardiac safety report and the proposed labeling. The QT team had issued a QT waiver in July 2012 under IND 105188. The QT team commented that evolocumab is a large targeted protein and thus has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that evolocumab has the potential to delay ventricular repolarization. The QT team believed that the applicant's proposed labeling in Section 12.2 Pharmacodynamics, namely: "In clinical studies, treatment with [TRADENAME] had no effect on the QTc interval and no relationship between [TRADENAME] concentration and QTc was observed." is reasonable.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Overall incidence of anti-evolocumab binding antibody development after at least 1 dose of evolocumab was 0.1% (7 out of 4846 participants) in the integrated phase 2 and phase 3 trials. No neutralizing antibodies were detected in any participant. There does not appear to be a temporal correlation between the development of binding antibodies and specific adverse events such as hypersensitivity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The evolocumab 140 mg dose administered subcutaneously every two weeks and the 420 mg dose administered subcutaneously every month led to similar reductions in LDL-C and there were no clinically remarkable differences in the safety profile for the two different dosing regimens. See Section 7.2.2 Explorations for Dose Response for additional information.

7.5.2 Time Dependency for Adverse Events

Time-to-Event Analysis of Adverse Events in Primary Hyperlipidemia and Mixed Dyslipidemia Trials

The table below summarizes the time-to-event onset for adverse events reported by ≥ 1% of participants in any treatment group of the integrated parent trials. For the adverse events of back pain, myalgia and nausea, the time-to-onset was several days shorter in the EvoMab groups as compared to the placebo or control groups. Overall, the times to onset of common adverse events in the integrated parent studies were similar across the treatment groups and there does not appear to be any notable pattern regarding the time of onset among the groups. Of note, no neurocognitive events were presented in the analyses of time-to-event onset for adverse events because none of these events occurred in ≥ 1% of participants in any treatment group.

Table 97: Summary of Event Onset for Adverse Events During the Parent Trials by Preferred Term in Descending Order of Frequency of Preferred Terms Reported by ≥ 1% of Participants in Any Treatment Group (Integrated Parent Analysis Set)

	Any Placebo (N=1526) n (%) or Median	Any Control (N=2080) n (%) or Median	EvoMab 140 mg Q2W or 420 mg QM (N=3201) n (%) or Median	Any EvoMab (N=3946) n (%) or Median
Nasopharyngitis				
Subjects with onset in period	77 (5.0)	99 (4.8)	154 (4.8)	231 (5.9)
Median time to 1st event (days) from period day 1	61	61	69	57
Upper respiratory tract infection				
Subjects with onset in period	43 (2.8)	56 (2.7)	103 (3.2)	127 (3.2)
Median time to 1st event (days) from period day 1	63	58	82	76

Headache Subjects with onset in period Median time to first event (days) from period day 1	46 (3.0) 51	66 (3.2) 35	97 (3.0) 42	119 (3.0) 36
Back pain Subjects with onset in period Median time to first event (days) from period day 1	43 (2.8) 68	56 (2.7) 67	97 (3.0) 61	115 (2.9) 55
Myalgia Subjects with onset in period Median time to first event (days) from period day 1	27 (1.8) 44	54 (2.6) 32	69 (2.2) 28	97 (2.5) 28
Arthralgia Subjects with onset in period Median time to first event (days) from period day 1	32 (2.1) 60	43 (2.1) 51	71 (2.2) 53	90 (2.3) 52
Influenza Subjects with onset in period Median time to first event (days) from period day 1	32 (2.1) 71	41 (2.0) 65	73 (2.3) 77	83 (2.1) 75
Nausea Subjects with onset in period Median time to first event (days) from period day 1	25 (1.6) 44	37 (1.8) 45	68 (2.1) 33	81 (2.1) 34
Diarrhea Subjects with onset in period Median time to first event (days) from period day 1	35 (2.3) 35	49 (2.4) 43	63 (2.0) 41	79 (2.0) 41
Cough Subjects with onset in period Median time to first event (days) from period day 1	20 (1.3) 58	26 (1.3) 54	56 (1.7) 85	78 (2.0) 70
N = number of subjects randomized in the integrated parent analysis set (IPAS); EvoMab = Evolocumab); QM = once monthly; Q2W = every 2 weeks;Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Any Control includes SC placebo and ezetimibe with or without SC placebo subjects. Any EvoMab includes any subject with EvoMab as a component of IP. Events with partial dates are excluded from median onset calculation. Coded using MedDRA version 17.0. Source: Modified from ISS Table 14-6.15.401 and Summary of Clinical Safety, Table 32.				

In the year 1 SoC-controlled period, the adverse events of bronchitis, myalgia and headache had a time-to-onset that was approximately 3 weeks shorter in the EvoMab group as compared to the control group; the remainder of the adverse events occurred earlier in the control group as compared to the EvoMab group.

7.5.3 Drug-Demographic Interactions

7.5.3.1 Race, Age, Sex, and Ethnicity

Age
The primary hyperlipidemia and mixed dyslipidemia integrated parent studies contained no pediatric participants (< 18 years of age), 1779 (29.5%) participants who were ≥ 65 years old, and 223 (3.7%) participants who were ≥ 75 years old. As shown in the table below, the most common adverse events (any evolocumab and any control, respectively) in the integrated parent studies for participants ≥ 75 years of age were nasopharyngitis (5.1% and 3.1%), fatigue (3.2% and 1.5%), and hypertension (3.2% and 1.5%). Regarding the imbalance in hypertension AEs, no safety signal was identified regarding changes from baseline for systolic and diastolic blood pressure and heart rate among treatment groups. Overall, although the numbers in this group are small and an increase in adverse events with age is not unexpected, there were more adverse events in the ≥ 75 years old group with longer duration of study than in the other groups.

Table 98: Analyses of Adverse Events in the ≥ 65 Years and ≥ 75 Years Subgroups

	≥ 65 Years Subgroup	≥ 75 Years Subgroup	Entire Integrated Population
Integrated Parent Studies			
N	Any EvoMab: 1193 Any control: 586	Any EvoMab: 158 Any control: 65	Any EvoMab: 3946 Any control: 2080
Overall incidence of AEs in subgroup	Any EvoMab: 619 (51.9%) Any control: 282 (48.1%)	Any EvoMab: 69 (43.7%) Any control: 30 (46.2%)	Any EvoMab: 2016 (51.1%) Any control: 1031 (49.6%)
Most common AEs with subject incidence (any EvoMab and any control)	• nasopharyngitis (5.7% and 4.2%) • myalgia (3.1% and 2.4%) • headache (3.1% and 2.9%) •all others < 3% in any EvoMab group	• nasopharyngitis (5.1% and 3.1%) • fatigue (3.2% and 1.5%) • hypertension (3.2% and 1.5%) • arthralgia (3.2% and 3.1%) • all others < 3% in any EvoMab group	• nasopharyngitis (5.9% and 4.8%) • upper respiratory tract infection (3.2% and 2.7%) • headache (3.0% and 3.2%) • back pain (3.0% and 2.7%) • myalgia (2.5% and 2.6%)
Year 1 SoC-controlled Period			
N	EvoMab+SoC: 852 SoC alone: 449	EvoMab+SoC: 105 SoC alone: 58	EvoMab+SoC: 2833 SoC alone: 1419
Overall subject incidence of AEs in subgroup	EvoMab+SoC: 543 (63.7%) SoC alone: 260 (57.9%)	EvoMab+SoC: 69 (65.7%) SoC alone: 36 (62.1%)	EvoMab+SoC: 1708 (60.3%) SoC alone: 781 (55.0%)
Most common AEs with subject incidence (EvoMab+SoC and SoC alone)	• nasopharyngitis (9.2% and 7.8%) • hypertension (4.1% and 2.4%) • arthralgia (3.5% and 3.3%) • osteoarthritis (3.2% and 1.8%) • headache (3.1% and 1.1%) • all others < 3% in EvoMab+SoC group	• urinary tract infection (6.7% and 5.2%) • fatigue (5.7% and 1.7%) • nasopharyngitis (5.7% & 3.4%) • hypertension (4.8% and 0%) • bronchitis(4.8% and 1.7%) • cough (3.8% and 3.4%) • all others < 3% in any EvoMab+SoC group	• nasopharyngitis (8.5% and 7.9%) • upper respiratory tract infection (4.2% and 4.0%) • arthralgia (3.4% and 2.5%) • back pain (3.1% and 2.5%) • hypertension (3.1% and 2.7%)
Year 2+ OLE Period			
N	Total: 258	Total: 23	Total: 954
Overall subject	Total: 192 (74.4%)	Total: 20 (87.0%)	713 (74.7%)

	≥ 65 Years Subgroup	≥ 75 Years Subgroup	Entire Integrated Population
incidence of AEs in subgroup (total)			
Most common AEs with subject incidence	• nasopharyngitis (14.3%) • back pain (7.4%) • hypertension (5.4%) • cough (5.0%) • oedema peripheral (3.9%) • cystitis (3.5%) • procedural pain (3.5%) • myalgia (3.5%) • pain in extremity (3.5%) • pneumonia (3.1%) • insomnia (3.1%) • all others < 3%	• nasopharyngitis (17.4%) • contusion (13.0%) • cough (13.0%) • insomnia (13.0%) • rhinitis (8.7%) • upper respiratory tract infection (8.7%) • arthralgia (8.7%) • dizziness (8.7%) • nausea (8.7%) • oedema peripheral (8.7%) • fall (8.7%) • angina pectoris (8.7%) • cystitis (8.7%) • sciatica (8.7%) • syncope (8.7%) • all others < 2 subjects in total group	• nasopharyngitis (11.7%) • upper respiratory tract infection (7.7%) • arthralgia (6.7%) • back pain (6.6%)

AE = adverse event; EvoMab = evolocumab (AMG 145); OLE = open-label extension; SoC = standard of care
Source: Summary of Clinical Safety, Table 99

Gender
Integrated Parent Studies:

For the number of participants reporting an adverse event, more women than men reported adverse events but the control group and EvoMab groups were balanced within each subgroup of female, male, and entire integrated population for the total number of participants reporting an adverse event (see table). Some observations about the common AEs:

- The increase in upper respiratory infection, hypertension and back pain in the EvoMab group as compared to the control group is largely driven by the male population.
- The increase in cough in the EvoMab group as compared to the control group is largely driven by the female population.
- The female population reported an increase in headache and dizziness in the EvoMab group as compared to control; this was not seen in the male population.
- The male population reported a larger increase in nausea in the EvoMab group as compared to control than the female population.

Similar to the observation for the entire integrated population, more SAEs were reported in the EvoMab group than the control group regardless of gender. While there were some differences in AEs between the male and female groups, this reviewer did not believe there were any gender-specific risks and that the small differences were more likely by chance.

Year 1 SoC-controlled Period:

Similar to the observation for the entire integrated population, more AEs and AEs that led to discontinuation were reported in the EvoMab group than the control group regardless of sex.

The male population reported an increase in SAEs in the EvoMab group as compared to control; this was not seen in the female population.

Some observations about the common AEs:

- The increase in nasopharyngitis and diarrhoea in the EvoMab group as compared to the control group is largely driven by the male population.
- The increase in upper respiratory tract infection, hypertension and influenza in the EvoMab group as compared to the control group is largely driven by the female population.

While there were some differences in AEs between the male and female groups in both study periods, this reviewer believes this reflects the play of chance and does not represent any sex-specific risks.

Table 99: Adverse Events in Females as compared to Males

	Females		Males		Entire Integrated Population	
Integrated Parent Studies						
N	Any Control (N = 1081) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 1557) n (%)	Any Control (N = 999) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 1644) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)
Number of subjects reporting AEs	570 (52.7)	840 (53.9)	461 (46.1)	759 (46.2)	1031 (49.6)	1599 (50.0)
SAEs	21 (1.9)	42 (2.7)	22 (2.2)	53 (3.2)	43 (2.1%)	95 (3.0%)
Number of subjects reporting AEs leading to discontinuation of IP (3 most common AEs in women)	28 (2.6)	42 (2.7)	20 (2.0)	29 (1.8)	48 (2.3)	71 (2.2)
Nausea	2 (0.2)	5 (0.3)	1 (0.1)	1 (0.1)	3 (0.1)	6 (0.2)
Myalgia	5 (0.5)	5 (0.3)	5 (0.5)	6 (0.4)	10 (0.5)	11 (0.3)
Pain In Extremity	0 (0.0)	3 (0.2)	1 (0.1)	1 (0.1)	1 (0.0)	4 (0.1)
Most common AEs in EvoMab group						
Nasopharyngitis	51 (4.7)	71 (4.6)	48 (4.8)	83 (5.0)	99 (4.8)	154 (4.8)
Upper Respiratory Tract Infection	32 (3.0)	42 (2.7)	24 (2.4)	61 (3.7)	56 (2.7)	103 (3.2)
Urinary Tract Infection	32 (3.0)	52 (3.3)	2 (0.2)	5 (0.3)	34 (1.6)	57 (1.8)
Back Pain	37 (3.4)	55 (3.5)	20 (2.0)	44 (2.7)	57 (2.7)	99 (3.1)
Myalgia	20 (1.9)	34 (2.2)	35 (3.5)	36 (2.2)	55 (2.6)	70 (2.2)
Influenza	25 (2.3)	39 (2.5)	16 (1.6)	34 (2.1)	41 (2.0)	73 (2.3)
Arthralgia	23 (2.1)	38 (2.4)	22 (2.2)	34 (2.1)	45 (2.2)	72 (2.2)
Pain In Extremity	20 (1.9)	34 (2.2)	19 (1.9)	29 (1.8)	39 (1.9)	63 (2.0)
Headache	43 (4.0)	70 (4.5)	23 (2.3)	28 (1.7)	66 (3.2)	98 (3.1)
Fatigue	24 (2.2)	32 (2.1)	16 (1.6)	28 (1.7)	40 (1.9)	60 (1.9)
Hypertension	13 (1.2)	19 (1.2)	13 (1.3)	27 (1.6)	26 (1.3)	46 (1.4)
Nausea	27 (2.5)	42 (2.7)	10 (1.0)	26 (1.6)	37 (1.8)	68 (2.1)
Cough	14 (1.3)	33 (2.1)	12 (1.2)	23 (1.4)	26 (1.3)	56 (1.7)
Diarrhoea	26 (2.4)	40 (2.6)	24 (2.4)	23 (1.4)	50 (2.4)	63 (2.0)
Dizziness	18 (1.7)	35 (2.2)	16 (1.6)	19 (1.2)	34 (1.6)	54 (1.7)
Year 1 SoC-controlled Period						
N	SoC (N = 694) n (%)	EvoMab + SoC (N = 1417) n (%)	SoC (N = 725) n (%)	EvoMab + SoC (N = 1416) n (%)	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)
All AEs	416 (59.9)	912 (64.4)	365 (50.3)	796 (56.2)	781 (55.0)	1708 (60.3)
SAEs	45 (6.5)	69 (4.9)	37 (5.1)	84 (5.9)	82 (5.8)	153 (5.4)
AEs leading to discontinuation of IP	0%	36 (2.5)	0%	22 (1.6)	0%	58 (2.0)
Most common AEs						
Nasopharyngitis	58 (8.4)	120 (8.5)	54 (7.4)	122 (8.6)	112 (7.9)	242 (8.5)

Upper Respiratory Tract Infection	24 (3.5)	69 (4.9)	33 (4.6)	50 (3.5)	57 (4.0)	119 (4.2)
Back Pain	18 (2.6)	42 (3.0)	17 (2.3)	47 (3.3)	35 (2.5)	89 (3.1)
Hypertension	17 (2.4)	45 (3.2)	22 (3.0)	44 (3.1)	39 (2.7)	89 (3.1)
Arthralgia	22 (3.2)	56 (4.0)	14 (1.9)	41 (2.9)	36 (2.5)	97 (3.4)
Myalgia	13 (1.9)	33 (2.3)	21 (2.9)	38 (2.7)	34 (2.4)	71 (2.5)
Influenza	21 (3.0)	49 (3.5)	16 (2.2)	35 (2.5)	37 (2.6)	84 (3.0)
Pain In Extremity	15 (2.2)	38 (2.7)	6 (0.8)	33 (2.3)	21 (1.5)	71 (2.5)
Diarrhoea	14 (2.0)	30 (2.1)	7 (1.0)	33 (2.3)	21 (1.5)	63 (2.2)
Headache	14 (2.0)	50 (3.5)	10 (1.4)	32 (2.3)	24 (1.7)	82 (2.9)

N = number of subjects randomized in the integrated extension SoC-controlled period analysis set; EvoMab = Evolocumab; SoC = Standard of Care. Coded using MedDRA version 17.0.
Modified from ISS Tables 14-6.2.5, 14-6.2.2., 14-6.4.50., 14-6.4.53., 14-6.4.56., 14-6.4.59., 14-6.5.2., 14-6.5.53., 14-6.5.50., 14-6.5.59., 14-6.5.56., 14-6.3.50., 14-6.3.53., 14-6.3.56. and 14-6.3.59.

Race

The study population was 83% white, 9% Asian, 6% black and 2% other. The table below summarizes the reported adverse events by race. Although the sample size among the groups varies, for the most part, the adverse event reporting was similar across race groups. There were some differences such as myalgia was reported as an adverse event that led to discontinuation in a higher percentage of subjects in the Asian population as compared to the other groups in the integrated parent studies.

Table 100: Adverse Events by Race

	White		Asian		Black		Entire Integrated Population	
Integrated Parent Studies								
N	Any Control (N=1754) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N=2724) n (%)	Any Control (N=184) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 229) n (%)	Any Control (N = 106) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 188) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)
Number of subjects reporting AEs	867 (49.4)	1336 (49.0)	86 (46.7)	121 (52.8)	51 (48.1)	103 (54.8)	1031 (49.6)	1599 (50.0)
SAEs	32 (1.8)	80 (2.9)	5 (2.7)	7 (3.1)	4 (3.8)	6 (3.2)	43 (2.1%)	95 (3.0%)
Number of subjects reporting AEs leading to discontinuation of IP	41 (2.3)	56 (2.1)	4 (2.2)	7 (3.1)	3 (2.8)	4 (2.1)	48 (2.3)	71 (2.2)
Nausea	6 (0.3)	10 (0.4)	1 (0.5)	0	0	1 (0.5)	3 (0.1)	6 (0.2)
Myalgia	10 (0.6)	7 (0.3)	0	3 (1.3)	0	0	10 (0.5)	11 (0.3)
Most common AEs in EvoMab group								
Nasopharyngitis	78 (4.4)	127 (4.7)	17 (9.2)	23 (10.0)	1 (0.9)	4 (2.1)	99 (4.8)	154 (4.8)
Upper Respiratory Tract Infection	43 (2.5)	75 (2.8)	8 (4.3)	12 (5.2)	3 (2.8)	11 (5.9)	56 (2.7)	103 (3.2)
Back Pain	49 (2.8)	84 (3.1)	2 (1.3)	2 (1.1)	3 (2.8)	8 (4.3)	57 (2.7)	99 (3.1)
Myalgia	52 (3.0)	54 (2.0)	1 (0.5)	6 (2.6)	2 (1.9)	7 (3.7)	55 (2.6)	70 (2.2)

Influenza	32 (1.8)	47 (1.7)	2 (1.1)	6 (2.6)	3 (2.8)	11 (5.9)	41 (2.0)	73 (2.3)
Arthralgia	39 (2.2)	58 (2.1)	3 (1.6)	8 (3.5)	2 (1.9)	3 (1.6)	45 (2.2)	72 (2.2)
Year 1 SoC-controlled Period								
N	Any Control (N=1206) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N=2437) n (%)	SoC (N = 122) n (%)	EvoMab + SoC (N = 231) n (%)	SoC (N = 72) n (%)	EvoMab + SoC (N = 132) n (%)	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)
All AEs	660 (54.7)	1446 (59.3)	81 (66.4)	166 (71.9)	33 (45.8)	79 (59.8)	781 (55.0)	1708 (60.3)
SAEs	69 (5.7)	131 (5.4)	8 (6.6)	14 (6.1)	4 (5.6)	8 (6.1)	82 (5.8)	153 (5.4)
AEs leading to discontinuation of IP	0	52 (2.1)	0	2 (0.9)	0	4 (3.0)	0%	58 (2.0)
Most common AEs								
Nasopharyngitis	84 (7.0)	187 (7.7)	28 (23.0)	49 (21.2)	0	4 (3.0)	112 (7.9)	242 (8.5)
Upper Respiratory Tract Infection	47 (3.9)	90 (3.7)	7 (5.7)	17 (7.4)	2 (2.8)	7 (5.3)	57 (4.0)	119 (4.2)
Back Pain	31 (2.6)	76 (3.1)	2 (1.6)	10 (4.3)	1 (1.4)	2 (1.5)	35 (2.5)	89 (3.1)
Hypertension	33 (2.7)	77 (3.2)	3 (2.5)	11 (4.8)	3 (4.2)	5 (3.8)	39 (2.7)	89 (3.1)
Arthralgia	32 (2.7)	83 (3.4)	4 (3.3)	9 (3.9)	0	2 (1.5)	36 (2.5)	97 (3.4)
Myalgia	31 (2.6)	64 (2.6)	3 (2.5)	5 (2.2)	0	1 (0.8)	34 (2.4)	71 (2.5)

N = number of subjects randomized in the integrated extension SoC-controlled period analysis set; EvoMab = Evolocumab (AMG 145); SoC = Standard of Care. Coded using MedDRA version 17.0.
Source: Modified from ISS: Tables 14-6.3.8., 14-6.3.11, 14-6.3.14., 14-6.3.17., 14-6.3.20., 14-6.3.23., 14-6.4.14., 14-6.4.11., 14-6.4.8., 14-6.4.17., 14-6.4.20., 14-6.4.23., 14-6.5.8., 14-6.5.11., 14-6.5.14., 14-6.5.17., 14-6.5.20. and 14-6.5.23.

7.5.3.2 Therapeutic settings (statin-intolerant, monotherapy, and combination with statin groups)

A summary of adverse events in the 4 phase 2 and phase 3 therapeutic settings (statin-intolerant, monotherapy, and combination with statin groups) are summarized in the tables below. For the statin intolerant group, the overall incidence of participants who experienced at least 1 adverse event or led to discontinuation of investigational product was greater than for the other therapeutic settings for both the evolocumab and control groups. The incidences of treatment emergent CTCAE ≥ grade 3 or grade 4 and serious adverse events was low and overall similar between the integrated phase 2 and phase 3 therapeutic settings for both the evolocumab and control groups.

Table 101: Summary of Participant Incidence of Adverse Events for Specified Therapeutic Settings for Parent Studies (Integrated Parent Analysis Set)

	Monotherapy (Studies 20101154, 20110114, and subjects in 20110109 in the diet-alone background therapy stratum)	Combination Therapy With Statins (Studies 20101155, 20110115, 20110231, 20120348, 20120356, 20090158, 20110117, and subjects in 20110109 in the low, high, or maximal background drug therapy cohorts)	Statin Intolerant (Studies 20090159 and 20110116)	Entire Integrated Population
Integrated Parent Studies				
N	Any EvoMab: 651 Any control: 480	Any EvoMab: 2965 Any control: 1466	Any EvoMab: 330 Any control: 134	Any EvoMab: 3946 Any control: 2080
All AEs	Any EvoMab: 324 (49.8%) Any control: 236 (49.2%) Any placebo: 140 (49.8%)	Any EvoMab: 1479 (49.9%) Any control: 702 (47.9%) Any placebo: 613 (49.2%)	Any EvoMab: 213 (64.5%) Any control: 93 (69.4%)	Any EvoMab: 2016 (51.1%) Any control: 1031 (49.6%) Any placebo: 753 (49.3%)
SAEs	Any EvoMab: 9 (1.4%) Any control: 5 (1.0%) Any placebo: 4 (1.4%)	Any EvoMab: 90 (3.0%) Any control: 34 (2.3%) Any placebo: 32 (2.6%)	Any EvoMab: 11 (3.3%) Any control: 4 (3.0%)	Any EvoMab: 110 (2.8%) Any control: 43 (2.1%) Any placebo: 36 (2.4%)
AEs leading to discontinuation of IP	Any EvoMab: 8 (1.2%) Any control: 13 (2.7%) Any placebo: 8 (2.8%)	Any EvoMab: 46 (1.6%) Any control: 20 (1.4%) Any placebo: 16 (1.3%)	Any EvoMab: 21 (6.4%) Any control: 15 (11.2%)	Any EvoMab: 75 (1.9%) Any control: 48 (2.3%) Any placebo: 24 (1.6%)
Most common AEs (any EvoMab and any control)	• nasopharyngitis (4.3% and 4.0%) • upper respiratory tract infection (4.3% and 5.2%) • diarrhoea (3.2% and 2.9%) • headache (3.2% and 3.1%) • back pain (2.5% and 2.5%) • all others ≤ 2% in any EvoMab group	• nasopharyngitis (6.3 % and 4.9%) • upper respiratory tract infection (3.1% and 2.1%) • back pain (2.9 % and 2.9%) • headache (2.6% and 2.9%) • arthralgia (2.4% and 2.0%) • influenza (2.4% and 2.1%) • cough (2.0% and 1.1%) • all others < 2% in any EvoMab group	• myalgia (9.1 % and 14.2%) • headache (7.0% and 6.7%) • pain in extremity (5.8% and 1.5%) • muscle spasms (5.2% and 5.2%) • back pain (4.5% and 2.2%) • nasopharyngitis (4.5 % and 6.0%) • all others < 4% in any EvoMab group	• nasopharyngitis (5.9% and 4.8%) • upper respiratory tract infection (3.2% and 2.7%) • headache (3.0% and 3.2%) • back pain (3.0% and 2.7%) • myalgia (2.5% and 2.6%)

Data cutoff date 01APR2014.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Q2W = every 2 weeks; QM = monthly.
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product.
Coded using MedDRA version 17.0
Source: Modified from Table 7-4 Response to 06Nov2014 IR and Summary of Clinical Safety, Appendix Table 5

In the statin-intolerant group, the 3 most common adverse events where any evolocumab>any control: headache (7.0%; 6.7%), pain in extremity (5.8%; 1.5%) and back pain (4.5%; 2.2%).

In the monotherapy group, the 3 most common adverse events where any evolocumab> any control: nasopharyngitis (4.3%; 4.0%); diarrhea (3.2%; 2.9%), and headache (3.2%; 3.1%).

