CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL MEMORANDUM

BLA Number:	125522 (SDN 37, eCTD Seq. No. 0028)
Drug Name:	Evolocumab
Indication(s):	Treatment of primary hyperlipidemia and mixed dyslipidemia Treatment of homozygous familial hypercholesterolemia
Applicant:	Amgen Inc.
Document Reviewed:	Applicant's response to FDA information request
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Keywords: new onset diabetes mellitus, diabetes-related adverse events, subgroup analyses

Introduction

This is a statistical memorandum by the Division of Biometrics VII (DBVII) in response to a consult, via email dated May 4, 2015, from the Division of Metabolism and Endocrinology Products (DMEP) to comment on the validity of the subgroup analyses that were performed by Amgen, the Applicant for Biologics License Application (BLA 125522, PDUFA Goal Date: August 27, 2015) for evolocumab. Evolocumab is a PCSK-9[1] inhibitor, which Amgen proposes to be indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia. Amgen also proposes that evolocumab be indicated for the treatment of homozygous familial hypercholesterolemia (HoFH). The proposed dosing regimen in patients with primary hyperlipidemia or mixed dyslipidemia is 140 mg subcutaneously every 2 weeks (Q2W) or 420 mg subcutaneously every month (QM). The proposed dosing regimen in patients with HoFH is 420 mg subcutaneously (Q2W or QM). The aforementioned subgroup analyses were conducted in response to an information request (IR) by the FDA dated February 9, 2015. DBVII was asked to provide comments on the Applicant's analysis methods in response to Question 9 in the IR, which reads:

In the IPAS [integrated parent analysis set] and IECAS [integrated extension standard of care-controlled period analysis set] datasets, please evaluate the incidence of the following among all patients, patients with baseline impaired fasting glucose (i.e. 100-125 mg/dL), and patients with baseline normoglycemia: new onset diabetes and diabetes-related adverse events (i.e. using adverse events preferred terms). For new onset diabetes please perform analyses using: local and central laboratory data (defining a case as any individual with at least 2 post-baseline fasting blood glucose (FBG) measurements ≥ 126 mg/dL at any time in the trial), adverse event reporting data (i.e. using preferred terms consistent with a diagnosis of diabetes) and using concomitant medications data to capture initiators of new anti-diabetic medications at any time in the trial.

In addition, please provide a time-to-event analysis (including Kaplan-Meier curve) for new onset diabetes (using lab, AE, and medication data) in each of these subgroups, comparing "any evolocumab" to "any control". Furthermore, for each of these subgroups, present descriptive statistics for changes from baseline in glucose and HbA1c from baseline to each study visit.

Note that this document focuses solely on the statistical validity of the methods used to estimate the incidence and to perform time to event analyses for the outcomes of interest within the requested subgroups. This document excludes assessment of the graphical presentations provided by the Applicant for illustrating changes from baseline glucose or HbA1c to each study visit. Defer to clinical review by Dr. Eileen Craig for interpretation of these graphs.

Summary of the Applicant's Subgroup Analyses in Response to IR

This section summarizes the Applicant's definitions of safety outcomes, patient subgroups, and statistical subgroup analyses performed in response to Question 9 of the IR. All subgroup

[1] The proprotein convertase subtilisin/kexin type 9, also known as PCSK-9, gene helps regulate the amount of cholesterol in the bloodstream.

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analyses were performed in the two datasets requested: the integrated parent studies (IPAS) dataset and in the 1 year standard of care (SoC)-controlled period of the long-term extension studies (IECAS) dataset. The IPAS dataset comprises data from eleven 12-week studies and one 1-year study. The IECAS dataset comprises data from two studies.

Outcomes and Subgroups Analyzed

In accordance with the IR, the safety outcomes analyzed by the Applicant were new onset diabetes and diabetes-related adverse events (AEs). The Applicant used the three criteria (also referred to as the 3-component definition in this document) that were specified in the IR for identifying patients with new onset diabetes. A patient was considered to have new onset diabetes if they did not have diabetes at baseline and possessed any of the specified three criteria at a later time during the study. Baseline diabetes was determined by reported medical history of diabetes mellitus, diabetes medication use at baseline, or fasting blood glucose of at least 126 mg/dL at baseline for analyses based on the 3-component definition.

The Applicant also considered an alternate definition of new onset diabetes based on four criteria (also referred to as the 4-component definition), that is, the above specified 3-component definition together with a criterion for post-baseline HbA1c measurement of at least 6.5%. This additional criterion was based on the American Diabetes Association recommendations. Using this definition, a patient was considered to have new onset diabetes if they did not have diabetes at baseline and possessed any of four criteria at a later time during the study. Baseline diabetes was determined by reported medical history of diabetes mellitus, diabetes medication use at baseline, fasting blood glucose of at least 126 mg/dL at baseline, or HbA1c of at least 6.5% at baseline for analyses based on the 4-component definition.

Reviewer's Comment: The 4-component definition used by the Applicant was not specified in the IR. Therefore, please refer to clinical review for appropriateness of this definition for new onset diabetes. Note that a consequence of increasing the number of components considered is a reduction in the number of patients without baseline diabetes.

The analyses of new onset diabetes (3- or 4-component definition) were performed for the following subgroups of patients who do not have diabetes at baseline:

1. Patients with baseline impaired fasting glucose (IFG)
2. Patients with baseline normoglycemia
3. Patients with either normoglycemia or IFG at baseline

The other outcome requested to be analyzed was diabetes-related AEs. This outcome was defined by the Applicant as those AEs with preferred terms contained within the diabetes

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complication MedDRA high level group terms[2] and analyzed in the following patient groups, regardless of presence or absence of diabetes at baseline:

1. All patients
2. Patients with IFG at baseline
3. Patients who are normoglycemia at baseline

Reviewer's Comment: ***The use of baseline (or pre-treatment) characteristics is appropriate for identifying patients for subgroup analyses and is consistent with recommendations outlined in ICH E9 guidelines of good statistical principles.***

Statistical Analyses

The incidences of new onset diabetes (3- or 4-component definition) as well as the individual components of the respective definitions, and diabetes-related AEs were estimated within the specified subgroups for each treatment arm; refer to Applicant's response document for all arms considered. For each outcome, the incidence was determined by dividing the number of patients experiencing the outcome by the number of patients in the particular subgroup.

Reviewer's Comment: The Applicant provided pooled incidences, without confidence intervals, across all trials in the respective datasets. These pooled incidences did not account for study level differences, which is acceptable for descriptive purposes. Note that incidences within the individual components of the new onset diabetes definitions will be limited by small number of events.

For new onset diabetes, time to event analyses using Cox proportional hazard models were conducted to estimate the hazard ratio, that is, any evolocumab dose to any control for the IPAS dataset or evolocumab + SoC to SoC for the IECAS dataset. The corresponding 95% confidence intervals were also provided. Time to event was defined as the earliest among the following: time to AE onset date, time to initiation of first anti-diabetic medication during the study, HbA1c at least 6.5% (for 4-component definition analyses only), or first of two consecutive FBG measurements at least 126 mg/dL. For the IPAS dataset, the time to event analyses were performed separately for the 12-week studies and the 1-year study.

Kaplan Meier plots for the cumulative incidence of safety outcomes were presented by treatment group for the two datasets. Pointwise CIs were computed using log-based transformations.

Reviewer's Comments: The time to event subgroup analyses performed by the Applicant are generally acceptable. Please consider the following comments when interpreting the findings of the Applicant's subgroup analyses:

[2] The specific HLGTs used to identify diabetes related AEs are provided in Table 2 (page 9) of the Applicant's response document submitted April 5, 2015.

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1. ***The time to event analyses based on multiple studies do not appear to account for study level differences. Stratification by study is generally advised, especially in cases where the risks for the outcomes investigated are expected to vary across trials.***

2. ***It appears that analyses in the IECAS considered only the follow-up period during extension phases of the respective parent studies. Because patients could have switched from SoC in parent study to evolocumab in extension phase and vice versa, it is uncertain whether outcomes should be attributed to treatment received in extension phase or during parent study; in particular, outcomes that occur early in the extension phase.***

3. ***For rare outcomes, analyses based on exact methods to estimate absolute measures (e.g. stratified rate differences) might be useful alternatives to hazard ratios.***

4. ***Per request, the Applicant's time to event analyses were performed by combining all doses of evolocumab to form the evolocumab arm. Results from these analyses cannot be used to understand the risks within the proposed doses for marketing.***

Summary of Comments Regarding Applicant's Subgroup Analyses

There are no major statistical issues identified with the subgroup analyses performed by the Applicant in response to Question 9 of the FDA IR dated February 9, 2015. All subgroup analyses were based on baseline patient characteristics, which is consistent with good statistical principles set forth in ICH E9.

There are a few points for consideration when interpreting the findings from the time to event analyses. Firstly, when based on multiple studies, it is unclear from the information provided in the response document whether the Applicant's analyses were stratified by study. Stratification is generally advised to account for any differences in the risks across studies. Secondly, for analyses in the IECAS dataset, it appears that the Applicant considered only the follow-up period during extension phase. Because patients could have switched from SoC in parent study to evolocumab in extension phase and vice versa, it is uncertain whether outcomes should be attributed to treatment received in extension phase or during parent study; particularly for outcomes that occur early in the extension phase. Finally, as requested in the IR, the Applicant's time to event analyses were performed by combining all doses of evolocumab arm to form the evolocumab treatment arm for comparison to control. Therefore, results from these time to event analyses cannot be used to understand the risks within doses proposed for marketing.

Note that these subgroup analyses were not adjusted for multiple comparisons and based on subgroups defined after the study results were known. Therefore, caution is advised when interpreting results of the Applicant's analyses. In addition, from brief inspection of the Applicant's findings, the analyses were based on small numbers of outcomes. For rare outcomes, analyses based on exact methods to estimate absolute measures (e.g. stratified rate differences) might be a useful alternative to hazard ratios.

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/s/

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06/22/2015

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Concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125522
Drug Name:	Repatha (Evolocumab)
Indication(s):	Primary hyperlipidemia or mixed dyslipidemia; Homozygous family hypercholesterolemia
Applicant:	Amgen
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	PDUFA: 08/27/2015
Review Priority:	Standard
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Keywords: Missing data, Surrogate endpoint, Cardiovascular outcome

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1 EXECUTIVE SUMMARY

Amgen has submitted a biologics license application (BLA) for Repatha (evolocumab; also referred to as AMG 145 or EvoMab in this review) as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), as well as change other lipid outcomes, in adults with primary hyperlipidemia or mixed dyslipidemia and in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH). Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) antibody directed against 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. The inhibition of PCSK9 by evolocumab prevents PCSK9-mediated LDLR degradation, which leads to increases in LDLR, and results in decreases in serum LDL-C.