In the statin combination group, the 3 most common adverse events where evolocumab> any control: nasopharyngitis (6.3%; 4.9%), upper respiratory tract infection (3.1%; 2.1%), and arthralgia (2.4%; 2.1%).

7.5.4 Drug-Disease Interactions

7.5.4.1 Diabetes or Metabolic Syndrome

Analyses of adverse events, HbA1c levels, fasting blood glucose levels, and proteinuria were performed by the glucose tolerance parent baseline group (T2DM, metabolic syndrome and neither T2DM nor metabolic syndrome). In the table below, the adverse event of diabetes mellitus in the Type 2 Diabetes Mellitus group refers to events of worsening diabetes. As all subjects in the Type 2 Diabetes Mellitus group had diabetes at the beginning of the parent study, any reported adverse events of diabetes mellitus would be a worsening of their baseline condition (verbatim terms: worsening of diabetes, diabetes mellitus, worsening of diabetes mellitus, worsening diabetes, diabetes mellitus exacerbated, and diabetes mellitus aggravated). The results between EvoMab and control groups were similar in the three different glucose tolerance groups (see table).

Table 102: Analyses of Adverse Events in the Glucose Tolerance Parent Baseline Group

	Type 2 Diabetes Mellitus	Metabolic Syndrome	Neither Type 2 Diabetes nor Metabolic Syndrome	Entire Integrated Population
Integrated Parent Studies				
N	Any EvoMab: 548 Any control: 255	Any EvoMab: 1315 Any control: 688	Any EvoMab: 2083 Any control: 1187	Any EvoMab: 3946 Any control: 2080
Overall subject incidence of AEs in subgroup	Any EvoMab: 247 (45.1%) Any control: 125 (49.0%)	Any EvoMab: 678 (51.6%) Any control: 337 (49.0%)	Any EvoMab: 1091 (52.4%) Any control: 569 (50.0%)	Any EvoMab: 2016 (51.1%) Any control: 1031 (49.6%)
Overall subject incidence of SAEs in subgroup	Any EvoMab: 20 (3.6%) Any control: 13 (5.1%)	Any EvoMab: 44 (3.3%) Any control: 11 (1.6%)	Any EvoMab: 46 (2.2%) Any control: 19 (1.7%)	Any EvoMab: 110 (2.8%) Any control: 43 (2.1%)
Most common AEs with subject incidence (any EvoMab and any control)	• nasopharyngitis (5.8% and 4.7%) • back pain (2.7% and 2.7%) • fatigue (2.6% and 0.4%) • influenza (2.6% and 2.4) • upper respiratory tract infection (2.4% and 2.4) • muscle spasms (2.0% and 1.6%) • dizziness (2.0% and 1.6%) • diabetes mellitus (2.0% and 1.6%) • all others < 2% in any EvoMab group	• nasopharyngitis (5.2% and 4.5%) • upper respiratory tract infection (3.7% and 3.2%) • back pain (3.0% and 2.9%) • headache (2.9% and 3.3%) • cough (2.6% and 1.3%) • pain in extremity (2.4% and 1.6%) • arthralgia (2.4% and 2.0%) • influenza (2.1% and 2.2%) • nausea (2.1% and 2.3%) • all others <2% in any EvoMab group	• nasopharyngitis (6.3% and 4.9%) • headache (3.6% and 3.5%) • myalgia (3.2% and 3.3%) • upper respiratory tract infection (3.1% and 2.5%) • back pain (3.0% and 2.6%) • arthralgia (2.4% and 2.4%) • diarrhoea (2.2% and 2.4%) • nausea (2.1% and 1.6%) • influenza (2.0% and 1.8%) • fatigue (2.0% and 2.0%) • all others < 2% in any EvoMab group	• nasopharyngitis (5.9% and 4.8%) • upper respiratory tract infection (3.2% and 2.7%) • headache (3.0% and 3.2%) • back pain (3.0% and 2.7%) • myalgia (2.5% and 2.6%)
HbA1c (range of the mean change from baseline)	Any EvoMab: 0.09% to 0.37% Any control: 0.07% to 0.13%	Any EvoMab: -0.04% to 0.05% Any control: -0.02% to 0.07%	Any EvoMab: 0% to 0.08% Any control: -0.03% to 0.03%	Any EvoMab: 0.01% to 0.08% Any control: 0% to 0.05%
Fasting blood glucose levels (range of the mean change from baseline)	Any EvoMab: 0.08 to 0.84 mmol/L Any control: -0.03 to 0.51 mmol/L	Any EvoMab: -0.05 to 0.05 mmol/L Any control: -0.02 to 0.12 mmol/L	Any EvoMab: 0.03 to 0.21 mmol/L Any control: -0.01 to 0.12 mmol/L	Any EvoMab: 0.04 to 0.19 mmol/L Any control: 0.02 to 0.15 mmol/L
Proteinuria (with no baseline proteinuria)	Any EvoMab: 29 (6.1%) Any control: 21 (9.4%)	Any EvoMab: 76 (6.4%) Any control: 35 (5.6%)	Any EvoMab: 93 (4.8%) Any control: 46 (4.3%)	Any EvoMab: 198 (5.5%) Any control: 102 (5.3%)

	Type 2 Diabetes Mellitus	Metabolic Syndrome	Neither Type 2 Diabetes nor Metabolic Syndrome	Entire Integrated Population
Year 1 SoC-controlled Period				
N	EvoMab+SoC: 359 SoC alone: 201	EvoMab+SoC: 982 SoC alone: 456	EvoMab+SoC: 1492 SoC alone: 762	EvoMab+SoC: 2833 SoC alone: 1419
HbA1c (range of the mean change from baseline)	EvoMab+SoC: 0.18% to 0.34% SoC alone: 0.09% to 0.35%	EvoMab+SoC: -0.04% to 0.02% SoC alone: 0.02% to 0.09%	EvoMab+SoC: -0.06% to 0.07% SoC alone: -0.04% to 0.04%	EvoMab+SoC: 0.02% to 0.11% SoC alone: 0.02% to 0.11%
Fasting blood glucose levels (range of the mean change from baseline)	EvoMab+SoC: 0.27 to 0.62 mmol/L SoC alone: -0.09 to 0.39 mmol/L	EvoMab+SoC: -0.01 to 0.08 mmol/L SoC alone: -0.04 to 0.07 mmol/L	EvoMab+SoC: 0.10 to 0.14 mmol/L SoC alone: 0.08 to 0.15 mmol/L	EvoMab+SoC: 0.10 to 0.17 mmol/L SoC alone: 0.04 to 0.14 mmol/L
Proteinuria (with no baseline proteinuria)	EvoMab+SoC: 43 (13.7%) SoC alone: 20 (10.8%)	EvoMab+SoC: 81 (9.1%) SoC alone: 43 (10.5%)	EvoMab+SoC: 93 (6.7%) SoC alone: 45 (6.4%)	EvoMab+SoC: 217 (8.4%) SoC alone: 108 (8.3%)
Year 2+ OLE Period				
N	Total: 89	Total: 370	Total: 495	Total: 954
HbA1c (range of the mean change from baseline)	Total: 0.28% to 0.70%	Total: -0.80% to 0.09%	Total: -0.11% to 0.15%	Total: -0.20% to 0.70%
Fasting blood glucose levels (range of the mean change from baseline)	Total: -9.94 to 0.93 mmol/L	Total: -0.03 to 0.54 mmol/L	Total: 0.08 to 0.23 mmol/L	Total: -0.11 to 0.26 mmol/L
Proteinuria (with no baseline proteinuria)	Total: 0 (0%)	Total: 0 (0%)	Total: 2 (0.4%)	Total: 2 (0.2%)

AE = adverse event; EvoMab = evolocumab; HbA1c = hemoglobin A1c; OLE = open-label extension; SoC = standard of care
The range of the mean change from baseline in hemoglobin A1c (HbA1c) and fasting blood glucose levels are the minimum and maximum values for the mean change from baseline in each parameter for each treatment group across the post-baseline scheduled visits.
Source: Summary of Clinical Safety, Table 101

7.5.4.2 Hepatic Impairment

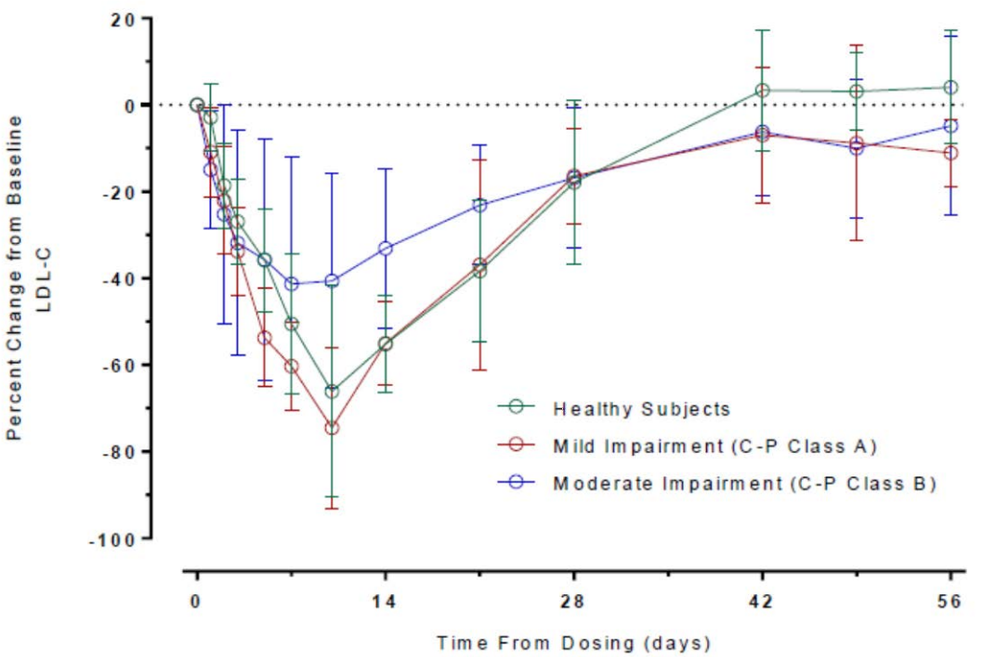
The phase 2 and 3 trials had an exclusion criterion of AST or ALT > 2 x ULN at screening which, for the most part, excluded participants with active liver disease or hepatic dysfunction from entering the trials. Therefore, individuals with mild, moderate, or severe hepatic impairment by Child-Pugh categories could be not analyzed in the phase 2 and phase 3 studies (and hence, in the IPAS and IECAS). Of note, evolocumab is not eliminated by liver enzymes and transporters; rather, evolocumab is eliminated through nonspecific (linear) elimination via the reticuloendothelial system and specific target-mediated (nonlinear) clearance. Evolocumab clearance is not expected to be affected by hepatic impairment. The applicant does not propose a dosage adjustment in the label for patients with hepatic impairment.

Hepatically impaired participants were evaluated in Study 20120341, an open-label, parallel-group study designed to compare the PK of evolocumab in participants with mild and moderate hepatic impairment compared with that in healthy participants. Participants were assigned equally to 1 of 3 groups (n=8 participants in each group) depending on their degree of hepatic impairment (Child-Pugh class A [mild], class B [moderate], or healthy participants). Patients with severe hepatic impairment (Child-Pugh class C) have not been studied. The majority of participants were men (83%), white (75%), and not Hispanic (79%). The mean (SD) age of participants at baseline was 48.7 (5.0) years.

After a single 140 mg SC dose, evolocumab exposure, as assessed by C_{max} and AUC_{last}, decreased with increasing hepatic impairment. Median t_{max} was 4.5 or 5.0 days in both hepatically impaired (mild or moderate) and healthy subjects. Compared with healthy subjects with no hepatic impairment, participants with mild and moderate hepatic impairment had least squares mean AUC_{last} values that were 39% and 47% lower, respectively (p = 0.090) and least squares mean C_{max} values that were 21% and 34% lower, respectively (p = 0.18).

Although the sample size is small in each group which limits the finding, there were numerical differences in the pharmacodynamic responses in the healthy group as compared to the moderate hepatic impaired group. Although maximum LDL-C reduction in the healthy group was numerically greater than the moderate hepatic impairment group, it was numerically lower than in the mild hepatic impairment group and the concentration-time curves overlapped for the three cohorts (see figure).

Figure 13: Geometric Mean Percentage Change From Baseline (± Standard Deviation) of Ultracentrifugation LDL-C (mg/dL) Over Time (Phase 1 Study 20120341)



C-P = Child-Pugh; LDL-C = low-density lipoprotein cholesterol; UC = ultracentrifugation.
Source: Table 14-11.2 of CSR 20120341 in Module 5.3.3.3.

Adverse events were reported in 1 (13%) participant in the healthy group (preferred term of hemorrhoids), 4 (50%) participants in the mild hepatic impairment group (preferred terms of diarrhea, vomiting, headache, breast mass, depression and pruritic rash) and 2 (25%) participants in the moderate hepatic impairment group

(preferred terms of diarrhea, ascites, decreased appetite, parotitis, pustular rash, tachycardia and urinary tract infection). A serious adverse event of depression was reported in 1 (4%) participant with mild hepatic impairment who had a > 40-year history of depression.

No participant had creatine kinase > 5 times the upper limit of normal (ULN) at any assessment or post-baseline ALT > 3 times the ULN. Three participants with moderate hepatic impairment had AST > 3 times the ULN at a single post-baseline assessment, and 1 participant with mild hepatic impairment had AST > 3 times the ULN at both post-baseline assessments. Three participants with moderate hepatic impairment had total bilirubin > 2 times the ULN at a single post-baseline assessment. Two of the elevated liver related tests at a post-baseline assessment (AST > 3 times the ULN in Subject 34166001012 and total bilirubin > 2 times the ULN in Subject 34166003013) occurred in participants who did not have these elevations at either the screening visit or at study day 1. For both participants, the elevation occurred on study day 29 and had resolved by the next assessment at study day 57.

7.5.4.3 Renal Impairment

The phase 2 and 3 trials had an exclusion criterion for moderate to severe renal impairment (< 30 mL/min/1.73 m^2); therefore, analyses for these participants are quite limited, as only 4 participants had eGFR < 30 mL/min/1.73 m^2.

The applicant states that, at baseline, the following number of participants was randomized in the integrated parent (ie, controlled blinded) trials:

- 4026 (67%) with mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m^2),
- 670 (11%) with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2), and
- 4 (0.1%) with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).

During the integrated parent studies, the median duration of exposure to investigational product (IP) (2.8 months) was the same for the any evolocumab and any control groups, regardless of the level of renal impairment.

Of the participants in the integrated parent studies, a total of 3013 (68%), 511 (11%), and 3 (0.1%) participants with mild, moderate, and severe renal impairment, respectively, were randomized in the year 1 standard of care (SoC)-controlled period of the long-term extension studies at the time of the data cutoff date for the 120-day Safety Update (01 July 2014). During the year 1 SoC-controlled period, the median duration of exposure to IP was approximately 10 to 11 months in the evolocumab plus SoC group, regardless of the level of renal impairment; no IP was administered in the SoC alone group.

Of note, the Modification of Diet in Renal Disease (MDRD) Study equation has limited accuracy above eGFR 60, so the number of participants that the applicant includes in the mild renal impairment category is likely an over-estimate (many may have a true GFR ≥90 mL/min/1.73m^2).

The table below summarizes the AEs, SAEs and AEs that led to discontinuation by the eGFR parent baseline subgroup. There were no clinically meaningful differences in the types and percentages of AEs reported across the renal impairment subgroups.

Table 103: Analysis of Adverse Events in the Baseline eGFR Subgroups

	Severe (eGFR < 30 mL/min/1.73 m^2)		Moderate (30 ≤ eGFR < 60 mL/min/1.73 m^2)		Mild (60 ≤ eGFR < 90 mL/min/1.73 m^2)		Entire Integrated Population	
Integrated Parent Studies								
	Any EvoMab (N = 3)	Any control (N = 1)	Any EvoMab (N = 438)	Any control (N = 232)	Any EvoMab (N = 2636)	Any control (N = 1390)	Any EvoMab (N = 3946)	Any control (N = 2080)
Overall subject incidence in subgroup – All AEs	2 (66.7%)	1 (100.0%)	250 (57.1%)	117 (50.4%)	1313 (49.8%)	697 (50.1%)	2016 (51.1%)	1031 (49.6%)
Overall subject incidence in subgroup – All SAEs	1 (33.3%)	0	17 (3.9%)	8 (3.4%)	64 (2.4%)	24 (1.7%)	110 (2.8%)	43 (2.1%)
Overall subject incidence in subgroup – AEs leading to IP discontinuation	1 (33.3%)	0	10 (2.3%)	5 (2.2%)	53 (2.0%	37 (2.7%)	75 (1.9%)	48 (2.3%)
Most common AEs with subject incidence (any EvoMab and any control)	• dizziness (33.3% and 0%) • myocardial infarction (33.3% and 0%) • muscle spasms (0% and 100%) • renal impairment (33.3% and 0%) • all others 0%		• nasopharyngitis (5.9% and 4.7%) • headache (4.3% and 4.3%) • URTI (3.9% and 0.9%) • cough (3.7% and 1.3%) • urinary tract infection (3.2% and 1.3%) • muscle spasms (3.2% and 3.4%) • back pain (3.0% and 2.6%) • myalgia (2.7% and 2.2%) • all others < 2.5% for any EvoMab		• nasopharyngitis (5.5% and 5.0%) • URTI (3.0% and 2.8%) • back pain (2.8% and 2.9%) • arthralgia (2.5% and 1.9%) • headache (2.5% and 2.7%) • myalgia (2.5% and 2.5%) • all others < 2.5% for any EvoMab		• nasopharyngitis (5.9% and 4.8%) • URTI (3.2% and 2.7%) • headache (3.0% and 3.2%) • back pain (3.0% and 2.7%) • myalgia (2.5% and 2.6%) • all others < 2.5% for any EvoMab	

	Severe (eGFR < 30 mL/min/1.73 m^2)		Moderate (30 ≤ eGFR < 60 mL/min/1.73 m^2)		Mild (60 ≤ eGFR < 90 mL/min/1.73 m^2)		Entire Integrated Population	
Year 1 SoC-controlled Period								
	EvoMab+SoC (N = 3)	SoC alone (N = 0)	EvoMab+SoC (N = 343)	SoC alone (N = 168)	EvoMab+SoC (N = 2017)	SoC alone (N = 996)	EvoMab+SoC (N = 2976)	SoC alone (N = 1489)
Overall subject incidence in subgroup – All AEs	2 (66.7%)	0	222 (64.7%)	97 (57.7%)	1333 (66.1%)	628 (63.1%)	1946 (65.4%)	910 (61.1%)
Overall subject incidence in subgroup – All SAEs	0	0	35 (10.2%)	17 (10.1%)	123 (6.1%)	63 (6.3%)	197 (6.6%)	100 (6.7%)
Overall subject incidence in subgroup – AEs leading to IP discontinuation	0	0	16 (4.7%)	1 (0.6%)	46 (2.3%)	1 (0.1%)	68 (2.3%)	2 (0.1%)
Most common AEs with subject incidence (EvoMab+SoC and SoC alone)	• atrial fibrillation (33.3% and 0%) • gastroesophageal reflux disease (33.3% and 0%) • all others 0%		• nasopharyngitis (7.3% and 8.9%) • hypertension (4.7% and 1.2%) • URTI (4.4% and 3.0%) • urinary tract infection (4.1% and 0.6%) • arthralgia (3.5% an 3.0%) • back pain (3.5% and 5.4%) • all others < 3.5% for EvoMab plus SoC		• nasopharyngitis (9.0% and 8.7%) • URTI (5.2% and 4.2%) • arthralgia (4.3% and 3.1%) • headache (3.6% and 1.6%) • hypertension (3.6% and 4.2%) • cough (3.5% and 3.1%) • all others < 3.5% for EvoMab plus SoC		• nasopharyngitis (8.9% and 8.6%) • URTI (5.1% and 4.3%) • arthralgia (4.0% and 3.0%) • back pain (3.8% and 3.2%) • hypertension (3.5% and 3.8%) • all others < 3.5% for EvoMab plus SoC	

AE = adverse event; eGFR = estimated glomerular filtration rate; EvoMab = evolocumab (AMG 145); IP = investigational product; SAE = serious adverse event; SoC = standard of care; URTI = upper respiratory tract infection
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356, 20110110, 20120138
Data cutoff date of 01 April 2014 for integrated parent studies and 01 July 2014 for year 1 SoC-controlled period

Source: Table 8 from Feb 2015 Information Request Response

7.5.5 Drug-Drug Interactions

No studies on potential drug-drug or drug-food interactions were done with evolocumab as no PK drug-drug interactions were expected with evolocumab.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the integrated parent trials, adverse events for the Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) system organ class were reported in 43 (1.1%) participants in the any evolocumab group and 17 (0.8%) participants in the any control group. Forty-three participants in the evolocumab group reported 44 total neoplasm events of which 22 were benign and 22 were solid malignant tumors; the 17 participants in the control group reported 18 total neoplasm events of which 8 were benign and 10 were solid malignant tumors. The most common adverse events in the any evolocumab group and the any control group were basal cell carcinoma (0.2% and < 0.1%), skin papilloma (0.2% and < 0.1%), and lipoma (0.1% in both groups). The other malignancies in the EvoMab group occurred as single events over multiple organ systems—no pattern was apparent.

In the year 1 SoC-controlled period, 57 (2.0%) and 34 (2.4 %) participants reported a neoplasm in the evolocumab plus SoC group and the SoC alone group, respectively. The 57 participants in the evolocumab plus SoC group reported 63 total neoplasm events of which 28 were benign and 35 were solid malignant tumors; the 34 participants in the control group reported 35 total neoplasm events of which 13 were benign neoplasms, 21 were solid malignant tumors, and 1 was a hematologic malignancy. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were basal cell carcinoma (0.3% in both groups), squamous cell carcinoma (0.2% and 0%), and skin papilloma (0.1% and 0.3%).

In the year 2+ OLE period, 36 (3.8%) participants reported 42 total neoplasm events of which 22 were benign, 15 were solid malignant tumors, and 5 were hematologic malignancies. The most common adverse events were basal cell carcinoma (0.4%), lipoma (0.4%), and skin papilloma (0.3%).

7.6.2 Human Reproduction and Pregnancy Data

No studies of evolocumab have been conducted in pregnant women. Also, no studies have been conducted to determine whether evolocumab is present in breast milk or to assess the effects of evolocumab in breast-fed infants.

Across the evolocumab clinical program, 7 pregnancies following maternal evolocumab exposure and 9 following paternal evolocumab exposure have been reported out of approximately 6800 subjects enrolled in evolocumab clinical studies. There have been no reports of lactation in the clinical program. The following table summarizes the 16 pregnancies with evolocumab exposure. The number of pregnancies with adequate data and follow-up are insufficient to make any conclusions regarding the effects of evolocumab during pregnancy.

Table 104: Tabular Summary of Pregnancies Following Evolocumab Exposure in the Clinical Program through 01 April 2014

Subject Number	Study Number	Time of Evolocumab Exposure[a]	Birth Outcome (normal delivery, abortion, unknown, etc.)
Maternal Exposure Pregnancies			
11411001012	20110114	1st Trimester	Full-term birth without complications
15516066007	20110110	1st Trimester	Spontaneous abortion not otherwise specified
15516066007	20110110	1st Trimester	Ectopic pregnancy
15516066007	20110110	8 months prior to conception	Elective termination for personal reasons
15466036003	20101154	1st Trimester	Lost to follow-up
15466043005	20110110	1st Trimester	Unknown (ongoing)
23356001010	20110271	1st Trimester	Follow up (ongoing)
Paternal Exposure Pregnancies			
10913001001	20110109	1st Trimester	Full-term birth without complications
15416016005	20110110	Unknown	Lost to follow-up
10916302038	20120138	1st and 2nd Trimesters	Lost to follow-up
10916302038	20110109	1st Trimester	Spontaneous abortion
15466013002	20101154	1st Trimester	Lost to follow-up
15866003018	20110110	1st, 2nd, and 3rd Trimesters	Full-term birth without complications
16866009037	20110168	1st Trimester	Elective termination not otherwise specified
15466030002	20110110	1st and 2nd Trimesters	Spontaneous abortion not otherwise specified
15856001009	20110110	1st,2nd, and 3rd Trimesters	Full-term birth without complications

a For paternal exposure pregnancies, time of exposure is the trimester of partner's pregnancy in which the male subject was on study drug.
Source: Summary of Clinical Safety, Table 104

7.6.3 Pediatrics and Assessment of Effects on Growth

Fourteen adolescent participants were included in the HoFH trials. All adolescent participants from 20110233 with the exception of 1 adolescent participant in part B continued in the 20110271 extension study. Three additional adolescent participants who did not participate in the 20110233 parent study were enrolled into Study 20110271. Of the 10 HoFH adolescents in Study 20110233 part B, 7 participants received evolocumab 420 mg QM, and 3 participants received placebo.

A similar safety profile was observed for these participants, although the numbers are quite limited. Adverse events were reported in 3 (42.9%) participants in the evolocumab group and 2 (66.7%) participants in the placebo group, and no preferred term was reported for > 1 adolescent participant in either treatment group. Growth, development and sexual maturation have not been investigated.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Evolocumab is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use. The effects of overdose of evolocumab are unknown. No off-target effects of potential overdose are known based on nonclinical or clinical study evaluations. There is no known antidote to evolocumab.

Evolocumab is not chemically or pharmacologically similar to other drugs with known abuse potential. There is no evidence to suggest a potential for drug abuse or misuse and none has been observed. Like other antibodies, evolocumab is unlikely to get across the blood brain barrier. An assessment of abuse potential was not performed.

The FDA Controlled Substance Staff (CSS) was consulted regarding the abuse potential of evolocumab. Based on evolocumab's general properties and structure, as well a review of the adverse event profile, CSS concluded that an abuse assessment of evolocumab is not needed.

7.7 Additional Submissions / Safety Issues

7.7.1 120-Day Safety Update for BLA: Primary Hyperlipidemia/Mixed Dyslipidemia and HoFH Populations

The findings of this 120-day Safety Update did not change the safety conclusions of the BLA and no new safety risks were identified. Of note, the 120-day safety update provided no new information regarding the parent, randomized, double-blind controlled trials, since all were complete before submission. The 120-day safety update only provides additional data for the open-label extension studies, both the open-label controlled period (year 1) and uncontrolled period (year 2+).