1.1 Conclusion and Recommendations

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. However, whether or not the effect of evolocumab on LDL-C, a surrogate endpoint, supports a conclusion that the benefits outweigh the risks for each of the indications sought by the applicant remains at question and was discussed at a recent Advisory Committee meeting.

1.2 Brief Overview of Clinical Studies

Six phase 3 studies were reviewed for this BLA submission. Results from five trials were submitted to support the primary hyperlipidemia or mixed dyslipidemia indication. Studies 20110114, 20110115, 20110116, and 20110117 were 12-week trials, while Study 20110109 was a 52-week trial. Study 20110114 evaluated the safety and efficacy of evolocumab monotherapy compared with placebo and ezetimibe. Study 20110115 evaluated the safety and efficacy of evolocumab compared with placebo in combination with a statin (atorvastatin, simvastatin, or rosuvastatin), with an additional ezetimibe control arm in patients receiving atorvastatin. Study 20110116 evaluated the safety and efficacy of evolocumab compared with ezetimibe in statin-intolerant subjects. Study 20110117 evaluated the safety and efficacy of evolocumab compared with placebo among heterozygous familial hypercholesterolemia (HeFH) patients on a stable statin dose. Study 20110109 evaluated the safety and efficacy of evolocumab compared with placebo in patients with hyperlipidemia, with background therapy (none, atorvastatin 10 mg, atorvastatin 80 mg, or atorvastatin 80 mg plus ezetimibe 10 mg) based on screening LDL-C, NCEP ATP III risk category, and statin therapy.

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The applicant also proposed an indication in HoFH. Study 20110233**,** which was composed of an open-label, 8-patient pilot study (Part A) followed by a randomized, double-blind placebo-controlled trial (Part B), evaluated the safety and efficacy of evolocumab compared with placebo in subjects with HoFH, where all subjects continued to receive a statin and about 93% of subjects also used ezetimibe.

1.3 Issues with the Application

- LDL-C is a surrogate endpoint in that it is not a direct measure of benefit with respect to a clinical outcome (i.e., it is not a direct measure of how the patient functions, feels, or survives). Treatment effects on LDL-C are intended to predict benefit with respect to risk of cardiovascular (CV) outcomes, but the validity of LDL as a surrogate has not been established for the PCSK9 drug class specifically and would require extrapolation from other data sources (e.g., CV outcome trials of statins). There were only a small number of CV events in the evolocumab clinical trials, and the effect of evolocumab on cardiovascular morbidity and mortality in any population has not been determined.

- 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.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Evolocumab (formerly known as AMG 145) is a fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin /kexin type 9 (PCSK9). Evolocumab is a lipid lowering therapy. Evolocumab modulates the levels of low-density lipoprotein receptor (LDLR) on the hepatic cell surface by inhibiting LDLR degradation and promoting recycling the receptor.

The proposed clinical uses were to treat adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, and adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH). Amgen proposed evolocumab doses for marketing of either 140 mg every 2 weeks or 420 mg monthly for the primary hyperlipidemia and mixed dyslipidemia indication. The proposed dose for the HoFH indication was 420 mg either monthly or every 2 weeks.

2.1.2 History of Drug Development

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The initial IND 105188 was submitted by Amgen on 15 May 2009. The purpose of this IND was to develop the drug for hypercholesterolemia. The division held a face-to-face end-of Phase 2 (EOP2) meeting with Amgen on 10 July 2012 to discuss the development of evolocumab. FDA stated that an indication for treatment as monotherapy or claims of superiority to ezetimibe/statin would require cardiovascular outcomes trial (CVOT) data. FDA also did not agree with Amgen's proposed definition of statin intolerance based on failing 1 or more statins.

On 10 April 2014, a pre-BLA clinical meeting was held. FDA noted that it expected that the approvability of a PCSK9 inhibitor, in the absence of cardiovascular outcome data, would be a topic for discussion with an advisory committee.

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

2.2 Data Sources

The data and final study reports were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link: \\CDSESUB1\evsprod\BLA125522\125522.enx

The information needed for this review was obtained from Module 1 FDA regional information, Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Reports.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

All required documents necessary for conducting a statistical review were submitted. The datasets for the three clinical trials were found to be in good organization and were provided as .xpt files. The analysis datasets included both derived and enriched data (such as formatted variables, derived endpoint, etc.). Across trials the variables for the primary analysis were consistently named. I was able to produce the results on the primary endpoints and secondary endpoints presented in the individual Clinical Study Reports.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study designs and primary endpoints of the trials reviewed in this submission are presented in Table 1. Five randomized, controlled trials were carried out to support an indication in primary hyperlipidemia or mixed dyslipidemia. Four of the phase 3 studies (20110114,

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20110115, 20110116, 20110117) were 12 weeks in duration and focused on different patient populations. Study 20110109 was a 52-week study to demonstrate the persistency of efficacy in evolocumab. The indication of HoFH was supported by study 20110233, which was a two-part phase 2/3 study. Part A was an open-label, single arm pilot study. Part B was a phase 3, double-blind, randomized, placebo-controlled, 12-week trial. Please see details in Table 1.

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Table 1 Summary of Study Designs and Endpoints

Trial No.	Study Population	Phase and Design	Primary Endpoint	# of subjects per Arm	Treatment period
Indication: Primary Hyperlipidemia or Mixed Dyslipidemia					
20110114	Subjects with a 10-year Framingham risk score of 10% or less	Phase 3, R, DB, DD, PG, placebo and ezetimibe-controlled, multicenter	**Co-primary endpoints**: Percent change from baseline in LDL-C at Week 12; Mean percent change from baseline in LDL-C at weeks 10 and 12	AMG 145 140mg Q2W and PO QD (n=153); AMG 145 420mg QM and PO QD (n=153); Placebo SC Q2W and 10mg ezetimibe QD (n=77); Placebo SC QM and 10mg ezetimibe QD (n=77); Placebo SC Q2W and PO QD (n=77); Placebo SC QM and PO QD (n =78)	12 weeks
20110115	Subjects with hyperlipidemia	Phase 3, R, DB, DD, placebo and ezetimibe-controlled, multicenter, with statin background therapy	**Co-primary endpoints:** Same as above	2 step randomization: Atorvastatin 80mg (n=439), Atorvastatin 10mg (n=442), Rosuvastatin 40mg (n=310), Rosuvastatin 5mg (n=343), Simvastatin 40mg (n=295). For each statin dose cohort and dose frequency, the allocation ratio is approximately 2:1 for AMG 145 vs control (see details in Table 3)	12 weeks
20110116	Hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor	Phase 3, R, DB, DD, PG, ezetimibe-controlled	**Co-primary endpoints:** Same as above	AMG 145 140mg SC Q2W and PO QD (n=103); AMG 145 420 mg SC QM and PO QD (n=102); Placebo SC Q2W and ezetimibe 10mg QD (n=51); Placebo SC QM and ezetimibe 10mg QD (n=51)	12 weeks
20110117	HeFH on a stable dose of a statin	Phase 3, R, DB, PG, placebo-controlled, multicenter	**Co-primary endpoints:** Same as above	AMG 145 140 Q2W (n=110); AMG 145 420mg QM (n=110); Placebo Q2W (n=54); Placebo QM (n=55)	12 weeks
20110109	Subjects with hyperlipidemia	Phase 3, R, DB, placebo-controlled, multicenter	Percent change in LDL-C from baseline at week 52	AMG 145 420mg QM (n=599); Placebo QM (n=302)	52 weeks
Indication: Homozygous Familial Hypercholesterolemia (HoFH)					
20110233	Subjects with homozygous familial hypercholesterolemia	Part A (phase 2): open label, single arm, multicenter pilot study; Part B (phase 3): R, DB, placebo-controlled	Percent change in LDL-C from baseline at week 12	Part B: AMG 145 420 mg QM (n=34), placebo QM (n=17)	12 weeks

R-randomized; DB - double-blind; PG- parallel group; DD - double-dummy; Q2W - every 2 weeks; QM - every month; PO - placebo oral; QD- Daily; SC - subcutaneous
Note that 20110109 was a phase 2 study which Amgen re-classified as a phase 3 study

3.2.2 Statistical Methodologies

Analysis Populations

As per the applicant's analysis plan, the full analysis set (FAS) was the primary analysis population, and included all randomized subjects exposed to at least one dose of investigational product (either SC or oral). All analyses used the planned randomized treatment.

Primary endpoints

The co-primary endpoints were percent change from baseline in reflexive LDL-C at week 12 and mean percent change from baseline in LDL-C at weeks 10 and 12 for studies 20110114, 20110115, 20110116, and 20110117. These four studies used a reflexive LDL-C approach: either calculated LDL-C (based on the Fridewald formula) was used, or if the calculated LDL-C was less than 40 mg/dL or triglycerides were greater than 400 mg/dL, directly measured (using ultracentrifugation) LDL-C was used. The primary endpoint in study 20110109 was the percent change in directly measured LDL-C at week 52, and the primary endpoint in study 20110233 was the percent change in directly measured LDL-C at week 12.

Secondary endpoints

Secondary endpoints included change from baseline in LDL-C and percent change from baseline in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, total cholesterol, ApoB/ApoA1 ratio, Lp(a), triglycerides, HDL-C, and VLDL-C.

Primary and secondary analyses

The applicant used a mixed effects model for repeated measures (MMRM) to assess the efficacy of evolocumab compared with placebo and ezetimibe. The MMRM included treatment group, stratification factor, scheduled visit, and the interaction of treatment and visit. An unstructured covariance matrix was used to estimate the covariance parameters within subject across the visits. The applicant performed analyses separately by each dose frequency (Q2W and QM). Analyses of secondary endpoints were based on analogous models.

Approach to multiplicity

The applicant used a Bonferroni approach to control the type I error rate across the placebo and ezetimibe comparisons in studies with multiple control arms. To preserve the family-wise two-sided 0.05 type I error rate across the multiple tests of primary and secondary endpoints, the Hochberg procedure was used to account for the multiple tests of secondary endpoints within each dose frequency. In studies 20110114, 20110115, 20110116, and 20110117, no multiplicity adjustment was made by the applicant across the evaluations of the two dose frequencies (Q2W and QM). This is not appropriate: the type I error rate within each study should be controlled at the two-sided 0.05 level across the multiple doses, controlled comparisons, and endpoints. That being said, the effects on LDL-C would be statistically persuasive even if a conservative

approach (e.g., Bonferroni) were used to additionally control the error rate across the two dose frequencies, so the statistical significance of effects of evolocumab on LDL-C is not at question.

3.2.3 Missing Data

Missing data in Study 20110114, 20110115, 20110116, 20110117

A majority of subjects had reflexive LDL-C measurements at week 10 and week 12. The percent of missing data at week 12 ranged from 2% to 16% across the trials, and proportions of missingness were largely similar between the treatment arms. Most non-missing measurements at week 12 were taken on subjects who were still on treatment (i.e., subjects on a Q2W SC arm had been treated at week 10 and subjects on a QM SC arm had been treated at week 8). On the other hand, large proportions of missing measurements were from subjects who had discontinued treatment. A detailed summary of missing data and treatment adherence results is provided in the Appendix.

Sensitivity analyses for the primary efficacy endpoints

No sensitivity analysis to assess the potential impact of missing data was conducted by the applicant. The primary MMRM used by the applicant assumes that the missing data were missing at random (MAR). This is the assumption that the statistical behavior of the missing data (given the observed responses and model covariates) was the same as the observed data. The interest is in estimating the intention-to-treat (ITT) effect, i.e., the difference in LDL-C reduction between treatment arms *regardless of adherence to treatment.* Therefore, the MAR assumption is likely not plausible because the majority of patients with missing data were no longer on treatment (while the majority of non-missing data were from patients on treatment), and the effects of treatment on LDL-C likely go away after patients discontinue therapy.

FDA analysis approach

FDA's approach to handle missing data used different imputation strategies depending on whether the patient with missing data was on or off treatment. Patients who had discontinued study therapy were assumed to no longer benefit from the study medication, i.e., their missing values at week 12 were assumed to shift back toward their baseline values. Patients who were still on treatment at the end of the study had their missing values imputed under an MAR assumption based on observed LDL-C measurements from their treatment arm. Multiple imputation was used to account for the uncertainty in the imputation process and results from the imputed datasets were combined using Rubin's method.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

3.2.4.1 Patient Disposition

Study 20110114 randomized 615 patients to the 6 treatment groups (evolocumab Q2W, evolocumab QM, placebo Q2W, placebo QM, ezetimibe Q2W, ezetimibe QM). A total of 614 (99.8%) subjects received investigational product (IP) and composed the full analysis set for the efficacy and safety analysis. Of these 614 subjects, 581 (94.6%) subjects completed SC IP. 33 (5.3%) subjects discontinued SC IP, including 12 (2.0%) because of adverse events. Other reasons included subject request, decision by sponsor, physician decision, and loss to follow-up.

Study 20110115 randomized 2067 patients to 1 of the 5 open-label statin cohorts (atorvastatin 10mg, atorvastatin 80mg, rosuvastatin 5mg, rosuvastatin 40mg, simvastatin 40mg). Of these 2067 patients, 1899 (91.7%) patients went to a second randomization step in which they were assigned with IP (evolocumab or placebo, with an additional ezetimibe arm for only the atorvastatin cohort). 1896 subjects received statin treatment and at least 1 dose of IP, comprising the applicant's full analysis set. Of these 1896 patients, 1807 (95.3%) patients completed SC IP and 89 (4.7%) patients discontinued SC IP, including 33 (1.7%) patients due to adverse events, 34 (1.8%) patients due to subject request, 2 (0.1%) subjects due to sponsor decision, 2 (0.1%) due to physician decision, 4 (0.2%) due to loss to follow up, and 14 (0.7%) for other reasons.

Study 20110116 randomized 307 patients to 1 of the 4 treatment groups (evolocumab Q2W, evolocumab QM, ezetimibe Q2W, ezetimibe QM). All randomized subjects received at 1 dose of study medication. Of the 307 patients, 293 (95.4%) patients completed SC IP and 14 (4.6%) patients discontinued SC IP, including 12 (3.9%) patients who had an adverse event, 1 (0.3%) patient due to subject request, and 1 (0.3%) patient who was lost to follow-up.

Study 20110117 randomized 331 patients to 1 of the 4 treatment groups (evolocumab Q2W, evolocumab QM, placebo Q2W, placebo QM). 329 (99.4%) subjects received IP and were defined as the full analysis set for the efficacy and safety analysis. Of these 329 subjects, 327(99.4%) subjects completed SC IP and 2 subjects discontinued SC IP due to subject request.

Study 20110109 randomized 905 subjects to 1 of 2 treatment groups (evolocumab 420 mg QM or placebo QM). 901 subjects received at 1 dose of study medication and were defined as the full analysis set for the efficacy and safety analysis. Of these 901 subjects, 800 (90.1%) subjects completed SC IP, and 101 (11.2%) subjects discontinued SC IP, including 16 subjects were withdrawal of informed consent, 16 subjects discontinued due to adverse event, 2 subjects were dead, 32 subjects discontinued as per subject request, 5 subjects discontinued as per sponsor's decision, and 1 subject discontinued due to investigator's decision, 11 subjects were lost to follow-up, and 18 subjects discontinued for other reasons.

Study 20110233 randomized 50 patients to 1 of the 2 treatment groups (evolocumab 420mg QM or placebo QM). 1 subject never received study medication. Of the 49 subjects receiving IP, 47 (96%) completed SC IP and 2 (4%) subjects discontinued.

The patient disposition tables were presented in the appendix for additional details.

3.2.4.2 Baseline Characteristics

Across the trials, patient demographics and baseline characteristics were summarized in Table 2. Most subjects enrolled in the studies were White (80%-94%). The average age across the studies for the indication of primary hyperlipidemia or mixed dyslipidemia ranged from 51-61 years. Study 20110233 in HoFH enrolled a younger population, with an average age of 31 years. The numbers of patients from sites in the USA varied across the studies. For instance, study 20110117 and study 20110233 only had about 6% and 4% patients from U.S.-sites. There were no striking imbalances between the treatment arms in important baseline characteristics across the studies.

Table 2 Baseline Characteristics for Studies

	20110114 (n= 614)	20110115 (n=1896)	20110116 (n=307)	20110117 (n=329)	20110109 (n=901)	20110233 (n=49)
Country						
USA	309 (50.3%)	558 (29.4%)	99 (32.2%)	19 (5.78%)	366 (40.6%)	2 (4.08%)
Sex						
Male	209 (34.0%)	1028 (54.2%)	166 (54.1%)	190 (57.8%)	430 (47.7%)	25 (51.0%)
Race						
ASIAN	58 (9.45%)	25 (1.32%)	10 (3.26%)	16 (4.86%)	57 (6.33%)	2 (4.08%)
BLACK	40 (6.51%)	75 (3.96%)	7 (2.28%)	3 (0.91%)	76 (8.44%)	0 (0%)
WHITE	510 (83.1%)	1782 (94.0%)	287 (93.5%)	296 (90.0%)	724 (80.4%)	44 (89.8%)
Age						
Mean (SD)	53 (12.1)	60 (9.9)	61 (9.8)	51 (12.6)	56 (10.6)	31 (12.8)
Median (IQR)	55 (45, 55)	61 (53, 61)	63 (56, 63)	52 (43, 52)	58 (50, 58)	31 (19, 31)
Age>65: Y	111 (18.1%)	671 (35.4%)	127 (41.4%)	49 (14.9%)	205 (22.8%)	0 (0%)
Reflexive LDL-C (mg/dL)						
Mean (SD)	143 (22.9)	109 (41.1)	193 (58.5)	155 (44.9)	100 (22.0)	349 (137)
Median (IQR)	142 (127, 142)	102 (83, 102)	179 (154, 179)	144 (124, 144)	96 (86, 96)	360 (207, 360)
Calculated LDL-C (mg/dL)						
Mean (SD)	143 (22.9)	109 (41.2)	193 (58.5)	156 (45.1)	100 (22.0)	348 (138)
Median (IQR)	142 (127, 142)	102 (83, 102)	180 (154, 180)	144 (124, 144)	96 (86, 96)	342 (205, 342)
Total Cholesterol (mg/dL)						
Mean (SD)	228 (29.7)	189 (46.1)	279 (60.9)	232 (48.7)	178 (27.4)	409 (135)
Median (IQR)	226 (208, 226)	183 (158, 183)	268 (236, 268)	221 (198, 221)	175 (160, 175)	398 (287, 398)
HDL-C (mg/dL)						
Mean (SD)	58 (18.7)	54 (15.9)	52 (15.9)	51 (15.6)	53 (15.7)	39 (12.9)
Median (IQR)	55 (45, 55)	51 (42, 51)	50 (40, 50)	49 (41, 49)	51 (42, 51)	38 (32, 38)
No-HDL-C (mg/dL)						
Mean (SD)	169 (27.2)	136 (45.1)	227 (60.4)	180 (49.5)	125 (26.1)	370 (140)
Median (IQR)	168 (149, 168)	127 (106, 127)	215 (186, 215)	170 (145, 170)	119 (107, 119)	365 (232, 365)

	20110114 (n= 614)	20110115 (n=1896)	20110116 (n=307)	20110117 (n=329)	20110109 (n=901)	20110233 (n=49)
ApoB (mg/dL)						
Mean (SD)	106 (18.1)	89 (26.1)	138 (32.8)	115 (27.5)	87 (16.3)	208 (71.4)
Median (IQR)	106 (93, 106)	85 (72, 85)	131 (116, 131)	111 (98, 111)	85 (76, 85)	191 (150, 191)
Triglycerides (mg/dL)						
Mean (SD)	131 (65.5)	135 (77.1)	171 (76.3)	125 (64.5)	123 (64.1)	108 (53.4)
Median (IQR)	115 (84, 115)	116 (86, 116)	152 (112, 152)	110 (82, 110)	107 (82, 107)	96 (68, 96)
VLDL (mg/dL)						
Mean (SD)	26 (12.4)	26 (13.0)	34 (14.6)	25 (11.4)	21 (12.1)	21 (11.9)
Median (IQR)	23 (17, 23)	23 (17, 23)	31 (23, 31)	22 (17, 22)	18 (13, 18)	21 (12, 21)

3.3 Results and Conclusions

3.3.1 Primary Hyperlipidemia or Mixed Dyslipidemia Studies

3.3.1.1 Primary Endpoint

Table 3 and Table 4 summarize results on LDL-C reduction from baseline at week 12 in the four 12-week studies based on the applicant's approach and FDA's approach. The results were consistent across the trials, demonstrating that evolocumab resulted in statistically significant reductions in LDL-C compared to ezetimibe and placebo at week 12. Based on the applicant's primary analysis, the estimated reduction in LDL-C for evolocumab ranged from 37% to 47% greater compared to ezetimibe and from 55% to 76% greater compared to placebo across the different studies and the two dose frequencies. According to the 52-week study, the reduction in LDL-C with evolocumab (QM) persisted through 52 weeks (see Table 5). Results based on FDA's analyses were similar to those based on the applicant's analyses, with treatment effect estimates attenuated by around 1%–3% (in absolute terms) compared to the applicant's results. There were also statistically significant reductions in the co-primary endpoint, mean LDL percent change at week 10 and week 12, in the four 12-week trials (studies 20110114, 20110115, 20110116, and 20110117, details were provided in appendix). Figure 1 summarizes results across the five phase 3 trials in primary hyperlipidemia or mixed dyslipidemia based on results from FDA's analysis approach. For completeness, results from analyses on calculated LDL were also provided in Table 19 and Table 20 in the appendix.