Exposure

The applicant submitted in December 2014 the 120-Day Safety Update for evolocumab for the indications of (1) hyperlipidemia and mixed dyslipidemia and (2) homozygous familial hypercholesterolemia (HoFH). This safety update provides updated safety data from the 3 ongoing extension studies (Studies 20110110, 20120138, and 20110271) up to a data cutoff date of 01 July 2014. The cumulative number of participants exposed to evolocumab at the data cutoff for BLA submission (01 April 2014) for ≥ 6, ≥ 12, ≥ 18, ≥ 24, and ≥ 30 months was 3286, 1797, 881, 611, and 165 subjects, respectively. The cumulative number of participants exposed to evolocumab at this data cutoff of 01 July 2014 for ≥ 6, ≥ 12, ≥ 18, ≥ 24, and ≥ 30 months was 3549, 2458, 1124, 709, and 491 participants, respectively (see table).

Table 105: Overall Summary of Cumulative Exposure in the Evolocumab BLA and 120-day Safety Update (Integrated Parent, Extension SoC-controlled Period, and Extension All-IP Period Analysis Sets)

	BLA					120-day Safety Update				
	Control		EvoMab			Control		EvoMab		
	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total
Number of Subjects	1526	3027	4783	4971	6026	1526	3072	4949	5115	6026
Total pt-year exposure	604	1737	4242	4427	6165	604	1989	5060	5246	7235
Number of Subjects										
≥ 3 months	1501	2988	4654	4839	5904	1501	3028	4720	4904	5904
≥ 6 months	294	1444	3276	3286	4571	294	1669	3536	3549	4704
≥ 12 months	287	718	1760	1797	2430	287	913	2456	2458	3669
≥ 18 months	1	55	843	881	1405	1	62	999	1124	1588
≥ 24 months	0	1	598	611	920	0	3	707	709	1156
≥ 30 months	0	0	61	165	328	0	0	317	491	860
≥ 36 months	0	0	0	0	0	0	0	1	5	8

Data cutoff dates: BLA, cumulative through 01APR2014; 120-day Safety Update, cumulative through 01JUL2014. Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356, 20110110, 20120138. a Any control includes placebo, ezetimibe, or standard of care. BLA = Biologics License Application; EvoMab = Evolocumab (AMG 145); Q2W = once every 2 weeks; QM = once monthly. Patients can contribute data to more than one treatment group. pt-year = patient years, where years are calculated as the sum of period durations for the treatment group across subjects divided by 365.25. Months are calculated by multiplying the patient years by 12 and rounding to the nearest whole month. Source: Applicant's Summary of Clinical Safety, 120-day Update Table 14-5.1.1.

Thus, the cumulative number of participants exposed to evolocumab for ≥ 12, ≥ 18, ≥ 24, and ≥ 30 months increased by 661, 243, 98, and 326 participants, respectively (see table).

In the 120-day Safety Update for the year 1 SoC-controlled period, the mean (SD) duration of evolocumab exposure in this period was 9.8 (2.7) months and the median was 10.1 months as compared to a mean of 8.1 months and median of 8.4 months at the April 2014 cut-off.

In the 120-day Safety Update for the year 2+ OLE period, the mean (SD) duration of evolocumab exposure in this period was 9.4 (7.4) months and the median was 13.8 months as compared to a mean of 12.6 months and median of 12.9 months at the April 2014 cut-off. This reduction in exposure during this period is due to the influx of new participants who completed the year 1 SoC-controlled period and entered the year 2+ OLE period (increased from 964 participants in the BLA to 1675 participants in the 120-day Safety Update), which reduced the mean and median exposure. Because of this, the incidence of adverse events decreases due to this influx of subjects with a short duration of additional exposure. Therefore, the 120-day safety update for the 2+ OLE does not provide much additional exposure and the updated numbers are only presented if clinically relevant.

In the 120-day Safety Update, a total of 100 participants with HoFH received evolocumab in Study 20110271, compared with 96 in the BLA (data cutoff of 01 April 2014). Mean (SD) exposure to evolocumab for these participants was 8.9 (5.1) months and the median was 7.5 months in the 120-day Safety Update, compared with 6.4 (5.0) months and 5.1 months, respectively, in the BLA. Exposure to evolocumab for these participants was ≥ 12 and ≥ 24 weeks for 98.0% and 69.0% of participants, respectively, in the 120-day Safety Update. The corresponding values in the BLA were 71.9% and 49.0% of participants, respectively.

Device Exposure

A total of 51,081 injections with auto-injector/pen (AI/pen) were reported in the 120-day Safety Update, compared with 30,521 injections with AI/pen in the BLA. All of these injections delivered evolocumab because the SoC group did not receive injections of IP.

The cumulative number of participants exposed to evolocumab using the AI/pen at the data cutoff for BLA submission (01 April 2014) for ≥ 6, ≥ 12, and ≥ 18 months was 1680, 105 and 1, respectively. The cumulative number of participants exposed to evolocumab using the AI/pen at this data cutoff of 01 July 2014 for ≥ 6, ≥ 12, and ≥ 18 months was 2013, 771 and 0, respectively (see table). The cumulative number of participants exposed to evolocumab using the pre-filled syringe (PFS) for ≥ 3 months at the data cutoff for BLA submission (01 April 2014) and at this data cutoff of 01 July 2014 was 0 (see table), since the PFS was only used in an 8-week bridging study that was completed before BLA submission.

Table 106: Overall Summary of Cumulative Exposure by Device in the Evolocumab BLA and 120-day Safety Update (Integrated Parent, Extension SoC-controlled Period, and Extension All-IP Period Analysis Sets)

	BLA					120-day Safety Update				
	Control		EvoMab			Control		EvoMab		
	Any Placebo	Any Control [a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total [b]	Any Placebo	Any Control [a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total
Number of Subjects	1526	2035	4783	4971	6006	1526	2035	4947	5113	6006
Total pt-year exposure	604	732	4123	4308	5040	604	732	5059	5244	5976
Number of Subjects Used AI/pen	821	1298	3165	3165	3891	821	1298	3982	3982	4633
Total pt-year exposure	207	328	1595	1595	1924	207	328	2233	2233	2561
Number of Subjects Used AI/pen										
≥ 3 months	803	1272	2937	2937	3641	803	1272	3198	3198	3871
≥ 6 months	1	1	1680	1680	1854	1	1	2013	2013	2043
≥ 12 months	0	0	105	105	189	0	0	771	771	1114
≥ 18 months	0	0	1	1	1	0	0	0	0	0
Number of Subjects Used AMD	0	0	82	82	82	0	0	158	158	158
Total pt-year exposure	0	0	19	19	19	0	0	30	30	30
Number of Subjects Used AMD										
≥ 3 months	0	0	81	81	81	0	0	92	92	92
Number of Subjects Used PFS	0	0	75	75	75	0	0	75	75	75
Total pt-year exposure	0	0	12	12	12	0	0	12	12	12
Number of Subjects Used PFS										
≥ 3 months	0	0	0	0	0	0	0	0	0	0

	BLA					120-day Safety Update				
	Control		EvoMab			Control		EvoMab		
	Any Placebo	Any Control [a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total	Any Placebo	Any Control [a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total
Number of Subjects Used Vial	705	737	1827	2059	2547	705	737	1916	2104	2547
Total pt-year exposure	396	404	2497	2682	3086	396	404	2784	2970	3374
Number of Subjects Used Vial										
≥ 3 months	698	729	1812	2041	2522	698	729	1902	2087	2522
≥ 6 months	293	293	1615	1625	1919	293	293	1756	1766	2060
≥ 12 months	287	287	1564	1577	1876	287	287	1637	1681	2015
≥ 18 months	1	1	643	681	693	1	1	692	807	863
≥ 24 months	0	0	597	610	618	0	0	618	620	622
≥ 30 months	0	0	60	164	218	0	0	215	427	536

Data cutoff dates: BLA, cumulative through 01APR2014; 120-day Safety Update, cumulative through 01JUL2014.
BLA = Biologics License Application; EvoMab = Evolocumab (AMG 145); AI/pen = autoinjector/pen; AMD = auto mini-doser; PFS = prefilled syringe; QM = once monthly; Q2W = every 2 weeks Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356, 20110110, and 20120138. Exposure via vial and syringe used the Process 1 evolocumab drug substance of evolocumab and exposure via any of the 3 devices (PFS, AI/pen, AMD) used the Process 2 evolocumab drug substance. Subjects can contribute data to more than 1 treatment group.
a Any includes placebo, placebo + ezetimibe (Standard of care and Study 20101154 ezetimibe patients are excluded from analysis).
b The BLA excluded ezetimibe-only subjects from 20101154 that did not receive investigational product in 20110110. pt-year = patients years, where years are calculated as the sum of period durations for the treatment group across subjects divided by 365.25. Months are calculated by multiplying the patient years by 12 and rounding to the nearest whole month. For subjects in Study 20110110, period duration contributes to AI/pen after the first AI/pen use and to vials prior to the first AI/pen use. For periods with only a single device option for subjects, the device exposure duration is set to the period duration. For studies with multiple device options, device exposure duration is the sum of time from being exposed to a device until switching to another device, ending the study, or the data cutoff date. Source: Applicant's Summary of Clinical Safety, 120-day Update Table 14-5.2.407.

Adverse Event Summary for the Primary Hyperlipidemia Trials

Year 1 SoC-controlled Period

As shown in the following table, in the year 1 SoC-controlled period, the cumulative incidence and severity of adverse events in the 120-day Safety Update were similar to those reported in the BLA. Adverse events were reported for 65.4% of participants in the evolocumab plus SoC group and 61.1% of subjects in the SoC alone group in the 120-day Safety Update, compared with 60.3% and 55.0% of participants, respectively, in the BLA. The 5 most common adverse events in the evolocumab plus SoC group, where EvoMab > SoC, were nasopharyngitis (8.9% evolocumab plus SoC group and 8.6% SoC alone group), upper respiratory tract infection (5.1% and 4.3%), arthralgia (4.0% and 3.0%), back pain (3.8% and 3.2%), and influenza (3.4% and 2.8%).

In the year 1 SoC-controlled period, serious adverse events were reported for 6.6% of participants in the evolocumab plus SoC group and 6.7% of participants in the SoC alone group in the 120-day Safety Update, compared with 5.4% and 5.8% of participants, respectively, in the BLA. The 5 most common serious adverse events in the evolocumab plus SoC group in the 120-day Safety Update were osteoarthritis (0.3% evolocumab plus SoC group and 0.1% SoC alone group), angina pectoris (0.2% and 0.1%), chest pain (0.2% and 0.2%), angina unstable (0.2% and 0.5%), and appendicitis (0.2% and 0.1%).

An adverse event leading to discontinuation of evolocumab in the evolocumab plus SoC group was reported for 2.3% of participants in the 120-day Safety Update, compared with 2.0% of participants in the BLA. The most common AEs that led to discontinuation of evolocumab in the evolocumab plus SoC group were Myalgia (0.3%), arthralgia (0.1%), fatigue (0.1%), injection site pain (0.1%) and headache (0.1%).

Of the 19 deaths reported in the primary hyperlipidemia trials, 4 deaths were reported between the 01 April 2014 data cutoff date for the BLA and the 01 July 2014 data cutoff date for the 120-day Safety Update (2 deaths in the Year 1 SoC-controlled period and 2 deaths in the 2+ OLE period). This is discussed in Section 7.3.1

Deaths: *Deaths in the 120-day Safety Update (01 July 2014 data cutoff).*

Table 107: Summary of Cumulative Subject Incidences of Adverse Events During the Year 1 SoC-controlled Period in the Evolocumab BLA and 120-day Safety Update (IECAS)

	Control in Parent Study		EvoMab in Parent Study		All	
	SoC n (%)	EvoMab + SoC n (%)	SoC n (%)	EvoMab + SoC n (%)	SoC n (%)	EvoMab + SoC n (%)
BLA	(N = 472)	(N = 943)	(N = 947)	(N = 1890)	(N = 1419)	(N = 2833)
All adverse events	265 (56.1)	567 (60.1)	516 (54.5)	1141 (60.4)	781 (55.0)	1708 (60.3)
Grade ≥ 2	152 (32.2)	277 (29.4)	280 (29.6)	623 (33.0)	432 (30.4)	900 (31.8)
Grade ≥ 3	26 (5.5)	48 (5.1)	59 (6.2)	123 (6.5)	85 (6.0)	171 (6.0)
Grade ≥ 4	3 (0.6)	8 (0.8)	6 (0.6)	10 (0.5)	9 (0.6)	18 (0.6)
Serious adverse events	24 (5.1)	48 (5.1)	58 (6.1)	105 (5.6)	82 (5.8)	153 (5.4)
Leading to discontinuation of investigational product	-	19 (2.0)	-	39 (2.1)	-	58 (2.0)
Serious	-	4 (0.4)	-	7 (0.4)	-	11 (0.4)
Non-serious	-	15 (1.6)	-	33 (1.7)	-	48 (1.7)
Fatal adverse events	1 (0.2)	1 (0.1)	3 (0.3)	2 (0.1)	4 (0.3)	3 (0.1)
120-day Safety Update	(N = 497)	(N = 995)	(N = 992)	(N = 1981)	(N = 1489)	(N = 2976)
All adverse events	310 (62.4)	640 (64.3)	600 (60.5)	1306 (65.9)	910 (61.1)	1946 (65.4)
Grade ≥ 2	179 (36.0)	339 (34.1)	344 (34.7)	747 (37.7)	523 (35.1)	1086 (36.5)
Grade ≥ 3	34 (6.8)	65 (6.5)	76 (7.7)	153 (7.7)	110 (7.4)	218 (7.3)
Grade ≥ 4	4 (0.8)	8 (0.8)	7 (0.7)	13 (0.7)	11 (0.7)	21 (0.7)
Serious adverse events	31 (6.2)	62 (6.2)	69 (7.0)	135 (6.8)	100 (6.7)	197 (6.6)
Leading to discontinuation of investigational product	-	24 (2.4)	-	44 (2.2)	-	68 (2.3)
Serious	-	5 (0.5)	-	8 (0.4)	-	13 (0.4)
Non-serious	-	19 (1.9)	-	37 (1.9)	-	56 (1.9)
Fatal adverse events	2 (0.4)	2 (0.2)	3 (0.3)	2 (0.1)	5 (0.3)	4 (0.1)

Data cutoff dates: BLA, cumulative through 01APR2014; 120-day Safety Update, cumulative through 01JUL2014.
Includes the following studies: 20110110, 20120138.
- = not applicable; BLA = Biologics License Application; N = number of subjects randomized in the integrated extension SoC-controlled period analysis set (IECAS); EvoMab = evolocumab (AMG 145); SoC = standard of care. Coded using MedDRA version 17.0.
Source: Applicant's Summary of Clinical Safety, 120-day Update Table 14-6.1.3.

A device related adverse event was reported for 52 of 2234 participants (2.3%) who used the autoinjector/pen (AI/pen) in the 120-day Safety Update, compared with 37 of 1951 participants (1.9%) who used the AI/pen in the BLA, and most of the events were consistent with injection site reactions (injection site bruising, erythema, pain, haematoma, haemorrhage, hypersensitivity, pruritus, rash, reaction or swelling). All of these events were reported during evolocumab treatment because participants assigned to SoC alone did not receive any placebo injections.

There were 54,078 injections reported using the AI/pen and 218 AI/pen complaint issues received cumulatively from the 3 clinical studies through 01 July 2014. During the interval from 01 April 2014 through 01 July 2014, 117 AI/pen complaint issues were reported from the same 3 studies. Of the 218 cumulative complaint issues, 4 have been reported to be AI/pen failures. The complaint code assigned to the 4 identified AI/pen failures is "syringe broken during/after use."

There were no serious device related adverse events.

Adjudicated Cardiovascular Events and Noncoronary Revascularizations in Primary Hyperlipidemia and Mixed Dyslipidemia Studies

During the adjudication process, there were no discordant results between adjudicators and no instances when the Clinical Endpoint Committee chairperson had to determine the final adjudication result. The adjudication process is ongoing and adjudication of 3 deaths (gastric cancer, malignant lung neoplasm, and pneumonia) that were newly reported in the 120-day Safety Update was not completed at the time of the data cutoff date of 01 July 2014.

As shown in the following table, in the year 1 SoC-controlled period, the evolocumab plus SoC group had 26 (0.9%) participants and the SoC alone group had 26 (1.7%) participants with positively adjudicated cardiovascular events; the corresponding percentages in the BLA were 22, 0.8% and 19, 1.3%, respectively.

Table 108: Cumulative Subject Incidences of Positively Adjudicated Cardiovascular Events and Noncoronary Revascularizations in the Evolocumab BLA and 120-day Safety Update (IECAS and IEAAS)

	BLA			120-day Safety Update		
	Year 1 SoC-controlled Period		Year 2+ OLE Period	Year 1 SoC-controlled Period		Year 2+ OLE Period
	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)	EvoMab + SoC (N = 954) n (%)	SoC (N = 1489) n (%)	EvoMab + SoC (N = 2976) n (%)	EvoMab + SoC (N = 1675) n (%)
Number of subjects with any positively adjudicated clinical event	19 (1.3)	22 (0.8)	12 (1.3)	26 (1.7)	26 (0.9)	17 (1.0)
Death	4 (0.3)	3 (0.1)	2 (0.2)	4 (0.3)	3 (0.1)	3 (0.2)
Cardiovascular	1 (0.1)	3 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)
Non-cardiovascular	2 (0.1)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)
Undetermined	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myocardial infarction (fatal and non-fatal)	5 (0.4)	6 (0.2)	3 (0.3)	5 (0.3)	8 (0.3)	3 (0.2)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal	5 (0.4)	6 (0.2)	3 (0.3)	5 (0.3)	8 (0.3)	3 (0.2)
Hospitalization for unstable angina	2 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)	1 (0.1)
Coronary Revascularization	8 (0.6)	11 (0.4)	7 (0.7)	14 (0.9)	12 (0.4)	8 (0.5)
PCI	8 (0.6)	6 (0.2)	5 (0.5)	13 (0.9)	7 (0.2)	5 (0.3)
Surgical	0 (0.0)	5 (0.2)	2 (0.2)	1 (0.1)	5 (0.2)	3 (0.2)

	BLA			120-day Safety Update		
	Year 1 SoC-controlled Period		Year 2+ OLE Period	Year 1 SoC-controlled Period		Year 2+ OLE Period
	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)	EvoMab + SoC (N = 954) n (%)	SoC (N = 1489) n (%)	EvoMab + SoC (N = 2976) n (%)	EvoMab + SoC (N = 1675) n (%)
Cerebrovascular Event	5 (0.4)	3 (0.1)	3 (0.3)	7 (0.5)	3 (0.1)	5 (0.3)
Transient ischemic attack	4 (0.3)	1 (0.0)	1 (0.1)	5 (0.3)	1 (0.0)	2 (0.1)
Stroke (fatal and non-fatal)	1 (0.1)	2 (0.1)	2 (0.2)	2 (0.1)	2 (0.1)	3 (0.2)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic with hemorrhagic conversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type undetermined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal	1 (0.1)	2 (0.1)	2 (0.2)	2 (0.1)	2 (0.1)	3 (0.2)
Ischemic	0 (0.0)	1 (0.0)	2 (0.2)	0 (0.0)	1 (0.0)	2 (0.1)
Ischemic with hemorrhagic conversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhagic stroke	1 (0.1)	1 (0.0)	0 (0.0)	2 (0.1)	1 (0.0)	1 (0.1)
Type undetermined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure event	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.0)	2 (0.1)
Heart failure hospitalization	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.0)	2 (0.1)
Urgent heart failure visit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	BLA			120-day Safety Update		
	Year 1 SoC-controlled Period		Year 2+ OLE Period	Year 1 SoC-controlled Period		Year 2+ OLE Period
	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)	EvoMab + SoC (N = 954) n (%)	SoC (N = 1489) n (%)	EvoMab + SoC (N = 2976) n (%)	EvoMab + SoC (N = 1675) n (%)
Non-coronary revascularization	3 (0.2)	5 (0.2)	2 (0.2)	3 (0.2)	7 (0.2)	4 (0.2)
Percutaneous	2 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)	3 (0.2)
Surgical	1 (0.1)	3 (0.1)	1 (0.1)	1 (0.1)	4 (0.1)	1 (0.1)

Data cutoff dates: BLA, cumulative through 01APR2014; 120-day Safety Update, cumulative through 01JUL2014.
BLA = Biologics License Application; N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab (AMG 145); OLE = open-label extension; PCI = percutaneous coronary intervention; SoC = standard of care.

Some cases from the phase 2 and phase 3 lipid lowering clinical studies had lipid values present in the adjudication package. Includes the following studies: 20110110, 20120138
Subject 10966418008 was randomized to placebo in the parent study and SoC in the extension study and died prior to the data cutoff, but the event does not contribute to this table since the event was not adjudicated prior to the snapshot.
Source: Applicant's Summary of Clinical Safety, 120-day Update Table 25

Adverse Event Summary for the HoFH Trials

The cumulative subject incidence of any adverse event was 68.0% in the 120-day Safety Update and 55.2% in the BLA. In Trial 20110271, the 5 most common adverse events were nasopharyngitis (9, 9.0%), influenza (7, 7.0%), anemia (5, 5.0%), headache (5, 5.0%) and carotid intima-media thickness increased (4, 4.0%). The only events that were newly reported for > 2% of HoFH subjects in Trial 20110271 between 01 April 2014 and 01 July 2014 were nasopharyngitis (4.0%) and anemia (3.0%).

The cumulative subject incidence of any serious adverse event was 10.0% (n=10) in the 120-day Safety Update and 7.3% (n=7) in the BLA. The majority were CV in nature (angina pectoris, aortic stenosis, aortic valve disease, carotid artery occlusion).

One participant (1.0%) discontinued evolocumab because of a non-serious adverse event; this event was reported previously in the BLA. There were no newly reported events in the 120-day Safety Update.

There were no fatal adverse events.

In the 120-day Safety Update, 66 HoFH participants in Trial 20110271 used the AI/pen for a mean (SD) of 3.1 (1.4) months and a median of 3.3 months. A device related adverse event was reported for 5 (5.0%) participants. In the BLA, 37 HoFH participants in trial 20110271 used the AI/pen for a median of 1.1 months, and a device related adverse event was reported for 2.7% of the participants. Most of the device related adverse events in the 120-day Safety Update were consistent with injection site reactions. None of the newly reported device related adverse events in the 120-day Safety Update were serious and none led to discontinuation of evolocumab treatment. A total of 4 adolescent participants with HoFH used the AI/pen in trial 20110271 for a median of 2.0 months and no device related adverse events were reported for these adolescents in the 120-day Safety Update.

Primary Hyperlipidemia Trials: Analysis of Adverse Events by Organ System Where Incidence in Evolocumab Group > Control Group

Vascular Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 5.9% of participants in the evolocumab plus SoC group and 4.8% of participants in the SoC alone group in the 120-day Safety Update, compared with

5.1% and 3.5% of participants, respectively, in the BLA. The most common Vascular Disorders in the evolocumab plus SoC group in the 120-day Safety Update continued to be hypertension (3.5% evolocumab plus SoC and 3.8% SoC alone) and hypotension (0.4% and 0.1%).

Gastrointestinal Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 13.1% of participants in the evolocumab plus SoC group and 10.3% of participants in the SoC alone group in the 120-day Safety Update, compared with 11.5% and 8.9% of participants, respectively, in the BLA. The most common Gastrointestinal Disorders in the evolocumab plus SoC group in the 120-day Safety Update continued to be diarrhea (2.5% evolocumab plus SoC and 1.7% SoC alone), nausea (1.7% and 1.0%), and vomiting (1.5% and 0.7%).

General Disorders and Administration Site Conditions

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 11.9% of participants in the evolocumab plus SoC group and 5.7% of participants in the SoC alone group in the 120-day Safety Update, compared with 10.8% and 4.8% of participants, respectively, in the BLA. The most common General Disorder and Administration Site Condition in the evolocumab plus SoC group in the 120-day Safety Update continued to be fatigue (2.5% evolocumab plus SoC group and 0.9% SoC alone group) and injection site-related AEs (such as bruising, pain, erythema). Of note, participants assigned to SoC alone in the extension studies did not receive any placebo injections.

Immune System Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 1.4% of participants in the evolocumab plus SoC group and 0.9% of participants in the SoC alone group of the 120-day Safety Update, and 1.1% and 0.8% of participants, respectively, in the BLA. The most common Immune System Disorders in the evolocumab plus SoC group in the 120-day Safety Update continued to be seasonal allergy (0.9% evolocumab plus SoC group and 0.5% SoC alone group) and hypersensitivity (0.2% in both groups). There was one new report of an SAE of anaphylactic reaction that is discussed in the hypersensitivity section and is unlikely to be due to evolocumab exposure.

Anti-evolocumab Antibody Formation

In the 120-day Safety Update, the cumulative incidence of anti-evolocumab binding antibody development after receiving at least 1 dose of evolocumab in the integrated phase 2 and phase 3 studies was 0.3% (13 of 4915 participants), compared with 0.1% (7 of 4846 participants) in the BLA. No neutralizing antibodies were detected in any participant.

The table below summarizes the temporal relationship between adverse events and positive binding antibody results that were newly reported in the 120-day Safety Update. No serious adverse events were temporally associated with a positive binding antibody result. There does not appear to be any adverse events, such as hypersensitivity, that are temporally related to positive binding antibodies.