Table 3 Primary Analysis of Percent Change in Reflexive LDL at Week 12 in Studies 20110114, 20110116, and 20110117

				Applicant's Approach		FDA's Approach	
	Baseline (mg/dL)	N	N*	LS Mean: % Change	Difference: Evolocumab -control (95% † CI)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
20110114—Monotherapy							

	Baseline (mg/dL)	N	N*	Applicant's Approach LS Mean: % Change	Applicant's Approach Difference: Evolocumab -control (95% † Cl)	FDA's Approach LS Mean: % Change	FDA's Approach Difference: Evolocumab -control (95% † CL)
Every 2 weeks (Q2W) †							
AMG 145 SC Q2W 140 MG + PO QD	142	153	133	-57		-54	
PLACEBO SC Q2W + **EZETIMIB**E QD 10 MG	143	77	70	-18	-39 (-43,-35)	-18	-36 (-41,-32)
PLACEBO SC Q2W + PLACEBO PO QD	140	76	69	-0	-57 (-61,-53)	-0	-54 (-59,-49)
Monthly (QM) †							
AMG 145 SC QM 420 MG + PO QD	144	153	136	-56		-55	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	144	77	69	-19	-38 (-41,-34)	-19	-37 (-41,-32)
PLACEBO SC QM + PLACEBO PO QD	144	78	70	-1	-55 (-58,-51)	-1	-54 (-59,-50)
20110116—In "statin-intolerant" subjects							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG + PO QD	192	103	98	-56		-55	
PLACEBO SC Q2W + **EZETIMIBE** QD 10 MG	195	51	49	-18	-38 (-44,-33)	-18	-37 (-42,-31)
Monthly (QM)							
AMG 145 SC QM 420 MG + PO QD	192	102	96	-53		-53	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	195	51	45	-15	-37 (-42,-32)	-16	-37 (-42,-31)
20110117—In HeFH subjects on a stable dose of a statin							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	161	110	104	-61		-61	
PLACEBO SC Q2W	151	54	51	-2	-59 (-65,-53)	-2	-59 (-66,-52)
Monthly (QM)							
AMG 145 SC QM 420 MG	154	110	103	-56		-56	
PLACEBO SC QM	152	55	46	5	-61 (-69,-55)	4	-60 (-67,-53)

Note: † 97.5% CL for study 20110114; N- number of subjects with baseline data; N* --- number of subjects with week 12 data

Q2W - every 2 weeks; QM - every month; PO - placebo oral; QD - Daily; SC - subcutaneous

Table 4 Primary Analysis of Percent Change in Reflexive LDL at Week 12 in Study 20110115

	Baseline (mg/dL)	N	N*	Applicant's Approach LS Mean: % Change	Applicant's Approach Difference: Evolocumab -control (95% † Cl)	FDA's Approach LS Mean: % Change	FDA's Approach Difference: Evolocumab -control (95% † CL)

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab -control (95% † Cl)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
20110115--ATORVASTATIN 10MG ADD-ON							
Every 2 weeks (Q2W) †							
AMG 145 SC Q2W 140 MG + PO QD	124	110	103	-62		-60	
PLACEBO SC Q2W **+ EZETIMIBE** QD 10 MG	127	56	49	-22	-40 (-47,-32)	-20	-40 (-47,-33)
PLACEBO SC Q2W + PO QD	123	56	51	10	-71 (-78,-64)	9	-69 (-76,-62)
Monthly (QM) †							
AMG 145 SC QM 420 MG + PO QD	126	110	101	-58		-56	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	119	55	52	-17	-41 (-49,-33)	-18	-39 (-46,-32)
PLACEBO SC QM + PO QD	124	55	51	1	-59 (-67,-51)	0	-57(-64,-49)
20110115--ATORVASTATIN 80MG ADD-ON							
Every 2 weeks (Q2W) †							
AMG 145 SC Q2W 140 MG + PO QD	94	109	102	-62		-61	
PLACEBO SC Q2W + **EZETIMIBE** QD 10 MG	99	56	50	-15	-47 (-59,-35)	-14	-46 (-57,-36)
PLACEBO SC Q2W + PO QD	100	55	46	14	-76 (-88,-64)	12	-72 (-83,-62)
Monthly (QM) †							
AMG 145 SC QM 420 MG + PO QD	94	110	100	-59		-57	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	92	54	52	-20	-39 (-50,-28)	-20	-38 (-48,-28)
PLACEBO SC QM + PO QD	95	55	51	12	-71 (-81,-60)	12	-69 (-79,-59)
20110115--ROSUVASTATIN 40MG ADD-ON							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	89	102	95	-57		-55	
PLACEBO SC Q2W	77	53	50	10	-68 (-77,-58)	7	-62 (-72,-52)
Monthly (QM)							
AMG 145 SC QM 420 MG	87	104	98	-52		-52	
PLACEBO SC QM	104	51	47	2	-55 (-66,-44)	1	-54 (-63,-44)
20110115--ROSUVASTATIN 5MG ADD-ON							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	119	113	100	-60		-56	
PLACEBO SC Q2W	116	58	52	8	-68 (-75,-62)	7	-63 (-71,-56)
Monthly (QM)							
AMG 145 SC QM 420 MG	123	115	104	-59		-57	
PLACEBO SC QM	120	57	55	5	-64 (-71,-58)	5	-63 (-70,-55)

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab -control (95% † Cl)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
20110115--SIMVASTATIN 40MG ADD-ON							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	114	98	95	-65		-63	
PLACEBO SC Q2W	110	49	45	5	-70 (-76,-63)	4	-67 (-76,-59)
Monthly (QM)							
AMG 145 SC QM 420 MG	124	99	90	-56		-54	
PLACEBO SC QM	109	49	43	4	-60 (-69,-51)	4	-58 (-67,-50)

Note: † 97.5 CL for atorvastatin cohorts; N- number of subjects with baseline data; N* --- number of subjects with week 12 data

Q2W - every 2 weeks; QM - every month; PO - placebo oral; QD - Daily; SC - subcutaneous

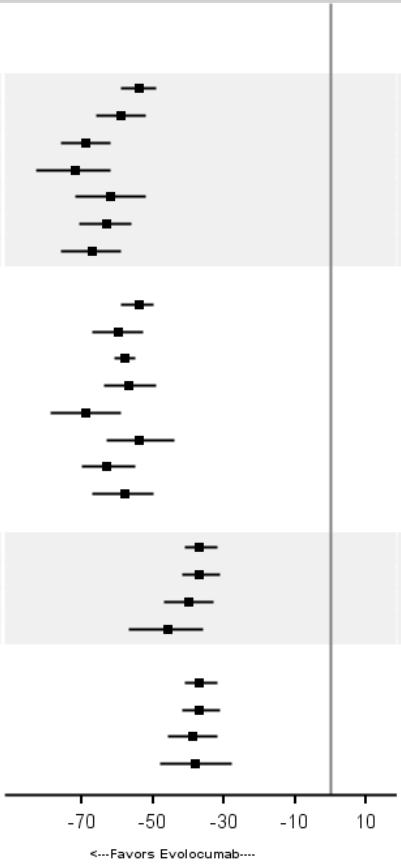
Table 5 Primary Analysis of Ultracentrifugation LDL Percent Change in Study 20110109 (Long-term study: 52 weeks)

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab -control (95% Cl)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
20110109							
Week 12							
AMG 145 SC QM 420 MG	104	599	582	-54		-53	
PLACEBO SC QM	104	302	294	-4	-58 (-61,-54)	4	-56 (-59,-53)
Primary endpoint: Week 52							
AMG 145 SC QM 420 MG	104	599	542	-50		-55	
PLACEBO SC QM	104	302	264	7	- 57 (-61,-53)	3	-58(-61,-55)

N* --- number of subjects with week 12 or week 52 data; QM - every month; SC - subcutaneous

Figure 1 Summary of Primary Analysis Results (FAS; Based on FDA's Approach)

Comparison Study	% change from baseline LS mean Evocumab	Control	Difference in % change from baseline LS mean difference (95% CL) Evocumab-control	Number of Patients Evocumab	Control	P_value
Evolocumab 140mg Q2W vs Placebo						
study 20110114	-54	0		153	76	<0.0001
study 20110117	-61	-2		110	54	<0.0001
study 20110115 Atorva 10mg	-60	9		110	56	<0.0001
study 20110115 Atorva 80mg	-61	12		109	55	<0.0001
study 20110115 Rosuva 40mg	-55	7		102	53	<0.0001
study 20110115 Rosuva 5mg	-56	7		113	58	<0.0001
study 20110115 Simva 5mg	-63	4		98	49	<0.0001
Evolocumab 420mg QM vs Placebo						
study 20110114	-55	-1		153	78	<0.0001
study 20110117	-56	4		110	55	<0.0001
study 20110109	-55	3		599	302	<0.0001
study 20110115 Atorva 10mg	-56	0		110	55	<0.0001
study 20110115 Atorva 80mg	-57	12		110	55	<0.0001
study 20110115 Rosuva 40mg	-52	1		104	51	<0.0001
study 20110115 Rosuva 5mg	-57	5		115	57	<0.0001
study 20110115 Simva 5mg	-54	4		99	49	<0.0001
Evolocumab 140mg Q2W vs Ezetimibe						
study 20110114	-54	-18		153	77	<0.0001
study 20110116	-55	-18		103	51	<0.0001
study 20110115 Atorva 10mg	-60	-20		110	56	<0.0001
study 20110115 Atorva 80mg	-61	-14		109	56	<0.0001
Evolocumab 420mg QM vs Ezetimibe						
study 20110114	-55	-19		153	77	<0.0001
study 20110116	-53	-16		102	51	<0.0001
study 20110115 Atorva 10mg	-56	-18		110	55	<0.0001
study 20110115 Atorva 80mg	-57	-20		110	54	<0.0001



3.3.1.2 Secondary Endpoints

The following describes results on a selected set of secondary endpoints:

Non-HDL-C: Across all trials, evolocumab led to statistically significantly greater reductions than the control arms in percent change in non-HDL-C at week 12. Compared with placebo, the estimated reduction from evolocumab ranged from 50% to 67% greater across the studies and two dose frequencies. Compared with ezetimibe, the estimated reduction from evolocumab ranged from 32% to 35% greater.

HDL-C: There were consistent trends toward greater increases in HDL-C on evolocumab than on placebo and ezetimibe, but results were not statistically significant for both dose frequencies in all studies. The estimated increases in HDL-C ranged from 3% to 11% greater compared to placebo, and from 4% to 9% greater compared to ezetimibe.

Total Cholesterol: Across the trials, total cholesterol was statistically significantly reduced at week 12 on evolocumab. The estimated reductions in total cholesterol from evolocumab ranged

from 30% to 46% greater compared to placebo. Compared with ezetimibe, the estimated reductions from evolocumab ranged from 20% to 26% greater.

Apolipoprotein B: Across the trials, ApoB was statistically significantly reduced at week 12. Compared with placebo, the estimated reduction in ApoB from evolocumab ranged from 41% to 61% greater. Compared with ezetimibe, the estimated reduction from evolocumab ranged from 33% to 37% greater.

Table 6 Analysis of Secondary Endpoints at Week 12 in Studies 20110114, 20110116, and 20110117, and at Week 52 in Study 20110109 (FAS; Applicant's MMRM)

	Non-HDL-C		HDL-C		Total Cholesterol		ApoB	
	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
20110114								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG +PO QD	-50		5		-36		-47	
PLACEBO SC Q2W + **EZETIMIBE** QD 10 MG	-15	-35 (-39,-32)	0	6 (2,9)	-11	-25 (-28,-22)	-13	-34 (-38,-30)
PLACEBO SC Q2W + PO QD	0	-50 (-53,-46)	-1	6 (3,10)	-1	-35 (-38,-32)	1	-48 (-52,-44)
Monthly (QM)								
AMG 145 SC QM 420 MG + PLACEBO PO QD	-50		5		-36		-47	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	-16	-33 (-37,-30)	1	4 (0,7)	-12	-23 (-26,-21)	-14	-33 (-36,-29)
PLACEBO SC QM + PO QD	2	-51 (-54,-48)	-5	9 (6,13)	0	-36 (-38,-33)	2	-48 (-52,-45)
20110116								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG + PO QD	-49		5		-38		-46	
PLACEBO SC Q2W + **EZETIMIBE** QD 10 MG	-17	-32 (-37,-27)	2	4 (-1,9)	-13	-25 (-29,-21)	-13	-33 (-38,-28)
Monthly (QM)								
AMG 145 SC QM 420 MG + PO QD	-46		6		-36		-43	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	-13	-33 (-37,-29)	2	5 (-0,10)	-11	-25 (-29,-22)	-10	-33 (-38,-28)
20110117								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG	-56		8		-43		-50	
PLACEBO SC Q2W	-1	-55 (-60,-49)	-1	9 (5,14)	-2	-41 (-45,-36)	-1	-49 (-55,-44)

	Non-HDL-C		HDL-C		Total Cholesterol		ApoB	
	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
Monthly (QM)								
AMG 145 SC QM 420 MG	-50		5		-37		-45	
PLACEBO SC QM	5	-55 (-62,-48)	-4	9 (3,15)	3	-40 (-46,-34)	5	-49 (-56,-43)
20110109								
Monthly (QM)								
AMG 145 SC QM 420 MG	-42		6		-28		-41	
PLACEBO SC QM	8	-50 (-54,-46)	0	5 (3,8)	5	-33 (-36,-31)	3	-44 (-48,-41)

PO - placebo oral; QD - Daily; SC - subcutaneous

Table 7 Analysis of Secondary Endpoints at week 12 in Study 20110115 (Stain add-on study; FAS; Applicant's

	Non-HDL-C		HDL-C		Total Cholesterol		ApoB	
	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
20110115--ATORVASTATIN 10MG								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG + PO QD	-53		7		-37		-51	
PLACEBO SC Q2W + **EZETIMIBE** QD 10 MG	-18	-35 (-41,-29)	-2	9 (5,13)	-14	-23 (-27,-18)	-16	-35 (-40,-30)
PLACEBO SC Q2W + PO QD	8	-62 (-67,-56)	0	7 (3,11)	6	-43 (-47,-38)	8	-59 (-64,-54)
Monthly (QM)								
AMG 145 SC QM 420 MG + PO QD	-53		8		-37		-47	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	-15	-38 (-44,-31)	-0	8 (3,13)	-11	-25 (-30,-21)	-11	-36 (-42,-30)
PLACEBO SC QM + PO QD	2	-55 (-61,-48)	0	8 (3,13)	1	-38 (-43,-33)	0	-47 (-53,-42)
20110115--ATORVASTATIN 80MG								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG + PO QD	-55		9		-36		-50	
PLACEBO SC Q2W + **EZETIMIBE** QD 10 MG	-14	-41 (-50,-31)	1	8 (4,13)	-10	-26 (-33,-20)	-12	-37 (-45,-30)
PLACEBO SC Q2W + PO	12	-67 (-76,-57)	5	4 (-0,9)	9	-46 (-53,-39)	12	-61 (-69,-54)

	Non-HDL-C		HDL-C		Total Cholesterol		ApoB	
	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
QD								
Monthly (QM)								
AMG 145 SC QM 420 MG + PO QD	-50		7		-33		-46	
PLACEBO SC QM + **EZETIMIBE** QD 10 MG	-17	-33 (-41,-24)	0	7 (2,12)	-12	-20 (-26,-14)	-12	-34 (-42,-26)
PLACEBO SC QM + PO QD	10	-60 (-68,-52)	0	7 (2,12)	6	-39 (-45,-33)	7	-53 (-61,-45)
20110115--ROSUVASTATIN 40MG								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG	-50		5		-32		-44	
PLACEBO SC Q2W	10	-59 (-67,-52)	-0	5 (0,10)	5	-37 (-42,-32)	5	-50 (-57,-43)
Monthly (QM)								
AMG 145 SC QM 420 MG	-46		7		-30		-44	
PLACEBO SC QM	3	-49 (-58,-40)	1	5 (0,10)	1	-30 (-37,-24)	3	-47 (-55,-39)
20110115--ROSUVASTATIN 5MG								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG	-52		6		-36		-50	
PLACEBO SC Q2W	8	-60 (-66,-54)	3	3 (-1,8)	6	-43 (-47,-39)	6	-57 (-62,-51)
Monthly (QM)								
AMG 145 SC QM 420 MG	-52		7		-36		-49	
PLACEBO SC QM	6	-57 (-63,-52)	-0	7 (1,14)	3	-39 (-44,-35)	5	-53 (-58,-48)
20110115--SIMVASTATIN 40MG								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG	-57		11		-40		-54	
PLACEBO SC Q2W	4	-60 (-67,-54)	-0	11 (5,17)	2	-42 (-47,-37)	2	-56 (-62,-50)
Monthly (QM)								
AMG 145 SC QM 420 MG	-48		5		-33		-45	
PLACEBO SC QM	7	-56 (-64,-47)	-2	7 (2,12)	4	-37 (-44,-31)	7	-52 (-59,-46)

PO - placebo oral; QD - Daily; SC - subcutaneous

3.3.2 Homozygous Familial Hypercholesterolemia (HoFH)

The percent change from baseline in LDL-C at week 12 was the primary endpoint in study 20110233 part B for the indication of HoFH. The analysis results for the primary endpoint are presented in Table 8. Treatment with evolocumab QM 420 mg resulted in statistically significantly greater reduction in LDL-C compared with placebo in the full analysis set.

Based on the type of mutation identified, 28 patients (20 evolocumab, 8 placebo) were considered LDLR-defective in one or both alleles. Only one patient was identified as LDLR-negative; this individual did not show a reduction in LDL-C. The estimated effect of evolocumab was greater in the LDLR-defective group than the LDLR-indeterminate or –negative group, and the LDL-C reduction on evolocumab was not statistically significant among subjects with indeterminate/negative LDLR functional status. Based on FDA's analysis approach, the LDL-C reduction was 30% greater on evolocumab, with 95% confidence interval (-42, -16). The estimated mean percent change for evolocumab was -22%, and for the placebo group was 8%.