Table 109: Temporal Relationship between Adverse Events and Positive Binding Antibody Results (Participants with a Newly Reported Positive Binding Antibody Result in the 120-day Safety Update)

Subject ID	Study	Treatment	Positive	Negative Results	Adverse Events
11521003015	Year 1 SoC-controlled	EvoMab + SoC	OLE day 169	OLE day 1 OLE day 85	(None)
11521006051	Parent study Year 1 SoC-controlled	EvoMab 420 mg QM SoC only	OLE day 169	Parent day 1 Parent day 85 OLE day 85	(None)
11522002044	Year 1 SoC-controlled	EvoMab + SoC	OLE day 169	OLE day 85	OLE day 114 grade 1 nausea OLE day 193 grade 1 cystitis OLE day 255 grade 1 cystitis
11522002057	Parent study Year 1 SoC-controlled	EvoMab 420 mg QM EvoMab + SoC	OLE day 173	Parent day 1 Parent day 85 OLE day 84	OLE day 3 grade 1 rhinorrhea OLE day 91 grade 3 hemorrhoids OLE day 91 grade 2 large intestine polyp OLE day 168 grade 1 excoriation OLE day 168 grade 1 edema peripheral
11522003034	Year 1 SoC-controlled	SoC only	OLE day 169	OLE day 85	Parent day 70 grade 2 URTI (received placebo in parent)
11565012010	Parent study Year 1 SoC-controlled	EvoMab 420 mg QM EvoMab + SoC	OLE day 168	Parent day 1 Parent day 82 OLE day 1 OLE day 84	OLE day 83 grade 2 depression
11565012014	Year 1 SoC-controlled	EvoMab + SoC	OLE day 164	OLE day 1 OLE day 80	(None)

Data cutoff date: 01JUL2014. EvoMab = evolocumab; OLE = open label extension; QM = once monthly; SC = subcutaneously; SoC = standard of care; URTI = upper respiratory tract infection. The method used for adverse events listed included all adverse events occurring before and after the positive binding antibody result. These adverse events occurred before the positive antibody result (or at the beginning of study) through the date of the next negative finding.
Source: Table 35 from 120-say-safety-update

Hypersensitivity

As was done in the BLA submission, broad and narrow search strategies were used to assess multiple preferred terms possibly associated with hypersensitivity. In the narrow searches for the 120-day Safety Update, the cumulative subject incidence of potential hypersensitivity in the year 1 SoC-controlled period was 4.9% for evolocumab plus SoC and 3.6% for SoC alone. In comparison, in the BLA in the year 1 SoC-controlled period it was 4.4% for evolocumab plus SoC and 3.3% for SoC alone. Most of the hypersensitivity adverse events were in the Skin and Subcutaneous Tissue Disorders system organ class (ie, rash, urticaria, angioedema), which is discussed in more detail in that section.

Infections and Infestations

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 32.3% of participants in the evolocumab plus SoC group and 30.2% of participants in the SoC alone group in the 120-day Safety Update, compared with 28.8% and 27.3% of participants, respectively, in the BLA. The most common Infections and Infestations in the evolocumab plus SoC group in the 120-day Safety Update continued to be nasopharyngitis (8.9% evolocumab plus SoC and 8.6% SoC alone), upper respiratory tract infection (5.1% and 4.3%), and influenza (3.4% and 2.8%).

Metabolism and Nutrition Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 4.2% of participants in the evolocumab plus SoC group and 4.4% of participants in the SoC alone group in the 120-day Safety Update, compared with 3.6% and 3.1% of participants, respectively, in the BLA. The most common Metabolism and Nutrition Disorders in the evolocumab plus SoC group continued to be diabetes mellitus (1.0% evolocumab plus SoC and 0.7% SoC alone), gout (0.7% and 0.5%), and type 2 diabetes mellitus (0.7% and 0.5%).

Because diabetes related adverse events have been reported with statins, broad and narrow search strategies were used to assess safety risks with evolocumab therapy. In the narrow searches, the incidence of potential diabetes events in the year 1 SoC-controlled period was 2.2% for evolocumab plus SoC and 2.1% for SoC alone. In comparison, in the BLA in the year 1 SoC-controlled period it was 2.1% for evolocumab plus SoC and 1.6% for SoC alone.

Musculoskeletal and Connective Tissue Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 22.1% of participants in the evolocumab plus SoC group and 18.7% of participants in the SoC alone group in the 120-day Safety Update, compared with 19.1% and 15.2% of participants, respectively, in the BLA. The most common Musculoskeletal and Connective Tissue Disorders in the evolocumab plus SoC group continued to be arthralgia (4.0% evolocumab plus SoC and 3.0% SoC alone), back

pain (3.8% and 3.2%), pain in extremity (2.9% and 1.9%), and myalgia (2.8% and 2.6%).

There was one new serious report of rhabdomyolysis in the 120-day Safety Update that was reported during evolocumab treatment in the year 2+ OLE period.

- Subject 15966018001 is a 67-year-old white woman with a medical history that includes schizoaffective with bipolar disorder, self-mutilation, suicide attempt, hypertension, stroke, type 2 diabetes mellitus, hypothyroidism, and chronic obstructive pulmonary disease. Concomitant medications included metformin, glimepiride, losartan, omeprazole, bupropion hydrochloride, clonazepam, venlafaxine, and lithium, and recently initiated medications included zolpidem, chlorpromazine, benzatropine mesylate, valproate semisodium, hydroxyzine, and haloperidol. The subject was admitted to the hospital with muscle weakness, slurred speech, ataxia, and closed head injury after falling 3 times in the prior 2 days. Two days prior to this admission, she had just been discharged from the hospital after a 10-day stay due to weakness, ataxia, confusion, delirium and psychosis accompanied by both auditory and visual hallucinations, impaired concentration, and command delusions. The investigator reported a strong possibility that, for this previous admission, the subject may have been confused with her medication administration as her primary caregiver (husband) was also hospitalized. On the day of admission, vital signs, physical examination, chest x-ray, and electrocardiogram were normal. Urine chemistry showed low valproic acid level (30 mug/ml) and low lithium level (0.5 mmol/L). Laboratory tests showed hematocrit 32.3%, hemoglobin 10.1 g/dL WBC count 13.4 × 106/L, albumin 3.1 g/dL, glucose 222 mg/dL, sodium 131 mmol/L, estimated glomerular filtration rate 34 (normal ≥60), BUN 25 mg/dL (11 mg/dL at baseline of parent study [reference range 4 to 24 mg/dL]).,creatinine 1.6 mg/dL ((0.8 mg/dL at baseline of parent study [reference range 0.6 to 1.3 mg/dL]), and creatinine phosphokinase (CPK) 1593 U/L (178 U/L at baseline of parent study [reference range 25 to 192 U/L]). Urinalysis was normal. Troponin and toxicology studies were all negative. Clinical impressions included renal insufficiency, acute rhabdomyolysis, anemia, and falls likely due to her recent medications. Treatment included hydration with normal saline, morphine, and ondansetron. Additional treatment included zolpidem for insomnia and amantadine for involuntary movements. Five days after admission, laboratory tests showed decreased CPK 368 U/L. The outcome of the events acute rhabdomyolysis and renal failure were reported as resolved and the patient was discharged from the hospital on the same day. Approximately one month later, laboratory tests showed CPK 153 U/L, creatinine 1.1 mg/dL, and BUN 22 mg/dL. Evolocumab treatment was continued after the event. Other non-muscle-related serious adverse events were also reported for this subject in the 120-day Safety Update, including anxiety, depression, diabetic ketoacidosis, esophageal spasm, ataxia, psychotic disorder, suicidal ideation, hallucination, delirium, and confusional state.

In the year 1 SoC-controlled period, postbaseline CK > 10 x ULN was observed in 0.2% of participants and 0.6% of participants in the evolocumab plus SoC group and the SoC alone group, respectively; this included 1 participant in each group who had a postbaseline CK > 10 x ULN newly observed in the 120-day Safety Update. Many of these participants had confounding factors (such as strenuous physical exercise,

previous CK elevations, and concomitant statin therapy) that may have contributed to the events.

Nervous System Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 9.7% of participants in the evolocumab plus SoC group and 8.3% of participants in the SoC alone group in the 120-day Safety Update, compared with 8.4% and 7.0% of participants, respectively, in the BLA. The most common Nervous System Disorders in the evolocumab plus SoC group continued to be headache (3.3% evolocumab plus SoC and 1.9% SoC alone) and dizziness (1.7% and 1.8%). Other nervous system events of interest in the 120-day Safety Update for the evolocumab plus SoC group are amnesia (7, 0.2% evolocumab plus SoC and 1, 0.1% SoC alone) and memory impairment (7, 0.2% and 2, 0.1%).

Psychiatric Disorders

In the year 1 SoC-controlled period, adverse events in this system organ class were reported for 4.1% of participants in the evolocumab plus SoC group and 2.8% of participants in the SoC alone group in the 120-day Safety Update, compared with 3.3% and 2.3% of participants, respectively, in the BLA. The most common Psychiatric Disorders in the evolocumab plus SoC group continued to be insomnia (1.4% evolocumab plus SoC and 1.0% SoC alone), anxiety (1.0% and 0.5%), and depression (1.0% and 1.1%).

Neurocognitive Adverse Events

Neurocognitive events were evaluated in both the BLA and the 120-day Safety Update using the following high level group terms:

- deliria (including confusion)
- cognitive and attention disorders and disturbances
- dementia and amnestic conditions
- disturbances in thinking and perception
- mental impairment disorders

As summarized in the table below, in the year 1 SoC-controlled period, neurocognitive adverse events were reported for 0.8% of participants in the evolocumab plus SoC group and 0.2% of participants in the SoC alone group in the 120-day Safety Update, compared with 0.6% and 0.2% of participants, respectively, in the BLA.

Table 110: Cumulative Subject Incidences of Neurocognitive Adverse Events by High Level Group Term and Preferred Term in the Evolocumab BLA and 120-day Safety Update

	BLA		120-day Safety Update	
Year 1 SoC-controlled Period	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)	SoC (N = 1489) n (%)	EvoMab + SoC (N = 2976) n (%)
Number of subjects reporting adverse events	3 (0.2)	16 (0.6)	3 (0.2)	25 (0.8)
Deliria (incl confusion)	0 (0.0)	2 (0.1)	0 (0.0)	3 (0.1)
Confusional State	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.1)
Disorientation	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Disturbances in thinking and perception	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Illusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Mental impairment disorders	3 (0.2)	14 (0.5)	3 (0.2)	21 (0.7)
Amnesia	1 (0.1)	2 (0.1)	1 (0.1)	7 (0.2)
Memory Impairment	2 (0.1)	7 (0.2)	2 (0.1)	7 (0.2)
Dementia	0 (0.0)	2 (0.1)	0 (0.0)	3 (0.1)
Mental Impairment	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Dementia Alzheimer's Type	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Transient Global Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Year 2+ OLE Period	Total (N = 954) n (%)	Total (N = 1675) n (%)
Number of subjects reporting adverse events	0 (0.0)	2 (0.1)
Deliria (incl confusion)	0 (0.0)	1 (0.1)
Confusional State	0 (0.0)	1 (0.1)
Delirium	0 (0.0)	1 (0.1)
Disturbances in thinking and perception	0 (0.0)	1 (0.1)
Hallucination	0 (0.0)	1 (0.1)
Mental impairment disorders	0 (0.0)	1 (0.1)
Amnesia	0 (0.0)	1 (0.1)

Data cutoff dates: BLA, cumulative through 01APR2014; 120-day Safety Update, cumulative through 01JUL2014.
Searched terms are deliria (incl confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders. Includes all events that were reported in the evolocumab plus SoC group in the year 1 SoC-controlled period (IECAS) or in the year 2+ period (IEAAS) of the 120-day Safety Update.
BLA = Biologics License Application; EvoMab = evolocumab; SoC = standard of care; IP = investigational product.
Source: Summary of Clinical Safety, 120-day Update Table 42.

There was one new serious report of transient global amnesia in the evolocumab plus SoC group. Subject (11642001029) was diagnosed with migraine headache with disorientation and memory loss. Investigational product was continued, and the event resolved. Other neurocognitive events reported between 01 April 2014 and 01 July 2014 in the evolocumab plus SoC group included 5 new reports of amnesia and 1 new report each of confusional state, delusion, and dementia. No new events were reported in the SoC alone group.

For the 5 participants with a newly reported adverse event of amnesia, the time to onset of the events from the first dose of evolocumab in the open-label extension studies was known for 4 of the events and the average was 204 days. All events of amnesia in the year 1 SoC-controlled period were reported as nonserious. These events did have some confounding factors such as previous amnesia, history of posttraumatic stress disorder and sleep apnea, concurrent statins, gabapentin use, and sertraline use. Treatment with evolocumab was continued without interruption for all participants. Four events were ongoing as of the data cutoff date, 1 event end date was not provided. One participant (10966404025) had recurrent amnesia events. The first event occurred during the parent study and was reported to resolve when green coffee bean extract was discontinued. The subject was diagnosed with left carotid artery stenosis before the second amnesia event and underwent a left carotid endartectomy approximately 1 month after the amnesia event. The participant was taking concomitant statin during both amnesia events.

In the year 2+ OLE period, there were 2 newly reported neurocognitive events in the 120-day Safety Update.

- One participant (15966018001) reported concurrent serious adverse events of hallucination, delirium and confusional state between 01 April 2014 and 01 July 2014; the events began approximately 2.3 years after the participant initiated dosing with evolocumab 420 mg QM plus SoC in the long-term extension study. This participant was also described in the previous section with the event of rhabdomyolysis and has a complicated psychiatric history and was on multiple medications for the treatment of her psychiatric illness. The investigator believed that the event of delirium was secondary to lithium toxicity. Evolocumab dosing was not interrupted; the amnesia event resolved within 147 days and the other events resolved within 3 days.

- The other participant, a 60-year-old man (15911001003) with a medical history including asthma and sleep apnea, reported a nonserious adverse event of amnesia (verbatim “transient amnesia episode of 2 hour duration”). Evolocumab was continued and the event was reported as resolved on the same day.

- One participant with HeFH in trial 20110271 had a neurocognitive event of memory impairment. The participant (27165001003) was a 64-year-old woman with a medical history of epigastric discomfort who reported forgetfulness beginning approximately 1 month after initiation of evolocumab 420 mg QM dosing. The participant was taking a statin at the time of the event. Evolocumab treatment was not withheld or changed. The participant also reported other nonserious adverse events, including insomnia, hair loss, and joint stiffness. As of the data cutoff date, the event was ongoing and the participant was continuing in the study.

Skin and Subcutaneous Tissue Disorders

In the year 1 SoC-controlled period, adverse events were reported in this system organ class for 7.5% of participants in the evolocumab plus SoC group and 5.3% of participants in the SoC alone group in the 120-day Safety Update, compared with

6.3% and 4.3% of participants, respectively, in the BLA. The most common Skin and Subcutaneous Tissue Disorders in the evolocumab plus SoC group continued to be rash (1.2% evolocumab plus SoC group and 0.8% SoC alone group), contact dermatitis (0.7% and 0.5%), eczema (0.6% and 0.9%), pruritus (0.6% and 0.2%), and urticaria (0.5% and 0.3%).

Serious adverse events of angioedema and hyperhidrosis were reported for 2 (0.1%) of participants in the evolocumab plus SoC group and no participants in the SoC alone group in the 120-day Safety Update.

Angioedema was reported for 6 participants and idiopathic angioedema was reported for 1 participant in the integrated extension studies. Of these events, 1 case of angioedema was newly reported in the 120-day Safety Update. This CTCAE grade 3, serious adverse event of angioedema, which occurred approximately 10.5 months after Subject 11566008005 received the first dose of evolocumab, was considered by the investigator to be secondary to intravenous iron administration. The event resolved with no change in IP dose, and the subject continued with the study.

In the year 1 SoC-controlled period, adverse events of urticaria were reported for 0.5% of participants and 0.3% of participants in the evolocumab plus SoC group and the SoC alone group, respectively. These urticaria events were newly reported in the 120-day Safety Update for 3 participants in the evolocumab plus SoC group and no participant in the SoC alone group. In the year 2+ OLE period, adverse events of urticaria were reported for 0.4% of participants, including 2 participants with events that were newly reported in the 120-day Safety Update. No serious adverse events of urticaria were newly reported in the 120-day Safety Update in either the year 1 SoC-controlled period or the year 2 OLE period. Two of these events were temporally associated with initiation of new medications including antibiotics and piroxicam. Two participants with newly reported events of urticaria in the year 1 SoC-controlled period had prior adverse events during study: (15466061021; SoC alone) had prior adverse events of eczema, rash, lichenoid keratosis, and psoriasis; (15466002002; evolocumab plus SoC) had prior adverse events of pruritus, papular rash, miliaria, and erythema. Three participants with newly reported events of urticaria in the 120-day Safety Update were treated with antihistamines and 1 participant also received oral steroids.

HoFH Trials: Analysis of Adverse Events by Organ System Where Incidence in Evolocumab Group > Control Group

The cumulative incidence of adverse events by system organ class among participants with HoFH in trial 20110271 is summarized in the following table. No important differences were identified in analyses of adverse events by organ system or syndrome in the 120-day Safety Update compared with those reported in the BLA and no new safety risks were identified.

Table 111: Cumulative Subject Incidences of Adverse Events by System Organ Class in the Evolocumab BLA and 120-day Safety Update Trial 20110271 (HoFH Interim Analysis Set)

	BLA	120-day Safety Update
System Organ Class *Preferred Term*	Total (N = 96) n (%)	Total (N = 100) n (%)
Number of subjects reporting adverse events	53 (55.2)	68 (68.0)
Blood and Lymphatic System Disorders	4 (4.2)	8 (8.0)
Anaemia	2 (2.1)	5 (5.0)
Cardiac Disorders	6 (6.3)	6 (6.0)
Endocrine Disorders	0 (0.0)	0 (0.0)
Eye Disorders	1 (1.0)	1 (1.0)
Gastrointestinal Disorders	11 (11.5)	14 (14.0)
Diarrhoea	4 (4.2)	4 (4.0)
Vomiting	4 (4.2)	4 (4.0)
General Disorders and Administration Site Conditions	12 (12.5)	18 (18.0)
Injection Site Erythema	3 (3.1)	4 (4.0)
Injection Site Pain	3 (3.1)	4 (4.0)
Hepatobiliary Disorders	0 (0.0)	0 (0.0)
Immune System Disorders	1 (1.0)	1 (1.0)
Infections and Infestations	22 (22.9)	29 (29.0)
Injury, Poisoning and Procedural Complications	3 (3.1)	4 (4.0)
Investigations	8 (8.3)	12 (12.0)
Carotid Intima-Media Thickness Increased	2 (2.1)	4 (4.0)
Creatine Phosphokinase Increased	3 (3.1)	3 (3.0)
Metabolism and Nutrition Disorders	3 (3.1)	3 (3.0)
Musculoskeletal and Connective Tissue Disorders	6 (6.3)	10 (10.0)
Neck Pain	2 (2.1)	3 (3.0)
Tendonitis	2 (2.1)	3 (3.0)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2 (2.1)	2 (2.0)
Nervous System Disorders	13 (13.5)	19 (19.0)
Headache	5 (5.2)	5 (5.0)
Presyncope	2 (2.1)	3 (3.0)
Psychiatric Disorders	3 (3.1)	4 (4.0)
Renal and Urinary Disorders	3 (3.1)	4 (4.0)
Reproductive System and Breast Disorders	3 (3.1)	4 (4.0)
Respiratory, Thoracic and Mediastinal Disorders	4 (4.2)	5 (5.0)
Skin and Subcutaneous Tissue Disorders	8 (8.3)	8 (8.0)
Vascular Disorders	6 (6.3)	5 (5.0)

Data cutoff dates: BLA, cumulative through 01APR2014; 120-day Safety Update, cumulative through 01JUL2014.
BLA = Biologics License Application; N = number of HoFH subjects enrolled and dosed in Study 20110271; HoFH=Homozygous Familial Hypercholesterolemia; EvoMab=Evolocumab (AMG 145). Coded using MedDRA version 17.0. Adverse event summaries do not include positively adjudicated clinical endpoints.
Source: Summary of Clinical Safety, 12-day Safety Update, Table 44 of trial 20110271

HoFH Trial: Adolescents in 120-day Safety Update

Of the 14 adolescent participants with HoFH in trial 20110271, 10 received evolocumab 420 mg QM and 4 received evolocumab 420 mg Q2W. Adverse events were reported for 71.4% of adolescent participants with HoFH in the 120-day Safety Update, compared with 69.2% in the BLA. Influenza and blood creatine phosphokinase increased (n = 2 each) were the only preferred terms reported for > 1 adolescent participant with HoFH in the 120-day Safety Update.

7.7.2 Safety Update on the Cardiovascular Outcomes Trial FOURIER (protocol 20110118)

The FOURIER trial (Protocol 20110118) entitled, “A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When AMG 145 is Used in Combination With Statin Therapy In Patients with Clinically Evident Cardiovascular Disease” is being conducted in high CV risk patients receiving effective lipid-lowering therapy with statin (defined as atorvastatin 20, 40, or 80 mg daily or equivalent dose of another protocol-allowed statin). The primary endpoint is time to first event of CV death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization. Approximately 27,000 subjects will be randomized within 4 weeks of their most recent myocardial infarction or stroke.

In July 2014, FDA requested a summary of unblinded SUSARs (suspected unexpected serious adverse reactions) in the Cardiovascular Outcomes Trial FOURIER (protocol 20110118) as of 01 October 2014. The purpose of our requesting that the applicant submit a summary of any unblinded SAEs (i.e., unblinded because the SAE was believed to be related to drug) was to ensure that we would be aware of any very serious adverse outcomes that may have occurred among the >17,000 patients enrolled in the FOURIER trial that could plausibly affect the benefit/risk assessment even if one such event were to occur (e.g., if a case of fulminant hepatic failure were to occur).

Of note, an external independent Data Monitoring Committee (DMC) has been established to formally review all the accumulating unblinded safety data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects, and to determine whether there is cogent evidence to recommend alteration or termination of the study.

Cumulatively through 01 October 2014, a total of 17,608 participants were randomized in Trial 20110118, and a total of 69 serious unexpected adverse event reports assessed as possibly related to blinded investigational product by either the investigator or Amgen (i.e., SUSARs) involving 65 participants had been reported to Amgen. All 69 potential SUSARs were unblinded for the purpose of global regulatory

reporting. This total includes patients randomized to placebo (n=34) as well as to evolocumab (n=35).

Of note, events that are potential endpoints (PEPs): all cause death, myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure and transient ischemic attack are reported only as potential endpoints and not as SAEs.

Of the 69 potential SUSAR reports, 25 were reports of liver test abnormalities; 12 of these cases were among patients treated with placebo and 13 were among patients treated with evolocumab. In 5 of the (b) (4) cases, confounders were reported: prior history of LT increase (1 case), history of LT increase and concomitant leflunomide administration (1 case), concurrent diagnosis of hepatitis A (1 case), concomitant paracetamol administration (1 case), and alcohol abuse and concomitant ezetimibe administration (1 case). In 10 of the (b) (4) cases, the participants experienced no associated symptoms and the LT increase was identified on routine laboratory assessment, all within the first 6 months of starting IP with the exception of one case where the LT increase was identified 16 months after start of IP. In 2 cases, the LT increase was found during hospitalization for unstable angina in 1 participant and during work-up for malaise in 1 participant. (b) (4) In most cases, IP and statin were held (as per protocol). Most cases resolved without treatment, typically within 4 to 6 weeks of event identification. Two events were ongoing at time of last report. In 3 cases, IP was restarted with negative rechallenge. No cases met Hy's Law criteria. Twelve of the serious hepatic adverse events are summarized in the table below.

The remaining 44 adverse event reports were within the following System Organ Classes (SOC): Blood and lymphatic system disorders (n=1), Cardiac disorders (n=2), Ear and labyrinth disorders (n=1), Gastrointestinal disorders (n=6), General disorders and administrative site conditions (n=2), Hepatobiliary disorders (n=2), Injury, poisoning and procedural complications (n=1), Immune system disorders (n=1), Infections and infestations (n=4), Metabolism and nutrition disorders (n=3), Musculoskeletal and connective tissue disorders (n=2), Neoplasms benign, malignant and unspecified (n=2), Nervous system disorders (n=6), Renal and urinary disorders (n=3), Respiratory, thoracic and mediastinal disorders (n=4), Skin and subcutaneous tissue disorders (n=2), and Vascular disorders (n=2). There were no fatal related events reported to Amgen's safety update.

Table 112: Summary of Liver Test Increases from Trial 20110118 (FOURIER)*

MCN / Subject ID	Event	Baseline LFTs Normal (Y/N)	Time to Onset	Peak LFT Increase	Hy's Law (Y/N)	Action Taken	Outcome
(b) (6)	Abnormal	Yes	2.5	ALT 3xULN	No	IP and statin	Resolved

(b) (6)	LFTs		months	AST 4xULN TBL normal ALP normal		held	
Clinical summary: On concomitant statin since 2011. Subject was concurrently diagnosed with hepatitis A. No treatment for the event, which resolved between 2 and 6 months after onset. The investigator considered the event medically significant and possibly related to IP and atorvastatin. IP and atorvastatin had not been resumed.							
(b) (6)	ALT increased	Yes	16 months	ALT 2xULN AST normal TBL normal ALP<2xULN	No	Statin held; no action taken with IP	Resolved
Clinical summary: On concomitant statin since 2003. History of diabetes, and subject had recently started liraglutide for diabetes. No associated symptoms. No treatment for the event, which resolved in 1 week. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	Hepatic enzyme increased	Yes	1.5 months	ALT 4xULN AST 2xULN TBL normal ALP normal INR normal	No	IP and statin held	Resolved
Clinical summary: History of MI, CAD, hypertension, and smoking. On concomitant statin for unknown time prior to study; on concomitant acetylsalicylic acid (ASA), clopidogrel, ACE inhibitor, and beta-blocker. Elevated hepatic enzymes were discovered during hospitalization for unstable angina. No symptoms and no treatment for the event which resolved in 5 weeks. Investigator considered the event serious due to hospitalization, and assessed the event as possibly related to IP and atorvastatin. IP and statin on hold at time of last report.							
(b) (6)	Hepatic enzyme increased	Yes	13 months	ALT44xULN AST10xULN TBL<2xULN ALP 3xULN INR normal	No	IP and statin held	Resolved
Clinical summary: On concomitant statin since 2011; on concomitant ASA. Subject developed malaise, and 6 days later work-up showed increased hepatic enzymes. Hepatitis and viral work-up were negative. Gastroenterologist reportedly considered the event a toxic hepatitis and all medications were stopped with the exception of ASA. Reportedly no risk factors for LFT increase; no use of herbal or other oral supplements. No associated symptoms. No treatment for the event which resolved in 4 weeks. IP and statin have not been restarted. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	ALT increased	Yes	5.5 months	ALT 5xULN AST 3xULN ALP<2xULN TBL normal	No	IP and statin held	Resolved
Clinical summary: On concomitant statin since 2010; on concomitant ASA and on leflunomide for rheumatoid arthritis. History of LFT increase in past (not further described); CAD, diabetes mellitus, and hypertension. No associated symptoms. No treatment for the event which resolved in 2 weeks. IP and statin were restarted with negative rechallenge. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	Hepatic enzyme increased	Yes	3months (1st episode); 2 weeks after restart of	ALT 5xULN AST 3xULN ALP <2xULN TBL normal	No	IP and statin held; statin later dc'd and IP resumed	Resolved

			statin (2nd episode)				
Clinical summary: On concomitant ASA. History of CAD and hypertension. Reportedly no risk factors for LFT increase. Viral work-up negative; ultrasound negative. No associated symptoms. IP and statin held; event resolved after 1 month. Statin restarted with positive rechallenge. Statin then discontinued and event resolved ~6 weeks later. IP later restarted with negative rechallenge. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	ALT increased	Yes	3 months	ALT 8xULN AST 3xULN TBL normal ALP normal	No	IP and statin discontinued	Resolved
Clinical summary: On concomitant statin since 2012. Prior history of LFT elevation (not further specified). No associated symptoms. No treatment for the event which resolved after 1 month. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	Hepatic enzyme increased	Yes	3 months	ALT 6xULN AST 5xULN ALP >3xULN TBL normal	No	IP and statin discontinued	Resolved
Clinical summary: On concomitant statin. Hepatitis screen negative. Reportedly no risk factors for LFT increase and no prior history of LFT increase. No associated symptoms. No treatment for the event which resolved in 3.5 weeks. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	AST increased	Yes	3 months	ALT 3xULN AST 5xULN TBL normal ALP normal	No	IP held	Resolved
Clinical summary: On concomitant statin and ezetimibe since 2003. Alcohol use reported as a pre-disposing factor. Hepatitis screen negative; CMV and EBV positive but not clear if prior or current infection. No associated symptoms. No treatment for the event which was ongoing at time of last report (as of 1 week after event onset). The investigator considered the event medically significant and not related to IP.							
(b) (6)	Abnormal LFTs	Yes	3 months	ALT 3xULN AST 4xULN ALP >2xULN TBL normal	No	IP and statin held	Resolved
Clinical summary: On concomitant statin since 2012; on concomitant ACE inhibitor and antidepressant. History of CAD, MI, angina, cerebrovascular disease, and hypertension. Reportedly no risk factors for LFT increase; no history of hepatitis, alcohol, or drug use. No associated symptoms. No treatment for the event which resolved in 1.5 weeks. IP and statin were resumed with negative rechallenge. The investigator considered the event medically significant and possibly related to IP and atorvastatin.							
(b) (6)	ALT increased	Yes	5.5 months	ALT 4xULN AST <2xULN ALP 2xULN TBL normal	No	IP and statin held	Resolved
Clinical summary: On concomitant statin since 2012, on concomitant ASA, ACE inhibitor, and beta-blocker. History of CAD, MI, angina, and smoking. No associated symptoms. No treatment for the event which resolved in 4 weeks. The investigator considered the event medically significant and possibly related to IP and atorvastatin. IP and Atorvastatin were resumed (atorvastatin at a reduced dose of 20 mg instead of 80 mg); there was no event recurrence.							

[redacted] (b) (6)	ALT and AST increased	Yes	5.5 months	ALT 5xULN AST 5xULN ALP <2xULN INR 2.8	No (INR increase felt due to warfarin therapy)	Paracetamol held; no action taken with IP or statin	Ongoing
Clinical summary: On paracetamol for arthritis for 3 weeks prior to event onset; on concomitant atorvastatin and warfarin; previously on simvastatin. Reportedly no other risk factors for LFT increase and no prior history of LFT increase. No associated symptoms. No treatment for the event which was ongoing at time of last report (as of 1 day after event onset). The investigator considered the event medically significant and not related to IP.							
*Adverse event cases reported to Amgen with a receipt date on or before 01 October 2014. LFT: liver function tests; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TBL: total bilirubin; INR: international normalized ratio							

The other 5 adverse event reports were anaphylactic shock, syncope, and rash in 1 participant; bacterial sepsis with acute toxic hepatitis in 1 participant ; and immune thrombocytopenia, myalgia, and productive cough in 1 participant each.

1. Manufacturer Control No. (MCN) [redacted] (b) (6); Anaphylactic shock, Syncope, and Rash: A 59-year-old male participant [redacted] (b) (6)) with ischemic heart disease, MI, and hypertension experienced syncope, rash, and reported anaphylactic shock 5 months after initiation of evolocumab. As the participant self-administered the Week 24 evolocumab injection in his right shoulder (possibly as an IM injection), the injection site became hardened and there was a spurt of blood. Approximately 15 minutes later the participant felt lightheaded and drowsy and experienced a syncopal episode. He was taken to the hospital and on arrival had a BP of 96/64 mmHg, heart rate 78 bpm, and oxygen saturation 99% on room air, and he was afebrile. There was no angioedema, and no wheezing or stridor was noted. A local urticarial rash was noted on the right shoulder where the subject had been regularly administering the injections. The subject reported a localized rash and bloody discharge at the injection sites (all in the right shoulder) of the previous 4 evolocumab administrations. The subject was admitted overnight for observation and treatment with prednisolone, chlorphenamine, ranitidine, and intravenous fluids. He was discharged the next day; the rash had resolved. Investigation product was permanently discontinued; the subject continued on atorvastatin. The investigator reported the events as anaphylactic shock, syncope, and rash, and considered the events possibly related to IP. Per the investigator, the most likely diagnosis was vasovagal syncope; however, anaphylactic shock could not be ruled out. Anti-evolocumab antibodies were negative at the Week 24 assessment.

2. Manufacturer Control No. [redacted] (b) (6); Immune thrombocytopenia (ITP): A 55-year old male subject [redacted] (b) (6)) with a history of CAD, MI, hypertension, type 2 diabetes mellitus, smoking, computed tomography scan with ground glass disease and air trapping consistent with respiratory bronchiolitis-associated interstitial lung disease, and testicular cancer previously treated with chemotherapy (1989) was reported with immune thrombocytopenia 3.5 months after start of evolocumab. Concomitant medications included naproxen, acetylsalicylate calcium, a beta-blocker, an ACE inhibitor, insulin, and a glycemic control medication. The patient had no

history of thrombocytopenia and no known risk factors for the event; baseline platelet count was normal at 227 x 10^9/L. Approximately 2.5 months after starting evolocumab, the subject experienced small petechiae on his upper legs and black stools; 2 weeks later he reported generalized bruising. Around this time he self-treated with naproxen for a week for a painful hip. At 3.5 months after starting evolocumab, the subject was found to be thrombocytopenic (platelet count 13 – 16 x 10^9/L) and was hospitalized. The subject reportedly had no risk factors for thrombocytopenia. No etiology was identified and the subject was diagnosed with ITP. He was treated with dexamethasone, and atorvastatin and acetylsalicylate calcium were discontinued. Platelet counts fluctuated, but gradually improved to 87 x 10^9/L two months after event onset, and the petechiae, bruising, and black stools resolved. The investigator considered the event possibly related to IP, and IP was discontinued. Anti-evolocumab antibodies were negative at the Day 1 assessment; no further antibody testing has been performed.

3. Manufacturer Control No. (b) (6); Bacterial sepsis and Acute toxic hepatitis: A 68-year old male subject (b) (6) with a history of 3 days of fever in the week prior to start of IP, presented with intermittent fever and abdominal pain 2 weeks after IP start and was diagnosed with bacterial sepsis and acute toxic hepatitis. IP and atorvastatin were held. Hepatitis A, B, C, and D work-up negative. There was no hepatomegaly, and magnetic resonance cholangiopancreatography (MRCP) and abdominal CT were normal. Blood cultures obtained on an unknown date were negative, and etiology for the sepsis was not identified. The subject was treated with cefuroxime and metronidazole and the events resolved in 3 weeks. The investigator considered the event possibly related to IP, which was permanently discontinued at the participant's request. Statin was on hold at time of last report.

4. Manufacturer Control No. (b) (6); Myalgia: A 46-year old male subject (b) (6)) with elevated creatine phosphokinase (CK) at baseline (CK 312 IU/L; reference range 24-250 IU/L) developed severe myalgia 4 months after initiating IP. The subject had been receiving atorvastatin 80 mg for 4 months prior to the start of IP. Two weeks after the start of IP the subject experienced nonserious myalgia; atorvastatin 80 mg daily was switched to rosuvastatin 40 mg daily. At 4 months after the start of IP the subject developed severe muscle pain which was considered medically significant and involved significant disability. Creatine phosphokinase was 273 U/L and rosuvastatin was held. The subject received the next dose of IP one month later and developed myalgia; IP was discontinued. The myalgia resolved after 10 days. Creatine phosphokinase at the time of resolution was 285 IU/L. The investigator considered the event possibly related to IP. Six weeks after event resolution rosuvastatin was restarted at 5 mg and 6 weeks after that the dose was increased to 10 mg. There was no event recurrence after restarting rosuvastatin.

5. Manufacturer Control No (b) (6), Productive cough: A 73-year old male subject (b) (6) with a history of chronic obstructive pulmonary disease (COPD) and episodic productive cough developed a productive cough 9 months after initiating IP. The subject initiated IP, but IP was discontinued 2 weeks later at the subject's request. Approximately 9 months later IP was restarted. Three days after reinitiation, the subject presented with productive cough (250 ml sputum expectorated in 90 minutes), dyspnea and thoracic pain and was treated with increased doses of

fluticasone and albuterol inhalers. The event resolved the same day. The following day at a visit with his family doctor, a chest x-ray showed possible COPD exacerbation and the subject was treated with azithromycin and cortisone; however, the investigator later concluded the event was not a COPD exacerbation but was instead an episode of acute abundant bronchial expectorations. IP was discontinued. The investigator considered the event possibly related to IP.

Amgen did not submit narratives for cases in which the patients were found to be allocated to placebo, so I am unable to comment to what extent the serious hepatic adverse events in the placebo group were similar in nature to the events in the evolocumab group. However, at least at this preliminary stage, it is reassuring that the event counts of hepatic adverse events identified as SUSARs are essentially identical in each treatment group. Because this trial is still ongoing, these events are still in the process of being investigated. A full picture of the safety profile from this trial will require evaluation of both the evolocumab and placebo groups at the trial's conclusion.

8 Postmarket Experience

As this is the first marketing application for evolocumab, there are no postmarketing data at this time.

9 Appendices

9.1 Literature Review/References

Literature references were made throughout this document when relevant.

9.2 Labeling Recommendations

Labeling recommendations were made in a separate document.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was held on June 10, 2015.

1. DISCUSSION: Discuss the safety of evolocumab as observed in the clinical development program, and in your discussion comment on the following:

    a. Discuss your interpretation of the safety data with respect to any adverse effects related to diabetes, liver-related safety, muscle, neurological/neurocognitive events, hypersensitivity, as well as any other concerns you may identify.

    b. Discuss the adequacy of the current clinical database to characterize the safety of evolocumab. Consider the extent of drug exposure (i.e., number of patients and duration of exposure), the strengths/limitations of the study designs themselves, and the generalizability of the trial populations to the target patient population(s), if approved.

    c. Discuss your level of concern regarding the safety of achieving very low levels of LDL-C induced by evolocumab.

    The discussion included the following points regarding 1a and 1b:

    - Overall database is robust even though most are not at high CV risk. Weak safety signals for diabetes, pancreatitis and muscle adverse events.

- Overall database is limited, many studies are 12 weeks long which may only include 3 doses and there is only one double-blind 52-week trial. Many of subjects in 52-week trial would not be the target population for the drug. OLE studies are limited—self-selection and loss of power of randomization

- Concerned about potential broad use with few patient years of exposure; large CVOT unlikely to have a major safety signal; safety is difficult to assess with current database

- Population should be expanded; more minority representation, more sicker patients with intercurrent illness; longer duration studies needed

The discussion included the following points regarding 1c:

- Paucity of data on low LDL. Difficult to know how to counsel patients or physicians about LDL threshold in terms of safety

- Concerned that hsCRP does not decrease

- No efficacy data to inform us if low LDL levels (< 40 mg/dL) provides added benefit

- Special concern with young children and low LDL levels

2. DISCUSSION: The applicant has proposed two dosage regimens, which were selected to appeal to patient preference considerations (related to the dosing procedure/frequency) rather than to provide doses intended to allow titration with respect to the magnitude of LDL-C lowering. Healthcare providers who are uncomfortable with very low levels of LDL-C would either have to down titrate other lipid-altering drugs (e.g., statin) or discontinue evolocumab. Discuss whether you would have any concerns with evolocumab not being labeled with dosage regimens that provide varying degrees of LDL-C lowering, if approved.

The discussion included the following points:

- What is the strategy if you feel uncomfortable with the LDL level? Need guidance for practicing physicians.
- This is concerning. Uncertain benefit and faced with the possibility that physicians will back off on the statin dose. This is a real concern until you have data that provides reassurance that the second agent is providing some CV risk reduction.

- Some of the concern can be mitigated by choosing the appropriate patient population. If it is FH patients with elevated LDL levels and increased CV risk—this is not a big issue.

3. DISCUSSION: For homozygous familial hypercholesterolemia (HoFH), the applicant has proposed a recommended dose of evolocumab of either 420 mg once monthly or 420 mg every 2 weeks (Q2W). Discuss whether the applicant has provided adequate data to characterize the efficacy and safety of the 420 mg Q2W dosage in this population.

   The discussion included the following points:

   - Trial is not long enough in duration, insufficient evidence. 6% increase was inconsistent and may not be real.

   - Several panelists feel that the data does not provide convincing evidence of a meaningful difference between the 2 doses; however, there does not seem to be a major safety concern. Panelists are willing to accept the limited data given this HoFH population has few treatment options and this increased dose may provide a meaningful difference to some.

4. DISCUSSION: The goal of LDL-C-lowering therapy is to reduce the risk for cardiovascular (CV) disease. Historically, a change in LDL-C has been considered sufficient to establish the effectiveness of a lipid-altering drug intended for use to reduce cardiovascular risk, without any regulatory requirement to demonstrate evidence for benefit in a CV outcomes trial, provided the reduction is sufficiently robust and the product (or its class) does not have safety issues that raise concern that risk exceeds benefit.

   Discuss whether evolocumab-induced LDL-C lowering is sufficient to substitute for demonstrating its effect on clinical outcomes (i.e., to substitute for investigation in a CV outcomes trial) in one or more populations (e.g., different degrees of CV risk, familial vs. non- familial etiologies of hyperlipidemia, use with or without concomitant statins, etc.).

   The discussion included the following points:

   - LDL is a biomarker; it is a surrogate in some circumstances (FH). Mechanism of action with LDLR is compelling as it is similar to statins; genetic data reassuring.

- LDL as a surrogate is mechanism dependent. Using LDL as a surrogate in a larger primary hyperlipidemia population is problematic. LDL and apoB reductions are a reasonable surrogate in FH populations.
- LDL is context dependent. Starting point for LDL lowering is important. As the LDL level gets lower on the S-shaped curve, the true efficacy is unclear. At low LDL levels, benefit of additional LDL lowering may be negligible.
- CVOT needed in new drug class. Meta-analysis useful but individual data is important.

5. Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval in one or more patient populations (excluding HoFH)? We remind you that under the current regulatory pathway, it would not be required to successfully demonstrate an effect of evolocumab on CV outcomes after an approval based on changes in LDL-C.

    a. If yes, please explain your rationale and describe the patient population(s) for whom you believe that benefit/risk is favorable.

    b. If no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit/risk to support approval.

11 votes for ‘yes’ and 4 votes for ‘no’.

The discussion included the following points for the NO votes:

- Trials are too short and too small to assess safety. Cannot assess DM signal with only one double-blind, placebo-controlled 52 week trial. OLE studies are supportive but are not acceptable for substitution.
- If accelerated approval had been as option, this would have alleviated some of my concern. Otherwise it is a large target population and there is limited safety data and unclear benefit.
- Concerned that approval may hamper the successful completion of the CVOT.
- HeFH population is a tough call as they have increased need

The discussion included the following points for the YES votes:

- Approval is acceptable for the following patient populations: HeFH, high CV risk for secondary prevention, some panelists included high risk CVD with increased LDL on maximally tolerated statin therapy
- Should not be used in low CV risk without CVOT results
- Important to convey that statin should not be reduced or eliminated

6. VOTE: Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval for homozygous familial hypercholesterolemia?

    a. If yes, please explain your rationale.

    b. If no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit/risk to support approval.

15 votes for 'yes' and 0 votes for 'no'.

The discussion included the following points for the YES votes:

- Optimal dose and dosing schedule not clear.
- Some panelists did not support the 420 mg Q2W dose and others felt that the unique need of this HoFH population justified the uncertainty with this dose as this would likely be used by experts in HoFH management
- Children under 12 years of age not studied. Panelist hopes that younger children will be studied and the appropriate amount of data will be provided for use in younger children. Steroid hormones should be evaluated.

9.4 Screening Disposition in Trial 20110109

	n (%)
Number of subjects screened	**2120**
Number of subjects excluded prior to entering Lipid Stabilization period	**635 (30.0)**
Eligibility criteria met but did not enrol	118 (5.6)
Missing or incorrectly specified reason	3 (0.1)
Number of subjects not meeting the eligibility criteria	514 (24.2)
Fasting LDL-C < 75 mg/dL as determined by central laboratory at the initial screening visit	117 (5.5)
Subject did not provide informed consent	32 (1.5)
Fasting LDL-C det. by central lab at end of lipid stabilization < 75 mg/dL or meeting goal LDL-C values based on risk factor status (NCEP ATPIII risk categories)	24 (1.1)
Fasting triglycerides > 400 mg/dL by central laboratory at screening	23 (1.1)
Male or female < 18 or > 75 years of age	16 (0.8)
Type 1 diabetes, newly diagnosed or poorly controlled type 2 diabetes	125 (5.9)
Hyperthyroidism or hypothyroidism at screening	49 (2.3)
Uncontrolled hypertension, confirmed with repeat measurement	35 (1.7)
Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge.	28 (1.3)
Active liver disease or hepatic dysfunction	17 (0.8)
History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma)	13 (0.6)
Subject has any kind of disorder that, in opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures	12 (0.6)
Diagnosed with CHD or CHD risk equivalent and not receiving statin therapy, with LDL-C at screening <= 99 mg/dL	10 (0.5)
Unreliability as study participant based on investigator's (or designee's) knowledge of subject (eg, alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)	9 (0.4)
CK > 3 times the ULN at screening or at end of lipid stabilization period	8 (0.4)
Treatment in the last 3 months prior to LDL-C screening with systemic cyclosporine, systemic steroids, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane); *(Note: vitamin A in a multivitamin preparation is permitted)*	7 (0.3)
Subject took in last 6 weeks prior LDL-C screening:red yeast rice;>200 mg/day niacin;>1000 mg/day omega-3 fatty acid;lipid-reg drug (bileacid sequest resin, fibrate, deriv) other than statin or ezetimibe	6 (0.3)
Known sensitivity to any of the products to be administered	5 (0.2)
Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction	4 (0.2)
Current therapeutic anticoagulation with vitamin K antagonist (eg, warfarin), heparin, low-molecular weight heparin, direct thrombin inhibitor, or Factor Xa inhibitor. (Note: anti-platelet agents [eg, aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole] are permitted).	4 (0.2)

	n (%)
Number of Subjects not meeting the eligibility criteria (continued)	
Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 at screening, confirmed by a repeat measurement at least 1 week apart	3 (0.1)
Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 3 months prior to randomization	2 (0.1)
Subject is pregnant or breast feeding, or planning to become pregnant during treatment and/or within 15 weeks after the end of treatment	2 (0.1)
Subject has previously received AMG 145 (evolocumab) or any other investigational therapy to inhibit PCSK9	2 (0.1)
Uncontrolled cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia that are not controlled by medications, in the past 3 months prior to randomization	1 (0.0)
Planned cardiac surgery or revascularization	1 (0.0)
Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)	1 (0.0)
Number of subjects entering Lipid Stabilization Period	**1485 (70.0)**
Number of subjects randomized in investigational product (IP) period	**905**
Number of subjects not randomized into IP period	**580**
Number of subjects not meeting the eligibility criteria	539 (92.9)
Fasting LDL-C det. by central lab at end of lipid stabilization < 75 mg/dL or meeting goal LDL-C values based on risk factor status (NCEP ATPIII risk categories)	400 (69.0)
Fasting LDL-C < 75 mg/dL as determined by central laboratory at the end of the lipid stabilization period	11 (1.9)
Subject did not provide informed consent	8 (1.4)
Fasting triglycerides > 400 mg/dL by central laboratory at end of lipid stabilization period	4 (0.7)
Male or female < 18 or > 75 years of age	4 (0.7)
Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge	36 (6.2)
Type 1 diabetes, newly diagnosed or poorly controlled type 2 diabetes	31 (5.3)
Known sensitivity to any of the products to be administered	11 (1.9)
Unreliability as study participant based on investigator's (or designee's) knowledge of subject (eg, alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)	10 (1.7)
Active liver disease or hepatic dysfunction	9 (1.6)
CK > 3 times the ULN at screening or at end of lipid stabilization period	8 (1.4)
Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction	5 (0.9)
Treatment in the last 3 months prior to LDL-C screening with systemic cyclosporine, systemic steroids, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane); (Note: vitamin A in a multivitamin preparation is permitted)	5 (0.9)

	n (%)
Number of Subjects not meeting the eligibility criteria (continued)	
Hyperthyroidism or hypothyroidism at screening	4 (0.7)
Uncontrolled hypertension, confirmed with repeat measurement	4 (0.7)
Subject has any kind of disorder that, in opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures	3 (0.5)
Planned cardiac surgery or revascularization	2 (0.3)
Diagnosed with CHD or CHD risk equivalent and not receiving statin therapy, with LDL-C at screening <= 99 mg/dL	1 (0.2)
History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma)	1 (0.2)
Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 3 months prior to randomization	1 (0.2)
Subject took in last 6 weeks prior LDL-C screening:red yeast rice;>200 mg/day niacin;>1000 mg/day omega-3 fatty acid;lipid-reg drug (bileacid sequest resin, fibrate, deriv) other than statin or ezetimibe	1 (0.2)
Subject has previously received AMG 145 (evolocumab) or any other investigational therapy to inhibit PCSK9	1 (0.2)

Percentages are based on the “total number of subjects screened” (ie, 2120) for lipid stabilization period and on the “number of subjects in the lipid stabilization analysis set who were not randomized” (ie, 580) for the investigational product period. Subjects can record multiple reasons for screen failure or ineligibility. LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; CK = creatine kinase; ULN = upper limit of normal; PCSK9 = proprotein convertase subtilisin/kexin type 9.
Source: Applicant’s May 2015 response to FDA information request

9.5 Adverse Events in the Integrated Parent Analysis Set Excluding Trial 20110109

Table 113: Adverse Events during the Parent Trials by Preferred Term in Descending Order of Frequency Preferred Terms Reported by ≥ 1% of Participants in Any Treatment Group (Integrated Parent Analysis Set Excluding Trial 20110109)

	Control			EvoMab			
Preferred Term	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 638) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1357) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Number of participants reporting adverse events	240 (41.0)	289 (45.3)	278 (50.2)	397 (55.5)	543 (43.6)	608 (44.8)	20 (66.7)
Nasopharyngitis	23 (3.9)	25 (3.9)	22 (4.0)	74 (10.3)	40 (3.2)	51 (3.8)	3 (10.0)
Headache	19 (3.2)	16 (2.5)	20 (3.6)	16 (2.2)	32 (2.6)	42 (3.1)	6 (20.0)
Back Pain	8 (1.4)	19 (3.0)	13 (2.3)	15 (2.1)	29 (2.3)	33 (2.4)	3 (10.0)
Pain In Extremity	8 (1.4)	12 (1.9)	6 (1.1)	7 (1.0)	17 (1.4)	33 (2.4)	3 (10.0)
Fatigue	7 (1.2)	5 (0.8)	19 (3.4)	11 (1.5)	20 (1.6)	27 (2.0)	0 (0.0)
Nausea	6 (1.0)	9 (1.4)	12 (2.2)	13 (1.8)	21 (1.7)	26 (1.9)	0 (0.0)
Muscle Spasms	7 (1.2)	8 (1.3)	14 (2.5)	12 (1.7)	17 (1.4)	25 (1.8)	0 (0.0)
Myalgia	5 (0.9)	14 (2.2)	27 (4.9)	22 (3.1)	21 (1.7)	25 (1.8)	6 (20.0)
Upper Respiratory Tract Infection	15 (2.6)	9 (1.4)	13 (2.3)	21 (2.9)	22 (1.8)	25 (1.8)	3 (10.0)
Diarrhoea	10 (1.7)	18 (2.8)	14 (2.5)	15 (2.1)	21 (1.7)	23 (1.7)	1 (3.3)
Arthralgia	8 (1.4)	11 (1.7)	12 (2.2)	18 (2.5)	25 (2.0)	22 (1.6)	1 (3.3)
Dizziness	8 (1.4)	7 (1.1)	11 (2.0)	9 (1.3)	13 (1.0)	19 (1.4)	2 (6.7)
Cough	1 (0.2)	7 (1.1)	6 (1.1)	21 (2.9)	13 (1.0)	16 (1.2)	1 (3.3)
Urinary Tract Infection	7 (1.2)	8 (1.3)	8 (1.4)	3 (0.4)	14 (1.1)	16 (1.2)	0 (0.0)
Oedema Peripheral	3 (0.5)	5 (0.8)	5 (0.9)	5 (0.7)	5 (0.4)	14 (1.0)	0 (0.0)
Blood Creatine Phosphokinase Increased	1 (0.2)	6 (0.9)	2 (0.4)	11 (1.5)	6 (0.5)	13 (1.0)	0 (0.0)
Injection Site Pain	1 (0.2)	4 (0.6)	1 (0.2)	11 (1.5)	6 (0.5)	13 (1.0)	0 (0.0)
Contusion	1 (0.2)	5 (0.8)	4 (0.7)	5 (0.7)	12 (1.0)	11 (0.8)	0 (0.0)
Hypertension	5 (0.9)	9 (1.4)	5 (0.9)	10 (1.4)	16 (1.3)	11 (0.8)	0 (0.0)
Influenza	3 (0.5)	10 (1.6)	9 (1.6)	9 (1.3)	17 (1.4)	11 (0.8)	1 (3.3)
Injection Site Bruising	2 (0.3)	5 (0.8)	5 (0.9)	7 (1.0)	0 (0.0)	11 (0.8)	1 (3.3)
Musculoskeletal Pain	4 (0.7)	3 (0.5)	8 (1.4)	5 (0.7)	7 (0.6)	11 (0.8)	0 (0.0)