Table 8 Primary Analysis of Percent Change in UC LDL at Week 12

				Applicant's Approach		FDA's Approach	
	Baseline (mg/dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
FAS (N=49)							
AMG 145 SC QM 420 MG	356	33	29	-23		-22	
PLACEBO SC QM	336	16	15	8	-31 (-44,-18)	8	-30 (-42, 16)
Subgroup: LDLR indeterminate or negative (N=21)							
AMG 145 SC QM 420 MG	331	13	11	-11		-13	
PLACEBO SC QM	235	8	7	5	-16 (-41,9)	6	-20 (-47,7)
Subgroup LDLR-defective (N=28)							
AMG 145 SC QM 420 MG	372	20	18	-30		-27	
PLACEBO SC QM	437	8	8	11	-41 (-53,-28)	11	-37 (-52,-21)

N*-- number of subjects with week 12 data; QM - every month; SC – subcutaneous

Table 9 Analysis of Secondary Endpoints at Week 12 for Study 20110233

	Baseline (mg/dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
20110233-HoFH					
Non-HDL-C					
AMG 145 SC QM 420 MG	375	33	29	-22	
PLACEBO SC QM	359	16	16	8	-30 (-42,-18)
HDL					

	Baseline (mg/dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
AMG 145 SC QM 420 MG	39	33	29	4	
PLACEBO SC QM	39	16	16	4	0 (-9,9)
Total Cholesterol					
AMG 145 SC QM 420 MG	414	33	29	-19	
PLACEBO SC QM	398	16	16	8	-27 (-38,-16)
ApoB					
AMG 145 SC QM 420 MG	208	33	29	-19	
PLACEBO SC QM	209	16	16	4	-23(-35, -11)

N*--number of subjects with week 12 data; QM - every month; SC - subcutaneous

3.3.3 LDL-C as a Surrogate Endpoint and Cardiovascular Outcome Data

None of the primary or key secondary efficacy endpoints in the clinical trials supporting the effectiveness of evolocumab were direct measures of benefit on a clinical outcome, i.e., none were direct measures of how patients function, feel, or survive. The primary endpoint LDL-C is a surrogate endpoint intended to predict benefit with respect to the risk of CV outcomes. However, the validity of LDL as a surrogate for the effect of evolocumab (not a statin) and other PCSK9 inhibitors on CV outcomes has not been established and would require extrapolation from other data sources, including CVOTs of statins. Such considerations should be made in the context of findings from randomized trials of other non-statin therapies that have been demonstrated to lower LDL but have not been shown to reduce risk of CV outcomes.[1][2][3]

No evolocumab trial was designed to test a cardiovascular endpoint as an efficacy endpoint, but CV outcome data were collected and are summarized here. In the evolocumab trials, events of death by any cause, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure were adjudicated by an independent clinical endpoint committee (CEC).

In studies 20110114 and 20110116, no participant experienced a positively adjudicated cardiovascular event or a non-coronary revascularization. In study 20110117, 3 subjects experienced positively adjudicated cardiovascular events: all 3 subjects were in evolocumab group. In study 20110115, 9 subjects experienced positively adjudicated cardiovascular events: 5 subjects in the evolocumab group, 2 subjects in the placebo group, and 2 subjects in the

[1] The HSP2-THRIVE Collaborative Group. 2014. Effects of extended-release niacin with laropiprant in high-risk patients. NEJM; 3:203-212.
[2] Barter, P., et al. 2007. Effects of torcetrapib in patients at high risk for coronary events. *NEJM*; 357: 2109-22.
[3] Women's Health Initiative Investigators. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA*; 288: 321-333.

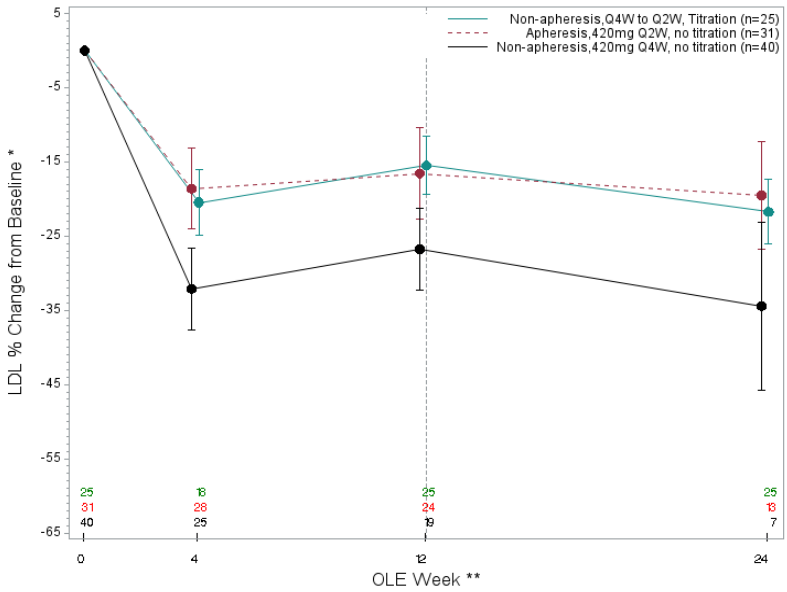
ezetimibe group. In study 20110109, 6 subjects in the evolocumab group and 2 subjects in the placebo group had positively adjudicated cardiovascular events. In study 20110233 in HoFH, no participant experienced a positively adjudicated cardiovascular event or a non-coronary revascularization.

FDA carried out an analysis based on CV outcome data from the integrated phase 3 studies using a Cox proportional hazards model stratifying by study (with treatment as the only covariate). The estimated hazard ratios (95% CI) for evolocumab compared to placebo and ezetimibe were 1.7 (0.6, 5.2) and 0.6 (0.1, 2.8), respectively. These confidence intervals are very wide and illustrate that the numbers of events were too small to make any reliable conclusions regarding potential CV risk reduction with evolocumab. The applicant is conducting an ongoing CV outcome trial to evaluate the potential effect of evolocumab on major adverse CV events.

3.3.4 Evaluation of 420 mg Q2W dose in HoFH population

Study 201102171 is an open-label, single arm, ongoing extension trial to evaluate the long-term safety, tolerability, and efficacy of evolocumab on LDL-C in subjects with severe familial hypercholesterolemia. The interim analysis set included 198 subjects who had received at least 1 dose of evolocumab before the data cutoff date (April 1, 2014), including 96 with HoFH. Two groups of participants were exposed to the evolocumab 420mg Q2W dose: (1) Non-apheresis participants who began the study on 420 mg QM and could be uptitrated to 420mg Q2W if the observed LDL-C reduction from baseline at open-label extension (OLE) week 12 was <5% and PCSK9 levels had not been maximally suppressed (≥100ng/mL); and (2) Apheresis participants who began with 420 mg Q2W. As presented in 2, the trend over time among the 25 patients who titrated from Q4W to Q2W dosing suggests a slightly greater mean LDL-C change at OLE Week 24 than OLE Week 12. (b) (4)

Figure 2 Percent Change of LDL over Time among HoFH



* Baseline refers to previous study baseline or OLE baseline for new enrollees
** Does not correspond to # of weeks on treatment with study medication

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section included the analysis results of the primary endpoint performed within subgroup levels for each study. For certain studies, some subgroups did not have sufficient subjects to support a reliable subgroup analysis. Table 10 summarized the subgroup analyses that were performed for the different trials. Subgroup analyses on the primary efficacy endpoints were performed using an MMRM in the ITT population with treatment, visit, stratification factor, and treatment by visit interaction as covariates in the model. The analysis was performed within the individual level that defined the subgroup. Formal tests for interaction were not performed. Results from subgroup analysis were presented in Table 21 to Table 28 in Appendix. All findings were consistent across levels of the subgroups.

Table 10. Listing of subgroup analyses performed in the phase 3 trials

Factor	Levels	Trials
Sex	Females; Males	All
Age	< 65 years; ≥ 65 years	Except 20110233
Race	White; Other	Except 20110115, 20110233
Region	US; non-US	Except 20110233
Diabetes	Metabolic syndrome; Type 2 diabetes mellitus; Neither	Except 20110233

5 SUMMARY AND CONCLUSIONS

5.1 Summary and Conclusions

4047 subjects were randomized in the phase 3 studies carried out to support the indication of primary hyperlipidemia or mixed dyslipidemia. 2447 subjects were randomized to the evolocumab group. The primary or co-primary endpoint for the 5 studies was the percent change from baseline in LDL-C at 12 weeks or at 52 weeks. Across the studies, evolocumab resulted in statistically significantly greater reductions in LDL-C compared to ezetimibe or placebo at week 12 or week 52.

The overall findings were found to be consistent across the applicant's primary analysis approach and an alternative FDA approach based on more appropriate assumptions about the missing data for subjects that discontinued treatment early. Treatment effect estimates were slightly attenuated in FDA's analyses.

LDL-C is a surrogate endpoint in that it is not a direct measure of clinical benefit to the patient (i.e., a measure of how the patient functions, feels, or survives). Treatment effects on LDL-C are intended to predict clinical benefit with respect to cardiovascular (CV) risk, but the validity of LDL as a surrogate for the effect of evolocumab and other PCSK9 inhibitors has not been established and would require extrapolation from other data sources, including CVOTs of statins. The number of adjudicated cardiovascular events in the evolocumab phase 3 program was too limited to make any reliable conclusions regarding CV risk reduction with evolocumab.

5.2 Labeling Recommendations

(b) (4)

6 APPENDICES

Table 11 Patient Disposition of Study 20110114

	Placebo		Ezetimibe		EvoMab	
	Placebo Q2W + Placebo QD	Placebo QM + Placebo QD	Placebo Q2W + Ezetimibe QD	Placebo QM + Ezetimibe QD	140 mg Q2W + Placebo QD	420 mg QM + Placebo QD
	(N = 77)	(N = 78)	(N = 77)	(N = 77)	(N = 153)	(N = 153)
Study 20110114	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
SC Investigational product accounting subjects who						
Never received SC IP	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received SC IP	76 (98.7)	78 (100.0)	77 (100.0)	77 (100.0)	153 (100)	153 (100)
Completed SC IP	72 (93.5)	73 (93.6)	71 (92.2)	74 (96.1)	141 (92.2)	150 (98.0)
Discontinued SC IP	4 (5.2)	5 (6.4)	6 (7.8)	3 (3.9)	12 (7.8)	3 (2.0)

Adverse event	2 (2.6)	2 (2.6)	3 (3.9)	0 (0.0)	4 (2.6)	1 (0.7)
Subject request	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.6)	4 (2.6)	1 (0.7)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Physician decision	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.3)	2 (1.3)	0 (0.0)
Other	1 (1.3)	1 (1.3)	1 (1.3)	0 (0.0)	2 (1.3)	0 (0.0)