	Control			EvoMab			
Preferred Term	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 638) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1357) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Oropharyngeal Pain	6 (1.0)	6 (0.9)	4 (0.7)	10 (1.4)	7 (0.6)	10 (0.7)	0 (0.0)
Sinusitis	4 (0.7)	1 (0.2)	9 (1.6)	11 (1.5)	8 (0.6)	10 (0.7)	0 (0.0)
Abdominal Pain	4 (0.7)	3 (0.5)	6 (1.1)	3 (0.4)	9 (0.7)	9 (0.7)	1 (3.3)
Bronchitis	6 (1.0)	7 (1.1)	2 (0.4)	8 (1.1)	19 (1.5)	9 (0.7)	1 (3.3)
Constipation	10 (1.7)	2 (0.3)	3 (0.5)	5 (0.7)	16 (1.3)	8 (0.6)	3 (10.0)
Gastroenteritis	5 (0.9)	3 (0.5)	2 (0.4)	5 (0.7)	8 (0.6)	7 (0.5)	1 (3.3)
Insomnia	3 (0.5)	4 (0.6)	0 (0.0)	7 (1.0)	5 (0.4)	7 (0.5)	0 (0.0)
Paraesthesia	2 (0.3)	0 (0.0)	6 (1.1)	4 (0.6)	7 (0.6)	7 (0.5)	0 (0.0)
Pharyngitis	6 (1.0)	3 (0.5)	3 (0.5)	4 (0.6)	3 (0.2)	7 (0.5)	0 (0.0)
Rash	5 (0.9)	2 (0.3)	6 (1.1)	7 (1.0)	11 (0.9)	7 (0.5)	0 (0.0)
Abdominal Distension	0 (0.0)	5 (0.8)	3 (0.5)	1 (0.1)	11 (0.9)	6 (0.4)	1 (3.3)
Asthenia	0 (0.0)	4 (0.6)	0 (0.0)	4 (0.6)	2 (0.2)	6 (0.4)	1 (3.3)
Cystitis	5 (0.9)	1 (0.2)	5 (0.9)	5 (0.7)	6 (0.5)	6 (0.4)	2 (6.7)
Epistaxis	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	4 (0.3)	6 (0.4)	1 (3.3)
Depression	2 (0.3)	2 (0.3)	7 (1.3)	0 (0.0)	1 (0.1)	5 (0.4)	0 (0.0)
Flatulence	1 (0.2)	2 (0.3)	3 (0.5)	7 (1.0)	2 (0.2)	5 (0.4)	1 (3.3)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.2)	5 (0.4)	1 (3.3)
Injection Site Erythema	0 (0.0)	7 (1.1)	6 (1.1)	7 (1.0)	9 (0.7)	5 (0.4)	1 (3.3)
Decreased Appetite	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.4)	3 (0.2)	4 (0.3)	1 (3.3)
Gastroenteritis Viral	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.3)	3 (0.2)	4 (0.3)	1 (3.3)
Pruritus	1 (0.2)	2 (0.3)	9 (1.6)	5 (0.7)	3 (0.2)	4 (0.3)	0 (0.0)
Pneumonia	0 (0.0)	3 (0.5)	0 (0.0)	8 (1.1)	4 (0.3)	3 (0.2)	0 (0.0)
Sinus Congestion	1 (0.2)	3 (0.5)	1 (0.2)	9 (1.3)	3 (0.2)	3 (0.2)	0 (0.0)
Excoriation	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.4)	2 (0.2)	2 (0.1)	1 (3.3)
Night Sweats	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.1)	2 (0.1)	1 (3.3)
Oral Herpes	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	1 (3.3)
Road Traffic Accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)	1 (3.3)
Wound	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)	1 (3.3)
Hyperhidrosis	1 (0.2)	3 (0.5)	2 (0.4)	0 (0.0)	2 (0.2)	1 (0.1)	1 (3.3)
Injection Site Swelling	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.1)	1 (0.1)	1 (0.1)	1 (3.3)
Malaise	0 (0.0)	2 (0.3)	2 (0.4)	3 (0.4)	4 (0.3)	1 (0.1)	1 (3.3)
Corneal Erosion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Face Oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Glucose Tolerance Impaired	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (3.3)
Helicobacter Infection	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Humerus Fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (3.3)
Inguinal Hernia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Injection Site Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Joint Stiffness	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Limb Injury	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (3.3)
Localised Oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Miliaria	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (3.3)
Scab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Spontaneous Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (3.3)
Vestibular Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)

Includes the following trials: 20090158, 20090159, 20101154, 20101155, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, and 20120356. The 52-week trial 20110109 is not included.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Eze=ezetimibe; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; IPAS = Integrated Parent Analysis Set. Coded using MedDRA version 17.0.
Source Data: adam.adsl; ISS Table 14-6.2.3

9.6 Serious Adverse Events in the Integrated Parent Analysis Set Excluding Trial 20110109

Table 114: Serious Adverse Events during the Parent Trials by System Organ Class (SOCs) and Preferred Term for Select SOCs (Integrated Parent Analysis Set Excluding Trial 20110109)

	Control			EvoMab			
System Organ Class Preferred Term	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 638) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1357) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Number of subjects reporting adverse events	12 (2.0)	11 (1.7)	7 (1.3)	15 (2.1)	36 (2.9)	26 (1.9)	0 (0.0)
BLOOD AND LYMPHATIC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Anaemia							
CARDIAC DISORDERS	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.4)	10 (0.8)	5 (0.4)	0 (0.0)
Acute Myocardial Infarction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)
Angina Pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Angina Unstable	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Atrial Fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Coronary Artery Disease	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)
Acute Coronary Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cardiac Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cardiac Failure Congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ventricular Fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
GASTROINTESTINAL	3 (0.5)	1 (0.2)	2 (0.4)	1 (0.1)	2 (.2)	2 (0.1)	0 (0.0)
Pancreatitis Acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Abdominal Pain Upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Gastrointestinal Haemorrhage	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Motility Disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrooesophageal Reflux Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hiatus Hernia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
InguinalHernia	1(0.2)	0(0.0)	1(0.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
INFECTIONS AND INFESTATIONS	3 (0.5)	2 (0.3)	1 (0.2)	1 (0.1)	6 (0.5)	2 (0.1)	0 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	4 (0.3)	2 (0.1)	0 (0.0)
INVESTIGATIONS	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)
Hepatic Enzyme Increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.2)	2 (0.1)	0 (0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.3)	2 (0.3)	2 (0.4)	0 (0.0)	6 (0.5)	2 (0.1)	0 (0.0)

NERVOUS SYSTEM DISORDERS	3 (0.5)	0 (0.0)	0 (0.0)	3 (0.4)	4 (0.3)	2 (0.1)	0 (0.0)
Cerebrovascular Accident	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Epilepsy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Grand Mal Convulsion	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic Stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Neurological Symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Syncope	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Transient Ischaemic Attack	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
PSYCHIATRIC DISORDERS	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)
Affective Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Alcohol Withdrawal Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Delirium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Depression	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Substance Abuse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
RENAL AND URINARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)	0 (0.0)
Glomerulonephritis Acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Renal Failure Acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Breast Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Penile Haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
RESPIRATORY, THORACIC ANDMEDIASTINAL DISORDERS	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
VASCULAR DISORDERS	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)
Deep Vein Thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Aortic Aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Arteriosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertensive Crisis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Peripheral Artery Stenosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Includes the following trials: 20090158, 20090159, 20101154, 20101155, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, and 20120356. The 52-week trial 20110109 is not included.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Eze=ezetimibe; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; IPAS = Integrated Parent Analysis Set. Coded using MedDRA version 17.0.
Source Data: adam.adsl; ISS Table 14-6.4.3

9.7 Adverse Events that Led to Discontinuation in the Integrated Parent Analysis Set Excluding Trial 20110109

Table 115: Adverse Events Leading to Discontinuation of Investigational Product During the Parent Trials by Select System Organ Class and Preferred Term (Integrated Parent Analysis Set Excluding Trial 20110109)

	Control			EvoMab			
System Organ Class Preferred Term	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 638) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1357) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Number of subjects reporting adverse events	10 (1.7)	11 (1.7)	24 (4.3)	3 (0.4)	29 (2.3)	28 (2.1)	1 (3.3)
CARDIAC DISORDERS	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Acute Myocardial Infarction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ventricular Fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
EAR AND LABYRINTH DISORDERS	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
EYE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
GASTROINTESTINAL DISORDERS	1 (0.2)	0 (0.0)	5 (0.9)	0 (0.0)	6 (0.5)	6 (0.4)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.1)	4 (0.3)	0 (0.0)
Abdominal Distension	(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Abdominal Pain	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Pancreatitis Acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
ADMINISTRATION SITE CONDITIONS							
Influenza Like Illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Injection Site Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Asthenia	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Chest Discomfort	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)
Injection Site Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
HEPATOBILIARY DISORDERS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Drug-Induced Liver Injury	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic Function Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
IMMUNE SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Drug Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
INFECTIONS AND INFESTATIONS	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
INVESTIGATIONS	3 (0.5)	2 (0.3)	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)
Blood Creatine Phosphokinase Increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)
Alanine Aminotransferase Increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic Enzyme Increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Liver Function Test Abnormal	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight Increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.3)	4 (0.6)	11 (2.0)	1 (0.1)	7 (0.6)	15 (1.1)	1 (3.3)
Myalgia	0 (0.0)	4 (0.6)	6 (1.1)	0 (0.0)	5 (0.4)	4 (0.3)	1 (3.3)
Arthralgia	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Pain In Extremity	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)	0 (0.0)
Back Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)
NERVOUS SYSTEMS DISORDERS	3(0.5)	0(0.0)	5(0.9)	0(0.0)	4(0.3)	6(0.4)	0(0.0)
Headache	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)
Burning Sensation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Dizziness	1 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Paraesthesia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Poor Quality Sleep	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cerebrovascular Accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ischaemic Stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
MuscleContractionsInvoluntary	1(0.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Syncope	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PSYCHIATRIC DISORDERS	0 (0.0)	2 (0.3)	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)
Disorientation	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Insomnia	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Mood Swings	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Libido Decreased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nightmare	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
RENAL AND URINARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	0 (0.0)	7 (1.3)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
VASCULAR DISORDERS	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Includes the following trials: 20090158, 20090159, 20101154, 20101155, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, and 20120356. The 52-week trial 20110109 is not included.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; Eze=ezetimibe; QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; IPAS = Integrated Parent Analysis Set. Coded using MedDRA version 17.0.
Source Data: adam.adsl; ISS Table 14-6.5.3

9.8 NCEP ATP III Risk Categories

Table 116: ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

§§Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

‖Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

¶Optional LDL-C goal <100 mg/dL.

#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

Source: 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.

9.9 A Selection of Narratives of Hepatic-related Serious Adverse Events

SAE AST/ALT Increased.
Subject No: 10966415011
Treatments:

- Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg

This subject was previously discussed in Section 5.3.1 Trial 20110109: DESCARTES

SAE Hepatic function abnormal.
Subject No: 11565005001
Treatments:

- Parent study and regimen: Study 20110115, Placebo SC QM
- Year 1: Evolocumab SC QM 420 mg + Standard of Care

Report: Hepatic function abnormal

This subject was previously discussed in Section 7.3.5.1: Hepatobiliary Disorders
Subject 11565005001 was a 66-year-old white woman participating in Study 20120138 who developed abnormal hepatic function (reported term: liver function abnormality). The subject's medical history included primary hyperlipidemia, unexplained jaundice event in 2007, and recurrent urinary tract infections. Concomitant medications included candesartan, nitrofurantoin in chronic (6 months before the event) use for recurrent urinary infections, ramipril, gabapentin, diclofenac, omeprazole, aluminum hydroxide magnesium carbonate, electrolytes with macrogol, codeine, paracetamol, salbutamol, budesonide, pseudoephedrine, fexofenadine, and mometasone. Previous and ongoing treatment for primary hyperlipidemia included simvastatin. The subject received placebo in the parent study from May 2013 to July 2013. In August 2013 the subject's laboratory tests included aspartate aminotransferase (AST) 22 U/L and alanine aminotransferase (ALT) 20 U/L. She received the first dose of evolocumab in Study 20120138 on 09 October 2013. On 09 December 2013, the subject experienced dyspepsia. Ten days later, the subject developed liver function abnormality with ALT 794 U/L (23xULN), AST 562 U/L (17xULN), and alkaline phosphatase 158 U/L. Three days later, the subject's laboratory tests included total bilirubin of 25 µmol/L, ALT of 817 U/L (24xULN), gamma glutamyltransferase (GGT) of 326 U/L, and alkaline phosphatase (ALP) of 156 U/L. Treatment after the onset of the event of liver function abnormality included domperidone and cholestyramine. Evolocumab and simvastatin were discontinued. Results were negative for hereditary hemochromatosis, hepatitis B surface antigen and hepatitis C, antinuclear antibody (ANA) showed 1/40 homogeneous pattern, and serum ferritin was 1599 µg/L. On 06 January 2014, results included total bilirubin of 26 µmol/L, ALT of 1052 U/L (31xULN), AST of 959 U/L (28xULN), and ALP of 172 U/L. Laboratory values on 10 January 2014 showed AST and ALT decreasing to levels of 884 U/L and 854 U/L, respectively, total bilirubin was 30 µmol/L and ALP was 176 U/L. On 15 January 2014, the subject underwent an abdominal ultrasound, which showed no abnormalities. There was no change from the previous ultrasound on 28 March 2013. On 22 January 2014, the subject underwent endoscopy and gastroscopy due to dysphagia, nausea and/or vomiting, which showed a normal upper gastrointestinal tract. On 30 January 2014, laboratory values included immunoglobulin A of 5.2 g/L, iron of 37 µmol/L, total bilirubin of 230 µmol/L, ALT of 636 U/L, AST of 833 U/L, ALP of 266 U/L, transferrin saturation of 64%, albumin of 28 g/L, and alpha fetoprotein of 39 Ku/L. On 03 Feb 2014, the subject's coagulation screening showed a thrombin time of 19 seconds. On 07 February 2014, the subject underwent a liver biopsy. Biopsy results showed lobular inflammation consisting of lymphocytes, polymorphonuclear leukocytes, and a few eosinophils. The portal tracts were expanded by chronic inflammatory cell infiltrate consisting of lymphocytes, histiocytes, and eosinophils. There was no evidence of ductular damage or granulomata. There was ductular reaction. There was focal zone 3 necrosis along with areas of portal to central bridging confluent necrosis. A few foci of spotty necrosis were seen. There were areas of dilated sinusoids within the necrotic component. Special stains Van Gieson (VG) and Martius, Scarlet and Blue ("MSB") showed focal mild fibrosis within necrotic component and mild fibrous expansion of portal tracts. There was no evidence of bridging fibrosis. Pearls, orcian, and periodic acid-schiff diastase (PASD) stains did not reveal any evidence of increased iron, copper associated protein or PASD inclusions. Negative screening for autoantibodies and negative viral screening was noted. The features were those of acute hepatitis with confluent necrosis and focal bridging necrosis with exclusion of viral and autoimmune etiology. The clinical diagnosis was drug-induced acute hepatitis. In April 2014, liver function tests were normalized with values of ALT 21 U/L, AST 27 U/L, albumin 33 g/L, alkaline phosphatase 108 U/L, and total bilirubin 20 µmol/L. The outcome of the event liver function abnormality was reported as resolved and the subject was discharged from the hospital on an unknown date. Evolocumab and simvastatin continued to be withheld. The subject's last dose of evolocumab prior to the event was on 04 December 2013. As of the data cutoff date of 01 April 2014, evolocumab was still being withheld and the subject was continuing in the study. The investigator reported that there was a reasonable possibility that the event of abnormal liver function was related to evolocumab. The investigator noted that medications such as simvastatin, nitrofurantoin, diclofenac and ramipril may have contributed to the liver dysfunction.

SAE AST/ALT Increased.

Subject No: 11466028005
Treatments:

- Parent study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe 10 mg
- Year 1: Evolocumab SC Q2W 140 mg + Standard of Care

Subject 11466028005 was a 44-year-old white woman participating in Study 20120138 who developed increased alanine aminotransferase and aspartate aminotransferase. The subject's medical history included dyslipidemia, hypertension, irritable bowel syndrome, migraine, seasonal allergies, sinus congestion and upper respiratory congestion. Concomitant medication included norethisterone, zestoretic, paracetamol, fluticasone, and amoxicillin. Previous and ongoing treatment for hyperlipidemia included atorvastatin and ezetimibe. The subject received placebo and ezetimibe in the parent study from March 2013 to May 2013. She received the first dose of evolocumab in Study 20120138 in July 2013. A month earlier, laboratory tests revealed alanine aminotransferase (ALT) 34 U/L, aspartate aminotransferase (AST) 26 U/L, alkaline phosphatase 64 /L, and direct bilirubin 0.2 mg/dL. Approximately 5.5 months later, in December 2013 at the week 24 study visit, the subject complained of upper respiratory congestion and sinus congestion. Laboratory tests on the same day revealed ALT 474 U/L (14xULN), AST 150 U/L (4xULN), alkaline phosphatase 354 U/L, and direct bilirubin 0.4 mg/dL. The subject had not experienced any previous episodes of AST or ALT elevation and there were no etiological or predisposing risk factors associated with the event. Two weeks after the initial elevated levels, laboratory tests were repeated and revealed liver function tests within normal ranges: ALT 33 U/L, AST 22 U/L, alkaline phosphatase 82 U/L, and direct bilirubin 0.3 mg/dL. The subject was continuing home dosing as of the data cutoff date of 01 April 2014. The investigator reported that the elevated liver function tests were not related to study participation; however, they were possibly related to upper respiratory infection. The investigator considered paracetamol as a co-suspect medication.

SAE hepatic enzyme increased.
Subject No: 11466014002

- Treatment: Evolocumab SC Q2W 140 mg + Placebo PO QD

Subject 11466014002 was a 59-year-old white woman participating in Study 20110114 who developed increased hepatic enzyme (reported term: elevated liver enzymes greater than 8 times upper level of normal [ULN]). Her medical history included hypercholesterolemia, hypertension, exertional dyspnea , asthma, sleep apnea, bilateral lower extremity edema, gastroesophageal reflux disease, gastric ulcer, irritable bowel syndrome, nocturia, urinary incontinence, osteoarthritis, osteopenia, compression fracture T4, fibromyalgia, night sweats, psoriasis, hypothyroidism, abdominal aortic aneurysm, insomnia, depression, and allergy to sulfa and amoxicillin. The subject had no history of prior or current use of alcohol, recreational drugs or special diets or exposure to environmental or industrial chemical agents. Concomitant medications included amlodipine, clonidine, losartan, levothyroxine, metoclopramide, nitrofurantion, pantoprazole, venlafaxine, pregabalin, zolpidem, acetyl salicylic acid, dicycloverine, vitamin D, and raloxifen. In February 2013, the subject received the first dose of evolocumab and oral placebo. Laboratory results on the same day revealed aminotransferase (ALT) of 23 U/L, aspartate aminotransferase (AST) of 16 U/L, direct bilirubin of 0.1 mg/dL, alkaline phosphatase of 86 U/L, total bilirubin of 0.2 mg/dL, creatine phosphokinase (CPK) of 82 U/L, and lactate dehydrogenase (LDH) of 198 U/L. On (b) (6), the subject underwent a planned left achilles tendon repair and removal of 3 bone spurs. During the peri-procedure period the subject received bupivicaine, cefazolin, dexamethasone, fentanyl, ketorolac, lidocaine, midazolam, and propofol. Post-operatively, starting on (b) (6), the subject received ciprofloxacin and oxycodone until 25 and 26 April 2013, respectively. On 23 April 2013, laboratory tests obtained prior to evolocumab administration revealed ALT and AST levels to be higher than 8 x ULN; ALT of 493 U/L, AST of 422 U/L, direct bilirubin of 0.6 mg/dL, alkaline phosphatase of 116 U/L, total bilirubin of 0.9 mg/dL, CPK of 2246 U/L, and LDH of 456 U/L. The subject was reported to be asymptomatic and instructed to stop evolocumab

on 26 April 2013. On 26 April 2013, laboratory tests revealed ALT of 127 U/L, AST of 45 U/L and CPK of 624 U/L. On 29 April 2013, laboratory tests revealed ALT of 71 U/L, AST of 23 U/L and CPK of 221 U/L. On 29 May 2013, laboratory tests revealed ALT of 21 U/L, AST of 16 U/L, direct bilirubin of 0.1 mg/dL, alkaline phosphatase of 76 U/L, total bilirubin of 0.3 mg/dL, CPK of 73 U/L, and LDH of 201 U/L. The event of increased hepatic enzyme was considered resolved on the same date. The last dose of evolocumab prior to the event elevated liver enzyme was on 08 April 2013. Evolocumab was discontinued and the subject received the last dose on 23 April 2013 and the last dose of oral placebo on 25 April 2013. The investigator reported that there was a reasonable possibility that the event increased hepatic enzyme was related to evolocumab. This reviewer agrees but the post-operative medications likely played a role in this AE. The subject completed the study in June 2013.

SAE Hepatotoxicity.
Subject No: 15466039016
Treatment:

- Parent Study: Evolocumab SC Q4W 350 mg
- Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care
- Years 2-5 treatment: Evolocumab SC Q4W 420 mg+ Standard of care

Subject 15466039016 was a 38-year-old white woman participating in Study 20110110 who experienced hepatotoxicity (reported term: liver toxicity). The subject's medical history included hypercholesterolemia, hypertension, gastritis and obesity. The subject had a negative history for recent surgery or anesthesia, no family history of liver disease, and a negative history of alcohol or drug use and no known exposure to liver toxins. Concomitant medications included Vitamin E, lisinopril, metformin, ranitidine, valsartan, and hydrochlorothiazide. The subject was in the parent study from August 2011 to October 2011 and received the last dose of evolocumab in the parent study in September 2011. The subject received the first dose of evolocumab in Study 20110110 in October 2011. On the same day, laboratory tests obtained prior to the first dose of evolocumab revealed alanine aminotransferase (ALT) 52 U/L, aspartate aminotransferase (AST) 32 U/L, uric acid 7.6 mg/dL and glucose 110 mg/dL. Baseline values obtained on August 2011 included ALT 70 U/L, AST 42 U/L, and total bilirubin 0.2 mg/dL. In January 2012, laboratory tests revealed ALT 48 U/L, AST 27 U/L, uric acid 7.0 mg/dL and glucose 112 mg/dL. In April 2012, the subject had symptoms of nausea, mild epigastric pain after eating, and vomiting. These symptoms continued, along with upper abdominal distention, gas, and poor appetite. In April 2012, laboratory tests showed: ALT 147 U/L (4.3xULN), AST 90 U/L (2.7xULN), uric acid 8.1 mg/dL, and glucose 124 mg/dL. Approximately 7 months after the first dose of evolocumab, in May 2012, the subject was still symptomatic with poor appetite, upper abdominal bloating and discomfort and foot pain. Clinical laboratory investigations showed: Test for *Helicobacter pylori* was positive; ALT >5 x upper normal limit; positive results for Hepatitis A virus total antibodies and Epstein Barr virus IgG, and negative results for Hepatitis A virus IgM, Epstein-Barr virus IgM, Hepatitis C virus, Hepatitis B surface antigen and Hepatitis B core total antibodies. The subject was not hospitalized. Treatment medication included combination of amoxicillin trihydrate, clarithromycin, and lansoprazole. The subject started feeling better and liver function tests improved after one week of therapy. Treatment with evolocumab was withheld at visit 28, 32, and 36 of the study. In July 2012, laboratory data showed ALT 71 U/L, AST 42 U/L, total bilirubin 0.2 mg/dL, direct bilirubin < 0.1 mg/dL, alkaline phosphatase 96 U/L, lactose dehydrogenase 145 U/L, uric acid 7.8 mg/dL, albumin 3.6 gm/dL, and glucose 110 gm/dL. On an unspecified date, laboratory tests showed a dramatic drop in the AST and ALT levels. The investigator reported that subject showed marked improvement of symptoms and had resumed a normal diet; liver related test results were also improved. The subject agreed to continue to receive study medication and evolocumab was restarted in August 2012 (visit 40). Repeated follow-up laboratory results showed: AST 67 U/L and ALT 100 U/L in September 2012 and AST 37 U/L and ALT 52 U/L in January 2013. Subsequent liver function tests

showed consistent improvement 8 months after the first dose of evolocumab. The event of hepatotoxicity was reported to have resolved in July 2012. In April 2013, liver function tests were normal. The subject's last dose of evolocumab prior to the event of hepatotoxicity was in April 2012 after which the evolocumab was withheld and again started in June 2012. Evolocumab was continued. As of the data cutoff date of 01 April 2014, the last dose of evolocumab was in May 2013. The investigator reported that there was no reasonable possibility that the event of hepatotoxicity was related to evolocumab. The investigator reported obesity as a risk factor for the event of hepatotoxicity.

9.10 A Selection of Narratives of Neurocognitive Adverse Events

- 10966434002: 46-year-old female subject participating in Study 20120138 who developed memory impairment. The subject's medical history included hypertension, anxiety, smoking, hypercholesterolemia and ovarian cyst. Concomitant medications reported included alprazolam and fish oil. Atorvastatin was previously documented from 12 March 2012 until 22 April 2013. The subject received the first dose of evolocumab 420 mg (QM) in parent Study 20110109 in April 2012 and the last dose was in March 2013. The subject received the first dose of evolocumab 420 mg (QM) during Study 20120138 in May 2013. Thirty days later, the subject developed memory impairment. The verbatim term reported was "occasional forgetfulness". Evolocumab was continued and the event was reported as ongoing. Baseline TSH on 05 March 2012 was 5.4 mU/L. The subject's LDL cholesterol levels were 32 and 58 mg/dL, respectively, before and after the event. The LDL cholesterol nadir was 14 mg/dL during the study. Evolocumab was held after a November 2013 visit with primary care physician. Subject did not disclose reason and did not allow site to obtain records from the primary care physician because of privacy concerns.

- 15566053008: 60-year-old male subject participating in Study 20110110 who developed amnesia. The subject's medical history included hypercholesterolemia, hypertension, memory loss, gastroesophageal reflux disease, peripheral neuropathy, spinal cord neoplasm, bone neoplasm, and hypersensitivity. Concomitant medications included aspirin, acetaminophen, simvastatin (started October 2012), hydrochlorothiazide, losartan, metoprolol, gabapentin, and ranitidine.The subject received the first dose of evolocumab 350 mg (QM) in parent Study 20101155 in November 2011 and the last dose in January 2012. The subject received the first dose of evolocumab 420 mg (QM) during Study 20110110 in January 2012. One hundred ninety-five days later, in August 2012, the subject developed amnesia. The verbatim term reported was "worsening memory loss". Evolocumab was continued and the event was reported as ongoing. Baseline TSH on 02 November 2011 was 1.53 mU/L. The subject's LDL cholesterol levels were 22 and 25 mg/dL, respectively, before and after the event. The LDL cholesterol nadir was 4 mg/dL during the study.

- 15566064001: 55-year-old male subject participating in Study 20110110 who developed disorientation. The subject's medical history included hypercholesterolemia, arthritis, lethargy, sleep disorder, dyspepsia, myalgia, erectile dysfunction, and hypersensitivity. Concomitant medications reported included aspirin, simvastatin 40 mg daily (started June 2011), loratidine, ibuprofen, and sildenafil. The subject received the first dose of evolocumab 105 mg (Q2W) in parent Study 20101155 inSeptember 2011 and the last dose in November 2011. The subject received the first dose of evolocumab 420 mg (QM) during Study 20110110 in December 2011. One hundred eleven days later, in April 2012, the subject developed disorientation. The verbatim term reported was "intermittent disorientation while driving a car lasting 1-2 minutes". Evolocumab was continued and the event was reported as ongoing. The subject was referred to his primary medical provider for further evaluation. The subject's LDL cholesterol levels

were 35 and 36 mg/dL, respectively, before and after the event. The LDL cholesterol nadir was 29 mg/dL during the study.

- 11666013001: 75-year-old male subject participating in Study 20120138 who developed mental status changes. The subject's medical history included hypercholesterolemia, hypertension, erectile dysfunction, and vertigo. Concomitant medications included aspirin, clopidogrel, diclofenac, lisinopril, metoprolol, and loteprednol etabonate. The subject received the first dose of evolocumab 420 mg (QM) in parent Study 20110116 in March 2013 and the last dose in May 2013. The subject received the first dose of evolocumab 140 mg (Q2W) during Study 20120138 in June 2013. The following day, the subject developed mental status changes. The verbatim term reported was "mental status change". Three days later the subject also developed nausea. Evolocumab was continued and the events of mental status change and nausea were both reported as resolved in 29 days. Baseline TSH on 19 March 2013 was 3.54 mU/L. Baseline TSH in Study 20120138 on 19 June 2013 was normal at 2.59 mU/L. The subject's LDL cholesterol levels were 31 and 30 mg/dL, respectively, before and after the event. The LDL cholesterol nadir was 24 mg/dL during the study.

- 15566064005: 61-year-old man participating in Study 20110110 and developed 2 events of mental impairment. The subject's medical history included hypercholesterolemia, emphysema, malignant melanoma, anxiety, depression, anemia, and arthritis. Concomitant medications reported included atorvastatin 10mg daily (started January 2009) alprazolam, cyanocobalamin, ferrous sulfate, and ibuprofen.The subject received the first dose of evolocumab in the parent study, Study 20101155, in November 2011 and the last dose in January 2012. The subject received the first dose of evolocumab during Study 20110110 in February 2012. One hundred seventeen days later, in May 2012, the subject developed mental impairment. The verbatim term reported was "intermittent decreased mental acuity-cyclic with onset 72 hours following IP, lasting 2 weeks". No treatment for the event was reported. Evolocumab was continued and the event was reported as resolved in 14 days. Baseline TSH in October 2011 was 2.07 mU/L. Imipramine was added to the subject's regimen in November 2012 for the treatment of depression. Three hundred four days after receiving the first dose of evolocumab during Study 20110110, in December 2012, the subject developed a second episode of mental impairment. The verbatim reported term was "worsened cyclic decreased mental acuity". Evolocumab was temporarily withheld and the event was reported as resolved in 18 days. The subject's LDL cholesterol levels were 44 and 74 mg/dL, respectively, before and after the first event and 74 and 42 mg/dL, respectively, before and after the second event. The LDL cholesterol nadir was 34 mg/dL during the study. Evolocumab was continued until August 2013 and then discontinued because of the subject's request due to an adverse event (intermittent palpitations) experienced while on IP.

9.11 A Selection of Narratives of Renal Adverse Events

- Subject 11551704027 was a 55-year-old white woman participating in Study 20110115 who developed acute glomerulonephritis. The subject's medical history included primary hypercholesterolemia, congestive heart failure, type 2 diabetes mellitus, hypertension, stroke/cerebral infarction, carotid or vertebral artery disease, obesity, and chronic pancreatitis. The subject's baseline urinalysis on 31 July 2013, prior to the first dose of evolocumab, showed 3+ proteinuria suggestive of pre-existing proteinuric renal disease. Concomitant medications included indapamide, glimepiride, and metformin. After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first and only dose of evolocumab (420 mg) on 31 July 2013. Two days later, on 02 August 2013, the

subject developed edema. The subject was seen by a cardiologist and treated with spironolactone and hydrochlorothiazide, following which there was no significant improvement. One week later, the subject started experiencing dyspnea with an increase in physical activity. On (b) (6), the subject reported feeling ill after receiving rosuvastatin; edema appeared, and weight increased by 8 kg. Rosuvastatin was withheld on (b) (6). Urinalysis revealed light yellow, slightly clear, acidic urine with a specific density of 1016, protein 1.97 g/L, sugar negative, singular pavement epithelium in visual field and white blood cells (WBC) and red blood cells (RBC) from 0 to 1 in visual field. On (b) (6), the subject underwent a physical examination that revealed mild edema of the upper extremities and severe leg edema (two-thirds of hip) and was hospitalized on the same day. The subject was noted to have hypoproteinemia, hyperlipidemia, and proteinuria (urinalysis results showed protein level of 1.97 g/L) while hospitalized. On (b) (6), urinalysis protein level was 1.86 g/L. The subject was diagnosed with acute glomerulonephritis due to the presence of signs of nephrotic syndrome. Concomitant medications indapamide and metformin were withheld on 13 August 2013. The subject was started on insulin on (b) (6). On (b) (6) the subject presented with edema of face and limbs; additionally, heavy proteinuria, hypoalbuminemia, hypercholesterolemia; lack of effect of diuretic therapy was noted. On (b) (6), nephrologist examination showed acute glomerulonephritis, diabetic nephropathy, and nephrotic syndrome. The nephrologist recommended discontinuation of rosuvastatin. Treatment included acetylsalicylic acid, bisoprolol fumarate, alpha-lipoic acid, combination of aspartic acid dipotassium and magnesium, prednisolone 40 mg oral and 60 mg intravenous, furosemide, torasemide, and spironolactone. In (b) (6), the subject was discharged from the hospital. The event of acute glomerulonephritis was reported as not resolved at the time of this report. The subject's first and last dose of evolocumab prior to the event was on 31 July 2013. Evolocumab was discontinued due to the event of acute glomerulonephritis. The subject completed the study on 28 October 2013. Anti-evolocumab antibodies were evaluated at baseline and week 12 and found to be negative. The investigator reported that there was a reasonable possibility that the event of acute glomerulonephritis was related to investigational product; statin therapy was considered a co-suspect medication.

- This 75 year old, Caucasian male (34866011003), in the evolocumab 140 mg Q2W group in Study 20120348, had a medical history of hypercholesterolemia, myocardial infarction, hypertension, former cigarette use, percutaneous coronary intervention, transient ischemic attack, benign prostate hypertrophy with prostate cancer, kidney stones, urinary hesitancy and protein in urine. Previous and concurrent treatment for the condition under study included atorvastatin. Concomitant medications included Lasix (furosemide), Aspirin (acetylsalicylic acid), bicalutamide, alfuzosin, losartan and Dexilant (dexlansoprazole). The subject received the first dose of evolocumab 140 mg Q2W on (b) (6). The next day the subject developed edema in his legs, and 2 weeks later, he was hospitalized for shortness of breath that increased with exertion. Echocardiogram revealed grossly normal left ventricular wall motion and ejection fraction with mild concentric left ventricular hypertrophy. Chest x ray showed linear atelectasis in the left lower lobe. There was no evidence of pneumonia, pulmonary edema or pleural effusion. Venous Doppler of lower extremities revealed no evidence of deep vein or saphenous vein thrombosis. A 24-hour urine collection showed 5.4 g of protein per day, and minimal change disease was diagnosed on renal biopsy. The event was reported to have resolved approximately 1 month later. Evolocumab was discontinued, and the participant withdrew from the study. The investigator reported that the event of nephrotic syndrome was secondary to minimal change disease and was not related to investigational product. This reviewer notes that minimal change disease can be idiopathic (primary) or associated with drugs, malignancy, or infection (secondary). While there is no compelling reason to suspect evolocumab, the evolocumab use is temporally related, and

since the cause of minimal change disease is often unknown, evolocumab can not be ruled out as a possible factor.

- One participant (15413007003), who received evolocumab 105 mg Q2W in Study 20101154, had an SAE of nephropathy. Further evaluation indicated that it was IgA nephropathy. This 49 year old, white, female had a medical history that included hypercholesterolemia, chronic low back pain secondary to hernia nucleus pulposus L4L5, allergy to fish causing oral angioedema, bacterial meningitis, reflux esophagitis, moderate mitralis valve insufficiency, varices and smoker. The investigator reported that the subject had no history of obstructive uropathy, hemorrhage/hypovolemia, recent systemic or local infection, rhabdomyolysis or recent exposure to iodinated contras material. Concomitant medications included furosemide, buprenorphine, paracetamol (since 1990), omeprazole and ibuprofen (19/Oct/2011-11/Jan/2012). In September 2011, prior to evolocumab administration, the subject's blood pressure was 142/84. Baseline urinalysis: urine specific gravity of 1.017, urine pH of 6.5, protein +1 (proteinuria), glucose was normal, bilirubin was negative, blood of +1 (hematuria), red blood cell count of 23/HPF and white blood cell count of 1/HPF. Baseline laboratory tests disclosed total bilirubin of 3 umol/L, urea of 4.8 mmol/L, creatinine of 70 umol/L, total protein of 66 g/L and albumin of 35 g/L. The subject received the first dose of blinded investigational product for hypercholesterolemia in October 2011. Approximately two months later (4 December 2011), the subject presented with increasing non pitting edema in both legs, resistant to therapy with furosemide. Despite developing non-pitting edema resistant to furosemide, the subject was given a dose of blinded investigational product on 16/Dec/2011. This was the last dose given as blinded investigational product was subsequently permanently discontinued. On 29/Dec/2011, the subject's blood pressure was 128/82 and urinalysis showed proteinuria and hematuria: increased red blood cell of 866 and urine microalbuminuria with urine microalbumin of 3537 mg/l. The following day, hypoalbuminemia and hyponatremia were detected. On 11/Jan/2012, laboratory tests disclosed albumin of 3.46 g/dL, cholesterol of 278 mg/dL, protein/creatinine ratio of 1.82 g/g and total protein of 6.0 g/dL. Kidney echocardiogram showed increased right kidney and corticomedular differentiation. Immunologic screening was negative. Treatment with Preterax (inapamide/perindopril erbumine), Venoruton (heparin sodium) and furosemide was started. At the week 14 visit, on 13/Jan/2012, the subject had elevated blood pressure. Urinalysis disclosed urine specific gravity of 1.012, urine pH of 6.5, protein +2 (proteinuria), glucose was normal, bilirubin was negative, blood of +3 (hematuria), red blood cell count of 134/HPF and white blood cell count of 4/HPF. Laboratory tests disclosed total bilirubin <3umol/L, total protein of 58 g/L, albumin of 28 g/L, and platelet count of 621G/L. Nephrotic syndrome characterized by edema of legs, hypoalbuminemia, hyperlipidemia, microscopic hematuria and proteinuria was diagnosed. No cardiac etiology of acute hypertension was suspected. The event term was updated from suspected renal failure to nephrotic syndrome. The subject underwent a kidney biopsy in February 2012 due to persistent nephrotic syndrome. Further investigations of kidney biopsy revealed an immunoglobulin A (IgA) nephropathy. Subject's vital signs on admission included blood pressure of 130/80 mmHg, and pulse of 63. Edema was significantly less with use of diuretics. The investigator reported that there was no reasonable possibility that the event IgA nephropathy was related to blinded investigational product.

- One 66-year old male (115516013006) who received evolocumab 420 mg QM and rosuvastatin 5 mg in Study 20110115 reported an adverse event of acute renal failure. Medical history included hypercholesterolemia, asthma, type 2 diabetes mellitus, hypertension, GERD, and peptic ulcer disease. Concomitant medications included rosuvastatin, hydrochlorothiazide, aspirin, rabeprazole, metformin, insulin, losartan, niacin, vitamins, naproxen, methocarbamol, acetaminophen, codeine, pantoprazole, loperimide, and dimenhydrinate. The subject received the first dose of evolocumab on (b) (6). The subject presented to the hospital 5 days later on (b) (6) reporting a five day history of nausea, vomiting, and diarrhea and

inability to maintain oral intake for the past 3 days all considered secondary to viral gastroenteritis. He also reported a previous one month history of feeling unwell with mild nausea and back pain. Upon admission, he was found to have acute kidney injury with a serum creatinine of 380 µmol/L, blood urea of 31 mmol/L, and a mild metabolic acidosis with a normal anion gap. The subject's baseline creatinine was 109 µmol/L in April 2013. Blood, urine, and stool cultures were negative (urine culture showed contaminants). White cell count remained elevated during the hospitalization in the 18,000-24,000/microliter range. A triphasic helical scan of the kidneys/abdomen and pelvis revealed no pathology. He received aggressive fluid resuscitation, bicarbonate replacement, and empiric antibiotic coverage (metronidazole and ciprofloxacin). The event was reported as resolved on (b) (6) and the subject was discharged home; creatinine had improved to 138 µmol/L. The subject's last dose of evolocumab prior to the event was on 03 June 2013. The investigational product was temporarily held and then restarted; he received the last scheduled dose on 29 July 2013. The subject's creatinine remained stable at 94 µmol/L and 100 µmol/L on 29 July 2013 and 26 August 2013, respectively.

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/s/

EILEEN M CRAIG
08/24/2015

JAMES P SMITH
08/24/2015

CLINICAL FILING CHECKLIST FOR BLA 125522

BLA Number: 125522	**Applicant: Amgen**	**Stamp Date: 8/27/14**
Drug Name: evolocumab/Repatha	**BLA Type: NME**	**PDUFA Date: 8/25/15 (STD) 4/27/15 (priority)**

Filing Meeting: Wed 10/8/14; 1-2p; WO 3270 Bldg 22
Filing Date: 10/25/14
Mid-cycle Review Meeting:
Wrap-up Meeting
Reviews signed-off in DARRTS: 5/1/15
Action Goal Date: 8/25/15
PDUFA Date: 8/25/14

Labeling Timeline:

The network location is:
url:gs:HgAAAAUBAAqmmoMBAAABAIKmgwEAAAABAgICAAMABD0wMDAwICgxKSAwOC8yNy8yMDE0IE9SSUctMSAvTXVsdGlwbGUgQ2F0ZWdvcmllcy9TdWJjYXRlZ29yaWVzBDAwMDAGMTI1NTIyA2JsYQA%3d

Primary Reviewers	
Clinical:	Eileen Craig
Nonclinical (Pharm-tox):	Calvin (Lee) Elmore/Karen Davis-Bruno
Clin Pharm:	Suryanarayana Sista/Immo Zadezensky
Pharmacometrics:	Justin Earp/ Nitin Mehrotra
Biometrics:	Shuxian (Susie) Sinks /Mark Rothmann
Product Quality Reviewers (OBP):	Sang Bong Lee/Bazarragchaa Damdinsuren/Chana Fuchs
Product Quality Microbiology Reviewers:	Michael Shanks and Lakshmi Narasimhan
CDRH (devices):	Lana Shiu
Patient Labeling (DBRUP):	Robin Duer
Advertising:	Ankur Kalola
CardioRenal (for QTc):	TBD
OSE/DMEPA (labeling/HF/REMS):	Mishale Mistry/Lena Maslov
OSI:	Cynthia Kleppinger
Project Manager:	Kati Johnson

Indications:
1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

[TRADENAME] is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB),

non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides(TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

1.2 Homozygous Familial Hypercholesterolemia

[TRADENAME] is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

The proposed dose is

- For primary hyperlipidemia or mixed dyslipidemia: 140 mg by subcutaneous (SC) injection every 2 weeks (Q2W) and 420 mg by SC injection every month (QM). Both dosing regimens led to similar reductions in LDL-C.
- HoFH: 420 mg SC QM and 420 mg SC Q2W

Background:
Evolocumab (AMG 145) is a first in class human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9).

Mode of Action
When PCSK9 binds to low-density lipoprotein receptor (LDLR), the LDLR is targeted for destruction rather than being recycled back to the cell surface, thereby reducing the levels of LDLR available for low-density lipoprotein cholesterol (LDL-C) clearance from the bloodstream. Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

Evolocumab has been evaluated for 2 lipid-lowering indications in 5710 subjects exposed to any dose of evolocumab during Phase 1, 2 and 3 studies.

1. For the treatment of adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia. In these populations, evolocumab was evaluated at 2 dosing regimens – 140 mg by subcutaneous (SC) injection every 2 weeks (Q2W) and 420 mg by SC injection every month (QM). Both dosing regimens led to similar reductions in LDL-C.

File name: Clinical Filing Checklist for BLA 125522 Evolocumab

2. In adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH). The doses evaluated in HoFH were 420 mg SC QM and 420 mg SC Q2W.

The clinical development of evolocumab included evaluation of the following 4 SC presentations:

- vial and syringe
- prefilled syringe (PFS)
- prefilled autoinjector/pen (AI/pen)
- automated mini-doser (AMD) – also referred to as 3.5 mL personal injector (b) (4) pen provide a single SC administration of 140 mg evolocumab. The prefilled AI/pen was used in the majority of the phase 3 studies, and 3 consecutively administered prefilled AI/pens were used within 30 minutes to deliver the 420 mg dose. The prefilled AI/pen and the PFS are included in this filing for approval.

Excerpts of Regulatory History:

Meeting Date/ Type	Meeting Purpose	Event/Notes
(b) (4)		

CLINICAL FILING CHECKLIST FOR BLA 125522

Meeting Date/ Type	Meeting Purpose	Event/Notes
[redacted] (b) (4)		
10 July 2012 End of Phase 2 (Clinical)	To discuss the proposed clinical development program and the device clinical study strategy from pivotal studies to commercial launch for the two indications of (1) hyperlipidemia and mixed dyslipidemia and (2) secondary prevention of heart disease.	•FDA stated that it would inappropriate to use AMG 145 as monotherapy in the general population before cardiovascular (CV) outcomes data are available. Thus, with the possible exception of an indication for a "statin-intolerant" population, it is unlikely that we would entertain a monotherapy indication without CV outcomes data. •FDA stated that based on the currently proposed designs, you intend to make superiority claims to ezetimibe [redacted] (b) (4) We would not include [redacted] (b) (4) before CV outcomes data for AMG 145 are available. [redacted] (b) (4) •FDA expressed concerns on having both 140 mg Q2W and 420 mg Q4W regimens. These dosing regimens seem to have approximately the same pharmacodynamic (PD) effect with regard to LDLC, [redacted] (b) (4) • Amgen suggested that both selected doses were more effective than other tested doses, were associated with more stable LDL levels, and were not associated with any higher incidence of adverse events or laboratory abnormalities. They noted that AMG 145 140 mg Q2W

Meeting Date/ Type	Meeting Purpose	Event/Notes
		provides a lower drug exposure, based on AUC, than the 420 mg Q4W dose; therefore, these dosages ought to be sufficient to identify dose-related adverse effects. • FDA stated that we would prefer the duration of the studies to be 24 weeks. • FDA did not agree with Amgen's proposed definition of statin-intolerance of failing 1 or more statins. FDA recommended the following definition for muscle-related statin-intolerance: the inability to tolerate at least two previous statins at the lowest approved daily dose as a result of muscle-related symptoms that began or increased during statin therapy and stopped with the discontinuation of statin therapy. Symptoms could include aches, pain, cramping, and/or weakness but should exclude those thought to be the result of strain, exertion, or trauma. Historical information regarding previous statins, doses, and muscle-related events that led to the diagnosis of "statin intolerance" should be recorded. We would require a design that would incorporate a blinded statin re-challenge arm in order to provide convincing evidence that you have successfully identified a distinct patient population. We recognize that subjects with a history of certain serious adverse effects (e.g., documented myositis or rhabdomyolysis on statin therapy) could not be enrolled in such a trial. • FDA was in agreement with the general design of the proposed CVOT and recommended it be submitted as a SPA. FDA stated as a result of the division's experience with the development programs of non-statin LDL-C-lowering drugs, we will require that the trial has accrued a minimum of 25% of the planned 1630 first secondary endpoint events before submission. It is also possible that the results of the ongoing IMPROVE-IT trial, which is studying the incremental contribution of ezetimibe on CV outcomes beyond simvastatin alone, might alter the division's approach to non-statin lipid-modulating drugs. If IMPROVE-IT fails to demonstrate a favorable effect of ezetimibe on clinical outcomes, it is possible that results from your CV outcomes trial may be required prior to approval. • FDA agreed that no dedicated studies to investigate drug-drug interactions were required, but systemic exposure data should be collected •FDA agreed that a thorough QT study is not required, but that safety ECGs be collected at baseline and at steady state
		(b) (4)

CLINICAL FILING CHECKLIST FOR BLA 125522

Meeting Date/ Type	Meeting Purpose	Event/Notes
[redacted] (b) (4)		
12 July 2013 – Written Responses Only	To obtain FDA feedback on: • The content and structure of the ISS and ISE • The data standardization plan and mock data submission	• The FDA found the proposed data standardization plan to be acceptable, but had questions regarding the primary endpoint for the phase 2 and phase 3 studies • FDA requested a discussion regarding the adjudication on reported adverse events, the process for positive adjudication, and a description of the adjudication packages to be submitted
30 October 2013 - Teleconference	To obtain advice on the submission of a data package to support the	• FDA noted the heterogeneity of response of HoFH subjects to evolocumab as a possible limitation. •Primary Endpoint: The FDA indicated that mean percent change in

Meeting Date/ Type	Meeting Purpose	Event/Notes
	indication of homozygous familial hypercholesterolemia (HoFH).	LDL-C from baseline to Week 12 is the expected primary endpoint for HoFH. FDA indicated that the "regulatory decision" will likely be based upon the mean percent change in LDL-C from baseline to Week 12 (currently a co-primary endpoint) for all 12 week Phase 3 trials. •An indication for HoFH would only be considered in parallel with or after an indication is granted for the general population with hyperlipidemia. The FDA stated that Amgen could pursue a Treatment IND to grant early access to the HoFH population pursuant to expanded access regulations
10 April 2014 – Pre-BLA (Clinical)	To reach agreement on the proposed structure, format, and content of the BLA	• FDA stated that we continue to believe that accrual of a minimum of 25% of MACE (with timely adjudication) prior to BLA submission is the appropriate method to encourage timely CVOT completion. If you decide to submit prior to reaching the 25% of endpoints threshold, you should include the number (%) of first secondary endpoint events that have been accrued, the number (%) that have been adjudicated and the results of adjudication (i.e., the number accepted as endpoints vs. rejected), and the number (%) of subjects that have been randomized at the time of BLA submission. • FDA reconfirmed that the FDA is unlikely to consider a monotherapy indication or an indication explicitly referencing "statin-intolerant" patients without positive outcomes data. FDA expects that the approvability of a PCSK9 inhibitor, in the absence of outcomes data, will be a topic for discussion with an advisory committee. • FDA stated that the proposed safety database was significantly less than what was estimated at the EOP2 meeting and we had concerns about the sufficiency of the safety database and duration of exposure to support the proposed indications. FDA stated that current estimates for the 1-year exposure would not constitute a complete file; therefore a new safety data-cut is required (01 April 2014 agreed to be the new data cut).
18 April 2014 post-Pre-BLA meeting information requests		FDA Request #3. The baseline characteristic data published in your NEJM report of the DESCARTES trial seem inconsistent with the "high-risk" population that you have indicated are most appropriate for evolocumab therapy. Specifically, more than half of the trial's population fall into the "diet alone" or "diet plus atorvastatin 10 mg" groups, which do not seem consistent with high-risk populations. Overall, it appears that only 271 patients were treated for a year with high-dose atorvastatin (with or without ezetimibe) combined with evolocumab. Considering the entire trial population, the majority (65%) of subjects were categorized as either low or moderate risk by the ATP-III classification. Furthermore, the mean baseline LDL-C among all patients was 104 mg/dL, which is quite well controlled and does not appear consistent with the population that you describe as having an unmet medical need (i.e., "high" LDL-C despite statin therapy). Especially since you believe that this trial represents the highest-quality safety data for your program, we continue to have concerns regarding long-term safety among the target population likely most appropriate for evolocumab before outcomes data are available. Thus, we anticipate having to rely substantially on data from your open-label controlled extensions that studied higher-risk populations. As we previously requested in the pre-BLA meeting preliminary comments, any information you can provide with regard to the numbers of patients that

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		have been treated with evolocumab for at least one year in relevant categories of demographic or baseline characteristics would be helpful to guide our decisions regarding agreements with your safety database. Please let us know if, and when, you would be able to provide additional information. FDA Post-Meeting Comments: It is our understanding that a data cutoff on April 1, 2014 would provide (b) (4) patients with ≥361 days exposure to evolocumab. We also note that (b) (4)%) of these subjects would come from your phase 3 program (b) (4) of them from your DESCARTES trial) and (b) (4)%) would come from your phase 2 program. We still question whether the summary of baseline characteristics that you have provided are consistent with the "high-risk" population that you have indicated as most appropriate for evolocumab therapy. This is an issue of concern that will be discussed during the review of your application. As we mentioned previously, we anticipate having to rely substantially on data from your open-label controlled extensions that studied higher-risk populations. Therefore, the controlled data from the 120-day safety update should be incorporated into updated analyses of the controlled phases of these trials and should not be submitted solely as a separate data presentation. Provided that the 120-day safety update is submitted as described above, we do not anticipate that an April 1, 2014 data cutoff for Studies 20110110, 20120138, and 20120271 would preclude filing of a BLA for the proposed indications of primary hyperlipidemia and mixed dyslipidemia and HoFH. Whether the safety database will be sufficient for approval of the proposed indications will be a subject of review. Additional FDA Request: As noted above, you anticipate that (b) (4)% ((b) (4)) of the subjects with ≥361 days of evolocumab exposure will come from your phase 2 program and its open-label extension studies. We note that you administered evolocumab differently in phase 2 (total volume per administration drawn from six sterile vials) with a formulation (70 mg/mL) that you do not intend to market and that you did not use in phase 3. Please explain how you plan to bridge your phase 2 and phase 3 programs for the evaluation of clinical safety.
30 April 2014 firm responds via email to IR of 4/18/14		Amgen Response to FDA Request #3 (excerpts): In designing DESCARTES, Amgen and its academic collaborators endeavored to enroll an appropriate at-risk cardiovascular population where it would be ethical to evaluate the treatment of hyperlipidemia with evolocumab compared to placebo in a blinded fashion for 1 year. To facilitate this, background lipid-lowering therapy was optimized to one of four treatment groups (diet alone; diet plus atorvastatin 10 mg; diet plus atorvastatin 80 mg; and diet plus atorvastatin 80 mg plus ezetimibe 10 mg) for individual subjects based on their LDL-C and cardiovascular risk according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III risk categories. On optimized therapy, eligible subjects needed to have a fasting LDL-C greater than 75 mg/dL and less than 100 mg/dL for subjects with coronary heart disease or risk equivalent, or an LDL-C of less than 130 mg/dL for subjects without coronary heart disease or risk equivalent unless they