Table 12 Patient Disposition of Study 20110115

	Placebo + Any Statin without Ezetimibe		Placebo+ Atrovastatin with Ezetimibe		EvoMab	
	Placebo Q2W	Placebo QM	Placebo Q2W+ Ezetimibe QD	Placebo QM+ Ezetimibe QD	140 mg Q2W	420 mg QM
	(N = 281)	(N = 278)	(N = 112)	(N = 109)	(N = 557)	(N = 562)
Study 20110115	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Statin therapy accounting subjects who continued						
SC Investigational product accounting subjects who						
Never received SC IP	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received SC IP	281 (100.0)	277 (99.6)	112 (100.0)	109 (100.0)	555 (100.0)	562 (100.0)
Completed SC IP	264 (94.0)	265 (95.3)	102 (91.1)	105 (96.3)	531 (95.3)	540 (96.1)
Discontinued SC IP	17 (6.0)	12 (4.3)	10 (8.9)	4 (3.7)	21 (4.3)	22 (3.9)
Adverse event	6 (2.1)	4 (1.4)	2 (1.8)	2 (1.8)	12(2.2)	7 (1.2)
Subject request	7 (2.5)	4 (1.4)	6 (5.4)	2 (1.8)	7 (1.3)	8 (1.4)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Physician decision	0 (0.0)	1 (0.4)	1 (0.9)	0 (0.0)	0(0.5)	0 (0.0)
Lost to follow-up	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Other	2 (0.7)	3 (1.1)	1 (0.9)	0 (0.0)	3 (0.5)	5 (0.9)

Table 13 Patient Disposition of Study 20110116

	Ezetimibe		EvoMab	
	Placebo Q2W + Ezetimibe QD	Placebo QM + Ezetimibe QD	140 mg Q2W + Placebo QD	420 mg QM + Placebo QD
	(N = 51)	(N = 51)	(N = 103)	(N = 102)
Study 20110116	n (%)	n (%)	n (%)	n (%)
SC Investigational product accounting				
Never received SC IP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received SC IP	51 (100.0)	51 (100.0)	103 (100.0)	102 (100.0)
Completed SC IP	48 (94.1)	48 (94.1)	98 (95.1)	99 (97.1)
Discontinued SC IP	3 (5.9)	3 (5.9)	5 (4.9)	3 (2.9)
Adverse event	3 (5.9)	3 (5.9)	4 (3.9)	2 (2.0)
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

Table 14 Patient Disposition of Study 201101117

Study 20110117	**Placebo Q2W (N = 55) n (%)**	**Placebo QM (N = 55) n (%)**	**Evomab Q2W 140 mg (N = 111) n (%)**	**EvoMab QM 420mg (N = 110) n (%)**
Investigational product accounting				
Subjects who never received IP	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
Subjects who received IP	54 (98.2)	55 (100.0)	110 (99.1)	110 (100.0)
Subjects who completed IP	53 (96.4)	54 (98.2)	109 (98.2)	108 (98.2)
Subjects who discontinued IP	1 (1.8)	1 (1.8)	1 (0.9)	2 (1.8)
Subject request	1 (1.8)	1 (1.8)	1 (0.9)	2 (1.8)

Table 15 Patient Disposition of Study 20110109

	Diet Only		Diet + Atrovastatin 10mg		Diet + Atrovastain 80mg		Diet + Atrovastain 80mg +Ezetimibe 10mg		Total	
	Placebo QM	EvoMab 420 mg QM	Placebo QM	EvoMab 420 mg QM	Placebo QM	EvoMab 420 mg QM	Placebo QM	EvoMab 420 mg QM	Placebo QM	EvoMab 420 mg QM
Study 20110109	N=38	N=74	N=129	N=256	N=73	N=146	N=63	N=126	N=303	N=602
Investigational Product accounting										
Subjects who never received IP	1 (2.6)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.5)
Subjects who received IP	37 (97.4)	74 (100.0)	129 (100)	254 (99.2)	73 (100.0)	145 (99.3)	63 (100.0)	126 (100.0)	302 (99.7)	599 (99.5)
Subjects who 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)
Subjects who 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)
Full 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 (0.0)	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)
Death	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Subject request	0 (0.0)	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 (0.0)	1 (1.4)	0 (0.0)	1 (0.4)	1 (1.4)	1 (0.7)	0 (0.0)	1 (0.8)	1 (0.3)	4 (0.7)
Investigator decision	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Lost to follow-up	1 (2.6)	3 (4.1)	1 (0.8)	2 (0.8)	0 (0.0)	2 (1.4)	0 (0.0)	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)	0 (0.0)	0 (0.0)	7 (5.6)	4 (1.3)	14 (2.3)

Table 16 Patient Disposition of Study 20110233 (HoFH)

	Placebo QM N=17	EvoMab 420 mg QM N=33
Investigational product accounting		
Subjects who never received IP	1 (5.9)	0 (0.0)
Subjects who received IP	16 (94.1)	33 (100)
Subjects who completed IP	16 (94.1)	31 (93.9)
Subjects who discontinued IP	0 (0.0)	2 (6.1)
Subject request	0 (0.0)	2 (6.1)

Table 17 Analysis of Mean Percent Change in Reflexive LDL at week 10 and 12 in studies 20110114, 20110115, 20110116

	Baseline (mg/dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
20110114					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG + PLACEBO QD	142	153	140	-57	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	143	77	75	-17	-39 (-43,-36)
PLACEBO SC Q2W +PLACEBO QD	140	76	76	-0	-56 (-60,-53)
Monthly (QM)					
AMG 145 SC QM 420 MG +PLACEBO QD	144	153	150	-59	
PLACEBO SC QM + EZETIMIBE QD 10 MG	144	77	72	-19	-40 (-43,-36)
PLACEBO SC QM + PLACEBO QD	144	78	74	-1	-57 (-61,-54)
20110116					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG + PLACEBO QD	192	103	101	-56	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	195	51	50	-19	-37 (-42,-32)
Monthly (QM)					
AMG 145 SC QM 420 MG + PLACEBO QD	192	102	100	-55	
PLACEBO SC QM + EZETIMIBE QD 10 MG	195	51	49	-17	-38 (-43,-34)
20110117					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG	161	110	109	-61	
PLACEBO SC Q2W	151	54	53	-1	-60 (-66,-54)
Monthly (QM)					

	Baseline (mg/dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
AMG 145 SC QM 420 MG	154	110	107	-63	
PLACEBO SC QM	152	55	54	3	-66 (-72,-59)

Table 18 Analysis of Mean Percent Change in Reflexive LDL at week 10 and 12 in study 20110115

	Baseline (mg/ dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
20110115--ATORVASTATIN 10MG					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG + PLACEBO QD	124	110	109	-61	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	127	56	50	-24	-38 (-43,-32)
PLACEBO SC Q2W + PO QD	123	56	53	8	-70 (-75,-64)
Monthly (QM)					
AMG 145 SC QM 420 MG +PLACEBO QD	126	110	106	-62	
PLACEBO SC QM + EZETIMIBE QD 10 MG	119	55	54	-18	-44 (-50,-37)
PLACEBO SC QM +PLACEBO QD	124	55	54	1	-63 (-70,-57)
20110115--ATORVASTATIN 80MG					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG +PLACEBO QD	94	109	108	-62	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	99	56	55	-17	-45 (-54,-35)
PLACEBO SC Q2W +PLACEBO QD	100	55	51	13	-75 (-84,-65)
Monthly (QM)					
AMG 145 SC QM 420 MG + PLACEBO QD	94	110	107	-65	
PLACEBO SC QM + EZETIMIBE QD 10 MG	92	54	53	-21	-44 (-52,-35)
PLACEBO SC QM + PLACEBO QD	95	55	54	10	-75 (-83,-66)
20110115--ROSUVASTATIN 40MG					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG	89	102	98	-58	
PLACEBO SC Q2W	77	53	51	7	-65 (-73,-57)
Monthly (QM)					
AMG 145 SC QM 420 MG	87	104	102	-62	
PLACEBO SC QM	104	51	49	1	-62 (-72,-52)
20110115--ROSUVASTATIN 5MG					
Every 2 weeks (Q2W)					

	Baseline (mg/ dL)	N	N*	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
AMG 145 SC Q2W 140 MG	119	113	106	-59	
PLACEBO SC Q2W	116	58	57	8	-67 (-73,-61)
Monthly (QM)					
AMG 145 SC QM 420 MG	123	115	109	-63	
PLACEBO SC QM	120	57	57	3	-67 (-73,-61)
20110115--SIMVASTATIN 40MG					
Every 2 weeks (Q2W)					
AMG 145 SC Q2W 140 MG	114	98	95	-65	
PLACEBO SC Q2W	110	49	47	3	-68 (-74,-62)
Monthly (QM)					
AMG 145 SC QM 420 MG	124	99	97	-61	
PLACEBO SC QM	109	49	46	6	-67 (-76,-59)

Table 19 Analysis Results of Calculated LDL in Study 20110114, 20110116, 20110117 at Week 12

	LS Mean: % Change	Difference : Evolovumab-Control:(95% CL)
20110114		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG + PLACEBO QD	-58	
PLACEBO SC Q2W + EZETIMIBE QD10 MG	-18	-40 (-45,-36)
PLACEBO SC Q2W + PO QD	1	-59 (-63,-54)
Monthly (QM)		
AMG 145 SC QM 420 MG + PLACEBO QD	-57	
PLACEBO SC QM + EZETIMIBE QD 10 MG	-19	-38 (-43,-34)
PLACEBO SC QM + PO QD	0	-57 (-62,-53)
20110116		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG + PLACEBO QD	-57	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	-18	-39 (-45,-34)
Monthly (QM)		
AMG 145 SC QM 420 MG +PLACEBO QD	-53	
PLACEBO SC QM + EZETIMIBE QD 10 MG	-15	-38 (-43,-33)
20110117		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG	-63	

	LS Mean: % Change	Difference : Evolovumab-Control:(95% CL)
PLACEBO SC Q2W	-2	-61 (-67,-55)
Monthly (QM)		
AMG 145 SC QM 420 MG	-57	
PLACEBO SC QM	4	-60 (-68,-53)