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		had reached maximal therapy (ie, atorvastatin 80 mg plus ezetimibe 10 mg). It is the position of Amgen that DESCARTES enrolled an appropriate at-risk cardiovascular population to evaluate long-term safety, tolerability, and efficacy of evolocumab alone and in combination with high-intensity and moderate-intensity lipid-lowering therapy. In DESCARTES, 36% and 33% of the subjects were high/moderately high and moderate risk by ATP-III risk categories, respectively. Using the DESCARTES NCEP risk-based treatment approach, approximately 88% of the subjects enrolled in DESCARTES ended up on high-intensity (45%) and moderate-intensity (43%) statin therapy. Furthermore, it is striking that approximately 21% of the DESCARTES subjects had mean LDL-C values of 117-120 mg/dL after forced titration to atorvastatin 80 mg plus ezetimibe 10 mg. In subjects allocated to diet alone or diet plus atorvastatin 10 mg, approximately 42% and 42%, had hypertension, respectively. In the diet alone group, 18% and 37% were high/moderately high and moderate risk by ATP III, respectively. In the diet plus atorvastatin 10 mg group, 22% and 36% were high/moderately high and moderate risk by ATP III, respectively… The population encompassing the datasets using 01 April 2014 as a data cut-off date (Tables 4-7) has a mean (SD) age of 57 (11) years and is approximately 54% female. Approximately 18% and 7% have a prior diagnosis of coronary artery disease and cerebrovascular or peripheral arterial disease, respectively. Approximately 11% have Type II diabetes mellitus while approximately one third have metabolic syndrome and mixed dyslipidemia. Approximately 40% are high and moderately-high risk by ATP-III; 31% are moderate risk. Given the evaluation of evolocumab monotherapy to determine the safety and efficacy of evolocumab in the absence of possible confounding factors from statins, as well as the evaluation of evolocumab in statin-intolerance, approximately 70% of the population studied was on lipid-lowering therapy at baseline with 69% on statins. Of the patients on statin therapy at baseline, approximately 37% and 48% were on high-and moderate-intensity statin, respectively. Please note that severe heart failure, type 1 diabetes, and poorly controlled, or newly diagnosed, type 2 diabetes are listed as exclusionary criteria for each of the phase 2 and 3 studies. (see tables 6 and 7 below)

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Table 6. Evolocumab-treated Subject Baseline Characteristics in Phase 2 Studies with ≥ 1 year Study Exposure (Exposure ≥ 361 days)

Report Topic	All Combined (Phase 2 and 3)	Any Phase 2	S154	S155	S158	S159	S231
Number of Subjects with ≥361 Days of Exposure	1761	1111	264	486	130	116	115
Female – n (%)	945 (53.7)	604 (54.4)	175 (66.3)	250 (51.4)	62 (47.7)	70 (60.3)	47 (40.9)
Age (years), mean (SD)	56.7 (11.3)	56.9 (11.5)	50.9 (11.7)	60.2 (9.7)	48.7 (12.4)	61.9 (8.6)	60.9 (9.1)
>= 65 Years Old – n (%)	478 (27.1)	316 (28.4)	29 (11.0)	177 (36.4)	16 (12.3)	52 (44.8)	42 (36.5)
Coronary artery disease (CAD) – n (%)	313 (17.8)	215 (19.4)	0	141 (29.0)	27 (20.8)	25 (21.6)	22 (19.1)
CVD or PAD – n (%)	112 (6.4)	80 (7.2)	1 (0.4)	48 (9.9)	8 (6.2)	10 (8.6)	13 (11.3)
Type II Diabetes Mellitus – n (%)	205 (11.6)	142 (12.8)	0	78 (16.0)	5 (3.8)	13 (11.2)	46 (40.0)
Triglycerides >= 150 mg/dL – n (%)	523 (29.7)	378 (34.0)	92 (34.8)	161 (33.1)	34 (26.2)	55 (47.4)	36 (31.3)
Low HDL-C – n (%)	552 (31.3)	358 (32.2)	92 (34.8)	156 (32.1)	55 (42.3)	33 (28.4)	22 (19.1)
Subjects with baseline metabolic syndrome (3 or more factors) and without	640 (36.3)	424 (38.2)	106 (40.2)	187 (38.5)	47 (36.2)	46 (39.7)	38 (33.0)

Report Topic	All Combined (Phase 2 and 3)	Any Phase 2	S154	S155	S158	S159	S231
diabetes mellitus – n (%)							
NCEP risk category – n (%)							
High risk	545 (30.9)	378 (34.0)	1 (0.4)	215 (44.2)	40 (30.8)	49 (42.2)	73 (63.5)
Moderately high risk	159 (9.0)	101 (9.1)	12 (4.5)	60 (12.3)	9 (6.9)	9 (7.8)	11 (9.6)
Moderate risk	551 (31.3)	338 (30.4)	96 (36.4)	153 (31.5)	32 (24.6)	33 (28.4)	24 (20.9)
Congestive Heart Failure – n (%)	41 (2.3)	31 (2.8)	0	25 (5.1)	2 (1.5)	1 (0.9)	3 (2.6)
Left ventricular systolic function known – n (%)	245 (13.9)	187 (16.8)	3 (1.1)	129 (26.5)	9 (6.9)	15 (12.9)	31 (27.0)
Normal systolic function (LVEF >= 50%) – n (%)	211 (12.0)	162 (14.6)	3 (1.1)	109 (22.4)	7 (5.4)	14 (12.1)	29 (25.2)
Mild dysfunction (LVEF 40-49%) – n (%)	30 (1.7)	21 (1.9)	0	18 (3.7)	0	1 (0.9)	2 (1.7)
Moderate dysfunction (LVEF 30-39%) – n (%)	4 (0.2)	4 (0.4)	0	2 (0.4)	2 (1.5)	0	0
Severe dysfunction (LVEF < 30%) – n (%)	0	0	0	0	0	0	0

Meeting Date/ Type	Meeting Purpose	Event/Notes

Report Topic	All Combined (Phase 2 and 3)	Any Phase 2	S154	S155	S158	S159	S231
Baseline Lipid medication – n (%)							
Statin	1251 (71.0)	743 (66.9)	0	484 (99.6)	130 (100.0)	14 (12.1)	115 (100.0)
Ezetimibe –	259 (14.7)	135 (12.2)	0	45 (9.3)	87 (66.9)	0	3 (2.6)
Per ACC/AHA definition – n (% of statin subjects)							
High-intensity	494 (39.5)	235 (31.6)	0	127 (26.2)	106 (81.5)	0	2 (1.7)
Moderate-intensity	596 (47.6)	352 (47.4)	0	308 (63.6)	21 (16.2)	2 (14.3)	21 (18.3)
Low-intensity	161 (12.9)	156 (21.0)	0	49 (10.1)	3 (2.3)	12 (85.7)	92 (80.0)
Statin therapy at baseline per Amgen definition – n (%)							
Intensive	526 (29.9)	267 (24.0)	0	145 (29.8)	118 (90.8)	0	4 (3.5)
Non-Intensive	725 (41.2)	476 (42.8)	0	339 (69.8)	12 (9.2)	14 (12.1)	111 (96.5)
LDL-c (mg/dL) at baseline - mean (SD)	127.2 (39.2)	139.0 (38.7)	142.5 (23.3)	120.7 (28.4)	154.4 (45.2)	190.9 (51.0)	138.3 (22.3)

Report Topic	All Combined (Phase 2 and 3)	Any Phase 2	S154	S155	S158	S159	S231
PCSK9 (ng/mL) at baseline - mean (SD)	439.6 (155.8)	429.5 (143.0)	346.5 (82.2)	444.6 (122.2)	607.1 (185.2)	386.8 (109.4)	401.3 (118.4)

Data cutoff date of 01 April 2014

Table 7. Evolocumab-treated Subject Baseline Characteristics in Phase 3 Studies with ≥ 1 year Study Exposure (Exposure ≥361 days)

Report Topic	All Combined (Phase 2 and 3)	Any Phase 3	S109	S114	S115	S116	S117
Number of Subjects with ≥361 Days of Exposure	1761	650	566	58	5	19	2
Female – n (%)	945 (53.7)	341 (52.5)	295 (52.1)	32 (55.2)	4 (80.0)	9 (47.4)	1 (50.0)
Age (years), mean (SD)	56.7 (11.3)	56.3 (10.9)	56.2 (10.7)	53.8 (12.6)	65.8 (6.1)	64.7 (9.0)	72.0 (2.8)
>= 65 Years Old – n (%)	478 (27.1)	162 (24.9)	135 (23.9)	12 (20.7)	3 (60.0)	10 (52.6)	2 (100.0)
Coronary artery disease (CAD) – n (%)	313 (17.8)	98 (15.1)	89 (15.7)	0	1 (20.0)	6 (31.6)	2 (100.0)
CVD or PAD – n (%)	112 (6.4)	32 (4.9)	26 (4.6)	2 (3.4)	1 (20.0)	3 (15.8)	0
Type II Diabetes Mellitus – n (%)	205 (11.6)	63 (9.7)	58 (10.2)	0	1 (20.0)	4 (21.1)	0
Triglycerides >= 150 mg/dL – n (%)	523 (29.7)	145 (22.3)	114 (20.1)	19 (32.8)	3 (60.0)	9 (47.4)	0
Low HDL-C – n (%)	552 (31.3)	194 (29.8)	166 (29.3)	14 (24.1)	3 (60.0)	10 (52.6)	1 (50.0)
Subjects with baseline metabolic syndrome (3 or more factors) and without diabetes mellitus – n (%)	640 (36.3)	216 (33.2)	183 (32.3)	21 (36.2)	3 (60.0)	8 (42.1)	1 (50.0)

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Meeting Date/ Type	Meeting Purpose	Event/Notes

Report Topic	All Combined (Phase 2 and 3)	Any Phase 3	S109	S114	S115	S116	S117
NCEP risk category – n (%)							
High risk	545 (30.9)	167 (25.7)	148 (26.1)	3 (5.2)	2 (40.0)	12 (63.2)	2 (100.0)
Moderately high risk	159 (9.0)	58 (8.9)	53 (9.4)	4 (6.9)	0	1 (5.3)	0
Moderate risk	551 (31.3)	213 (32.8)	191 (33.7)	16 (27.6)	2 (40.0)	4 (21.1)	0
Congestive Heart Failure – n (%)	41 (2.3)	10 (1.5)	10 (1.8)	0	0	0	0
Left ventricular systolic function known – n (%)	245 (13.9)	58 (8.9)	54 (9.5)	0	2 (40.0)	1 (5.3)	1 (50.0)
Normal systolic function (LVEF >= 50%) – n (%)	211 (12.0)	49 (7.5)	46 (8.1)	0	1 (20.0)	1 (5.3)	1 (50.0)
Mild dysfunction (LVEF 40-49%) – n (%)	30 (1.7)	9 (1.4)	8 (1.4)	0	1 (20.0)	0	0
Moderate dysfunction (LVEF 30-39%) – n (%)	4 (0.2)	0	0	0	0	0	0
Severe dysfunction (LVEF < 30%) – n (%)	0	0	0	0	0	0	0
Baseline Lipid medication – n (%)							
Statin	1251 (71.0)	508 (78.2)	497 (87.8)	0	5 (100.0)	4 (21.1)	2 (100.0)
Ezetimibe	259 (14.7)	124 (19.1)	122 (21.6)	0	0	0	2 (100.0)
Per ACC/AHA definition – n (% of statin subjects)							
High-intensity	494 (39.5)	259 (51.0)	256 (51.5)	0	2 (40.0)	0	1 (50.0)
Moderate-intensity	596 (47.6)	244 (48.0)	241 (48.5)	0	2 (40.0)	1 (25.0)	0
Low-intensity	161 (12.9)	5 (1.0)	0	0	1 (20.0)	3 (75.0)	1 (50.0)
Statin therapy at baseline per Amgen definition – n (%)							
Intensive	526 (29.9)	259 (39.8)	255 (45.1)	0	2 (40.0)	0	2 (100.0)
Non-Intensive	725 (41.2)	249 (38.3)	242 (42.8)	0	3 (60.0)	4 (21.1)	0
LDL-c (mg/dL) at baseline - mean (SD)	127.2 (39.2)	107.1 (30.9)	100.7 (22.3)	141.9 (19.9)	82.0 (16.7)	197.3 (58.7)	130.3 (26.5)
PCSK9 (ng/mL) at baseline - mean (SD)	439.6 (155.8)	456.9 (174.3)	478.6 (172.3)	285.2 (76.1)	391.8 (96.4)	296.1 (65.2)	504.5 (183.1)

Data cutoff date of 01 April 2014

Labeling:
In Module 1.14, the applicant submitted draft labeling text in SPL format. The proposed Package Insert and Patient Package Insert are submitted in Microsoft word format and includes an annotated version.

Some preliminary label issues (to be conveyed to the applicant at a later date):

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1. Contraindications should be included—active liver disease, pregnancy, hypersensitivity--see Zetia label as an example. Hyperprolinemia (see PRIVIGEN label as example). Evolocumab contains 220 mM proline.
2. Warnings and Precautions: Need to include Use with Statins, Liver Enzymes, Myopathy/Rhabdomyolysis—see Zetia label as an example.
3. Adverse Reactions:
    a. The short-term database for the primary hyperlipidemia and mixed dyslipidemia indication consists of data from the 12-week phase 2 and phase 3 trials (20101154, 20101155, 20090158, 20090159, 20110114, 20110115, 20110116, 20110117, and 20110231) and the two device home-use studies (20120348 and 20120356). The applicant will need to provide in this section the treatment duration (median and range), demographics (mean age and range, race, sex), 5 most common adverse events and 5 most common adverse reactions that led to treatment discontinuation and occurred at a rate greater than placebo/control. (b) (4) [redacted]

    b. The long-term database for the primary hyperlipidemia and mixed dyslipidemia indication is from the 52-week trial (20110109) (b) (6) [redacted]

    c. The applicant's Table 2 in Section 6 needs to be revised (b) (4) [redacted] The table should include a column for EvoMab adverse reactions from the to-be-marketed doses. (b) (4) [redacted]

    d. (b) (4) [redacted].

    e. (b) (4) [redacted].

    f. In the text, references to (b) (4) [redacted] should be replaced with numbers of patients treated with evolocumab. The number treated with placebo will appear in column headings of relevant tables.

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g. (b) (4)

h. (b) (4)

Risk Evaluation and Mitigation Strategy (REMS):
A risk management plan, Elements to Assure Safe Use (ETASU) and the Implementation System are not proposed.

Priority or Standard Review:
Amgen requested a Priority review of this application but this application will likely be designated a Standard review.

Pediatric Waiver:
Waivers Being Sought for the Indication for Primary Hyperlipidemia (b) (4)

Indication: Primary Hyperlipidemia	(b) (4)

Indication: Homozygous Familial Hypercholesterolemia
Evolocumab was granted orphan drug designation for the "treatment of homozygous familial hypercholesterolemia" and so the requirements set forth by the Pediatric Research Equity Act (PREA) do not apply.

Debarment Certification:
Amgen certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal, Food, Drug and Cosmetic Act in connection with this application.

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CLINICAL FILING CHECKLIST FOR BLA 125522

Financial Disclosures:
Amgen submitted a completed Form FDA 3454 attesting to the absence of financial interests and arrangements for all investigators that submitted financial information, with the exception of one clinical investigator.

Amgen certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but was unable to do so for thirteen (13) sub-investigators who participated in covered clinical studies for evolocumab.

One clinical investigator (b) (6) had a significant equity interest, as defined in 21 CFR 54.2(b), which consisted of approximately 2000 shares purchased decades ago. Dr (b) (6) enrolled at total of (b) (6) subjects: (b) (6)

Amgen has employed the following steps to minimize bias of the clinical study results by any of the disclosed arrangements or interests:

- Use of multiple clinical sites
- Clinical site monitoring
- Clinical site audits
- Independent and centralized assessment of efficacy response data

The efficacy and safety studies used multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurements of endpoints by someone other than the investigator to minimize bias.

Site Inspection:
Three trials were selected for site selection based on trial design and size of enrollment. Trial 20110109 (DESCARTES, n = 905), the only placebo-controlled, 52-week Phase 3 trial, was selected as one of the trials to be investigated. Trial 20110114(MENDEL-2, n=615), a 12-week, monotherapy, placebo- and ezetimibe-controlled phase 3 trial in hypercholesterolemic subjects with a 10-year Framingham Risk Score of ≤ 10%, and trial 20110115 (LAPLACE-2, n=1899), a 12-week combination therapy with atorvastatin, rosuvastatin or simvastatin, placebo- and ezetimibe-controlled phase 3 trial in subjects with primary hypercholesterolemia receiving background statin therapy were the other two trials selected.

In consultation with Dr. Cynthia Kleppinger (OSI, Good Clinical Practice Assessment Branch), the following sites were identified:

Trial 20110109

- Tomas Hala (Pardubice, Czechoslovakia)
- Ben Lasko (Toronto, Canada)
- Annesofie Krogsaa (Ballerup, Denmark)
- Michael Bolognese (Bethesda, MD, US)

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Trial 20110114

- Michael Bolognese (Bethesda, MD, US)
- Annesofie Krogsaa (Denmark)

Trial 20110115

- Annesofie Krogsaa (Denmark)
- Tomas Hala (Czechoslovakia)
- Vivek Awasty (Marion, OH, US) (Listed as two separate sites)

The sites below are recommended for consideration primarily based on the number of subjects enrolled, total risk ranking, and efficacy results.

Site # (Name, Address, Phone Number, email, fax #)	Protocol ID	# Subjects Enrolled at site/ total for trial	Indication
Site 1-1AF9XT (23201); CCBR Pardubice Tomas Hala; Trida Miru 2800 Pardubice 530 02 Czech Republic Phone: +420 464 629 124 FAX: +420 466 260 968 Email: tomas.hala@ccbr.com	20110109	42/905	Risk ranking #1 in Trial 109 and #5 in Trial 115. Highest enroller, low AE reporting, most deaths, large site specific efficacy effect size, outlier for protocol deviations (b) (4) INDs, and never been inspe d. Involved in (b) (4) trials.
Site 1-55N7TT (16300); Manna Research Incorporated; Ben Lasko; 2291 Kipling Avenue, Unit 117B;Toronto ON M9W 4L6, Canada Phone: +1-416-740-2895 FAX: +1-416-740-4517 Email:ben.lasko@mannaresearch.com	20110109	41/905	Risk ranking #2 in Trial 109 and #10 in Trial 114. High enroller, large site specific efficacy effect size, (b) (4) INDs, and never been inspected. Involved in (b) (4) trials.
Site 1-4HRP5T (25202); Centre for Clinical and Basic Research Ballerup Annesofie Krogsaa; Ballerup Byvej 222,Center for Clinical and Basic Research,Ballerup 2750, Denmark Phone: +45 4470 4459 FAX: +45 4468 4220 Email:AnneSofie.Krogsaa@ccbr.com	20110109	33/905	Risk ranking #7 in Trial 109. Involved in (b) (4) trials.
Site 1-51Q (66402); Bethesda Health Research Michael Bolognese; 10215 Fernwood Road, Suite 40, Bethesda MD 20817 USA Phone: +1-301-530-1166 FAX: +1-301-530-1295 Email: bethesdahealth@msn.com	20110109	35/905	Risk ranking #12 in Trial 109. US site, high number of screened/enrolled, high site specific efficacy effect size, and outlier for protocol violations. (b) (4) INDs, inspected (b) (4) NAI, (b) (4) -VAI. Involved i (b) (4) rials.

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Site # (Name, Address, Phone Number, email, fax #)	Protocol ID	# Subjects Enrolled at site/ total for trial	Indication
Site 1-51Q (66004) Michael Bolognese mbolognese@erols.com	20110114	24/615	Risk ranking #2 in Trial 114. US site, fairly high enroller, high site specific efficacy effect size.
Site 1-4HRP5T (22002) Annesofie Krogsaa	20110114	56/615	Risk ranking #7 in Trial 114 and highest enroller. Involved in 3 trials.
Site 1-4HRP5T (22002) Annesofie Krogsaa	20110115	50/1899	Risk ranking #2 in Trial 115, high enroller, high site specific efficacy effect size. Involved in (b) (4) trials, (b) (4) INDs, never inspected.
Site 1-1AF9XT (21007) Tomas Hala	20110115	25/1899	Risk ranking #5 in Trial 115
Site 1-65YIRL 1-59VDW6 (66002, 66080) Awasty Research Network LLC; Vivek Awasty; 980 South Prospect Street, Suite 2, Marion OH 43302, USA Phone: +1-740-375-8140 FAX: +1-740-942-6317 Email: vivek.awasty@awastyresearch.com	20110115	29/1899 13/1899	Two sites in 115. Risk ranking #12 and #19. Very high site specific efficacy effect size at site 1-65YIRL. (b) (4) INDs; inspected (b) (4) -VAI.

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			

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CLINICAL FILING CHECKLIST FOR BLA 125522

	Content Parameter	Yes	No	NA	Comment
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	BLA 351 (a)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? (1) Study Number: 20101154 Study Title: A Randomized, Placebo- and Ezetimibe-controlled, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Hypercholesterolemic Subjects With a 10-year Framingham Risk Score of 10% or Less (MENDEL: Monoclonal antibody against PCSK9 to reduce Elevated LDL-C in subjects currently Not receiving Drug therapy for Easing Lipid levels) Sample Size: 411 Arms:8 Location in submission: Module 5.3.5.1 (2) Study Number: 20101155 Study Title: LAPLACE -TIMI 57 - A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Combination with HMG-CoA Reductase Inhibitors in Hypercholesterolemic Subjects (LAPLACE: LDL-C Assessment w/ PCSK9 monoclonaL Antibody inhibition Combined with statin thErapy) Sample Size: 631 Arms:7 Location in submission: Module 5.3.5.1 (3) Study Number: 20101158 Study Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Subjects with Heterozygous Familial Hypercholesterolemia Sample Size: 168 Arms:3 Location in submission: Module 5.3.5.1 (4) Study Number: 20101159 Study Title: A Randomized, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C, Compared with Ezetimibe, in Hypercholesterolemic	X			

	Content Parameter	Yes	No	NA	Comment
	Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor (GAUSS-1) Sample Size: 160 Arms:5 Location in submission: Module 5.3.5.1				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? *Indication 1: Four 12-week, phase 3 trials for primary hyperlipidemia and mixed dyslipidemia* Pivotal Study #1 (Study 20110114) Indication: primary hyperlipidemia and mixed dyslipidemia Pivotal Study #2 (Study 20110115) Indication: primary hyperlipidemia and mixed dyslipidemia Pivotal Study #3 (Study 20110116) Indication: primary hyperlipidemia and mixed dyslipidemia Pivotal Study #4 (Study 20110117) Indication: primary hyperlipidemia and mixed dyslipidemia *Indication 2: Homozygous Familial Hypercholesterolemia (HoFH)* Pivotal Study #1 (Study 20110233, DB, pbo-controlled) Indication: HoFH Pivotal Study #2 (Study 20110271; interim data, OL, uncontrolled) Indication: HoFH	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			12 wks and one year
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		For the Parent Phase 3 studies: 286 (9%) from Canada; 986 (31% from US); 1644 (52%) from Europe; 236 (8%) from Asia Pacific
SAFETY					
21.	Has the applicant presented the safety data in a manner	X			

	Content Parameter	Yes	No	NA	Comment
	consistent with Center guidelines and/or in a manner previously requested by the Division?				
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			As this is a monoclonal AB and unlikely to prolong QT, it was agreed that in lieu of conducting a QTc study, the firm performed routine ECG monitoring in the proposed P3 LDL-C lowering studies. The QTc-IRT group conducted a review under the IND (105188, review dated 7/2/2012). The firm has submitted an Integrated Cardiac Safety Report, which is located as an Appendix to the Integrated Summary of Safety in Module 5, Section 5.3.5.3.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR BLA 125522

	Content Parameter	Yes	No	NA	Comment
	discussions?				
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Did address that the Japanese studies would be using lower statin doses
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Defer to stats
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Defer to stats
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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CLINICAL FILING CHECKLIST FOR BLA 125522

74 Day Letter Issues:

1. As we have stated previously, it will be a review issue whether evolocumab could be approved based on effects on lipid parameters such as LDL-C before CV outcomes data are available. Uncertainty is greater with regard to net clinical benefit when benefit of a drug is assessed solely by effects on a biomarker, regardless of whether the biomarker is considered a valid surrogate endpoint for a given patient population.

2. As we have stated previously, we believe it would be inappropriate to use evolocumab as first-line monotherapy in the general population before cardiovascular (CV) outcomes data are available. Thus, with the possible exception of mechanism to allow on-label prescribing of PCSK9 inhibitors to patients unable to take statins, or unable to tolerate an effective dose of statin use, it is unlikely that we would entertain a monotherapy indication without CV outcomes data.

3. As we have stated previously, if evolocumab is approved based on its effects on lipid parameters alone, we are unlikely to consider superiority claims to (b) (4) ezetimibe, (b) (4) until CV outcomes data for evolocumab are available.

Eileen Craig	10/20/14
Reviewing Medical Officer	Date
Clinical Team Leader	Date

File name: Clinical Filing Checklist for BLA 125522 Evolocumab

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EILEEN M CRAIG
10/20/2014

JAMES P SMITH
10/20/2014