Table 20 Analysis Result of Calculated LDL for Study 20110115 at Week 12

	LS Mean: % Change	Difference: Evolovumab-Control:(95% CL)
20110115--ATORVASTATIN 10MG		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG + PLACEBO QD	-65	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	-21	-44 (-51,-36)
PLACEBO SC Q2W + PLACEBO QD	10	-74 (-82,-67)
Monthly (QM)		
AMG 145 SC QM 420 MG + PLACEBO QD	-60	
PLACEBO SC QM + EZETIMIBE QD 10 MG	-17	-43 (-51,-35)
PLACEBO SC QM + PLACEBO QD	1	-61 (-69,-53)
20110115--ATORVASTATIN 80MG		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG +PLACEBO QD	-65	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	-15	-50 (-63,-37)
PLACEBO SC Q2W + PLACEBO QD	15	-79 (-93,-66)
Monthly (QM)		
AMG 145 SC QM 420 MG + PLACEBO QD	-62	
PLACEBO SC QM + EZETIMIBE QD 10 MG	-21	-41 (-52,-31)
PLACEBO SC QM + PLACEBO QD	12	-74 (-85,-64)
20110115--ROSUVASTATIN 40MG		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG	-60	
PLACEBO SC Q2W	10	-71 (-80,-62)
Monthly (QM)		
AMG 145 SC QM 420 MG	-56	
PLACEBO SC QM	3	-58 (-69,-47)
20110115--ROSUVASTATIN 5MG		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG	-63	

	LS Mean: % Change	Difference: Evolovumab-Control:(95% CL)
PLACEBO SC Q2W	8	-71 (-78,-64)
Monthly (QM)		
AMG 145 SC QM 420 MG	-61	
PLACEBO SC QM	5	-66 (-72,-59)
20110115--SIMVASTATIN 40MG		
Every 2 weeks (Q2W)		
AMG 145 SC Q2W 140 MG	-68	
PLACEBO SC Q2W	5	-73 (-80,-65)
Monthly (QM)		
AMG 145 SC QM 420 MG	-57	
PLACEBO SC QM	4	-61 (-70,-51)

Table 21 Subgroup Analysis Results by Age (Age < 65 years vs Age ≥ 65 years)

	Age < 65 years			Age ≥ 65 years		
	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)
20110109 at Week 52						
Monthly (QM)						
AMG 145 SC QM 420 MG	461	-49		138	-55	
PLACEBO SC QM	235	8	-57 (-62,-52)	67	1	-56 (-62,-49)
Primary endpoint at week 12 studies						
20110114						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	119	-58		34	-54	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	63	-17	-41 (-45,-37)	14	-22	-32 (-40,-24)
PLACEBO SC Q2W + PLACEBO QD	64	-1	-58 (-62,-53)	12	2	-56 (-64,-47)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	129	-56		24	-54	
PLACEBO SC QM + EZETIMIBE QD 10 MG	59	-17	-39 (-43,-34)	18	-23	-32 (-39,-24)
PLACEBO SC QM + PLACEBO QD	69	-2	-55 (-59,-50)	9	1	-56 (-65,-46)
20110116						

	Age < 65 years			Age ≥ 65 years		
	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	59	-55		44	-56	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	26	-17	-39 (-46,-32)	25	-19	-37 (-44,-30)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	59	-55		43	-50	
PLACEBO SC QM + EZETIMIBE QD 10 MG	36	-19	-36 (-43,-30)	15	-7	-44 (-53,-35)
20110117						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	92	-60		18	-63	
PLACEBO SC Q2W	44	-1	-59 (-67,-51)	10	-0	-62 (-72,-52)
Monthly (QM)						
AMG 145 SC QM 420 MG	91	-55		19	-62	
PLACEBO SC QM	53	5	-60 (-67,-52)	2	0	-62 (-85,-40)

Table 22 Subgroup Analysis by Age for Study 20110115 (Age < 65 years vs Age ≥ 65 years)

	Age < 65 years			Age ≥ 65 years		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
20110115--ATORVASTATIN 10MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	85	-62		25	-62	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	33	-22	-40 (-49,-32)	23	-23	-39 (-49,-29)
PLACEBO SC Q2W + PLACEBO QD	39	10	-72 (-79,-64)	17	10	-72 (-83,-61)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	72	-58		38	-58	
PLACEBO SC QM + EZETIMIBE QD 10 MG	37	-10	-49 (-57,-40)	18	-32	-26 (-36,-16)
PLACEBO SC QM + PLACEBO	29	1	-59 (-68,-50)	26	1	-59 (-68,-50)

	Age < 65 years			Age ≥ 65 years		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
PO QD						
20110115--ATORVASTATIN 80MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	68	-61		41	-65	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	31	-15	-46 (-60,-32)	25	-16	-49 (-62,-37)
PLACEBO SC Q2W + PLACEBO QD	44	18	-79 (-92,-66)	11	-3	-62 (-79,-45)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	68	-59		42	-59	
PLACEBO SC QM + EZETIMIBE QD 10 MG	34	-16	-42 (-56,-29)	20	-25	-33 (-47,-20)
PLACEBO SC QM + PLACEBO QD	37	14	-72 (-85,-59)	18	9	-68 (-81,-54)
20110115--ROSUVASTATIN 40MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	75	-57		27	-56	
PLACEBO SC Q2W	37	14	-72 (-84,-59)	16	1	-57 (-72,-41)
Monthly (QM)						
AMG 145 SC QM 420 MG	75	-51		29	-56	
PLACEBO SC QM	36	4	-56 (-68,-43)	15	-2	-54 (-70,-38)
20110115--ROSUVASTATIN 5MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	75	-59		38	-61	
PLACEBO SC Q2W	33	7	-67 (-75,-58)	25	9	-70 (-81,-60)
Monthly (QM)						
AMG 145 SC QM 420 MG	74	-59		41	-60	
PLACEBO SC QM	37	4	-63 (-71,-56)	20	7	-67 (-78,-56)
20110115--SIMVASTATIN 40MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	66	-64		32	-66	
PLACEBO SC Q2W	28	8	-73 (-83,-62)	21	0	-66 (-78,-54)
Monthly (QM)						

	Age < 65 years			Age ≥ 65 years		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
AMG 145 SC QM 420 MG	55	-56		44	-56	
PLACEBO SC QM	29	10	-66 (-77,-55)	20	-4	-52 (-64,-41)

Table 23 Subgroup Analysis by Gender (Female vs Male)

	Female			Male		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Contro (95% CI)
20110109						
Monthly (QM)						
AMG 145 SC QM 420 MG	309	-45		290	-56	
PLACEBO SC QM	162	8	-53 (-59,-47)	140	5	-61 (-66,-55)
20110114						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	104	-56		49	-61	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	53	-19	-37 (-41,-32)	24	-17	-44 (-52,-36)
PLACEBO SC Q2W + PLACEBO QD	48	1	-56 (-61,-52)	28	-2	-60 (-67,-53)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	101	-55		52	-59	
PLACEBO SC QM + EZETIMIBE QD 10 MG	52	-17	-38 (-42,-33)	25	-22	-37 (-44,-30)
PLACEBO SC QM + PLACEBO QD	47	0	-55 (-60,-50)	31	-3	-55 (-62,-49)
20110116						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	46	-51		57	-60	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	27	-18	-32 (-40,-25)	24	-17	-43 (-50,-36)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	46	-48		56	-58	
PLACEBO SC QM + EZETIMIBE QD 10 MG	22	-12	-35 (-43,-27)	29	-19	-39 (-46,-33)
20110117						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	44	-60		66	-61	
PLACEBO SC Q2W	25	-8	-53 (-64,-41)	29	4	-65 (-73,-56)
Monthly (QM)						

	Female			Male		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Contro (95% CI)
AMG 145 SC QM 420 MG	46	-55		64	-57	
PLACEBO SC QM	24	9	-64 (-75,-52)	31	1	-59 (-67,-50)
20110233						
Monthly (QM)						
AMG 145 SC QM 420 MG	16	-23		17	-24	
PLACEBO SC QM	8	8	-31 (-50,-12)	8	7	-31 (-51,-12)

Table 24 Subgroup Analysis by Gender for Study 20110115

	Female			Male		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
20110115--ATORVASTATIN 10MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	56	-58		54	-66	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	29	-23	-36 (-45,-26)	27	-21	-44 (-53,-35)
PLACEBO SC Q2W + PLACEBO QD	24	14	-72 (-82,-62)	32	7	-73 (-81,-64)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	44	-57		66	-59	
PLACEBO SC QM + EZETIMIBE QD 10 MG	28	-16	-41 (-51,-31)	27	-18	-41 (-50,-33)
PLACEBO SC QM + PLACEBO QD	28	2	-60 (-70,-49)	27	-0	-59 (-67,-50)
20110115--ATORVASTATIN 80MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	43	-61		66	-63	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	24	-13	-48 (-63,-32)	32	-16	-47 (-60,-34)
PLACEBO SC Q2W + PLACEBO QD	22	15	-76 (-92,-60)	33	13	-76 (-89,-63)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	48	-53		62	-62	
PLACEBO SC QM + EZETIMIBE PO QD 10 MG	28	-21	-32 (-47,-18)	26	-18	-44 (-58,-30)
PLACEBO SC QM + PLACEBO PO QD	24	14	-67 (-82,-52)	31	11	-73 (-86,-60)
20110115--ROSUVASTATIN 40MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	39	-54		63	-58	

	Female			Male		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
PLACEBO SC Q2W	21	10	-64 (-81,-47)	32	11	-69 (-81,-57)
Monthly (QM)						
AMG 145 SC QM 420 MG	46	-46		58	-57	
PLACEBO SC QM	22	6	-52 (-69,-36)	29	0	-57 (-70,-45)
20110115--ROSUVASTATIN 5MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	51	-55		62	-64	
PLACEBO SC Q2W	35	7	-62 (-72,-53)	23	10	-74 (-83,-65)
Monthly (QM)						
AMG 145 SC QM 420 MG	51	-58		64	-61	
PLACEBO SC QM	27	6	-64 (-74,-54)	30	4	-65 (-73,-57)
20110115--SIMVASTATIN 40MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	39	-64		59	-66	
PLACEBO SC Q2W	27	3	-67 (-80,-55)	22	6	-72 (-82,-62)
Monthly (QM)						
AMG 145 SC QM 420 MG	49	-51		50	-61	
PLACEBO SC QM	26	5	-56 (-69,-44)	23	2	-64 (-74,-54)

Table 25 Subgroup Analysis by Race (White vs Other)

	Other			White		
	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)
20110109						
Monthly (QM)						
AMG 145 SC QM 420 MG	123	-48		476	-51	
PLACEBO SC QM	54	13	-61 (-71,-50)	248	5	-56 (-61,-52)
20110114						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	21	-60		132	-57	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	14	-12	-47 (-57,-38)	63	-20	-37 (-42,-33)

	Other			White		
	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)
PLACEBO SC Q2W + PLACEBO QD	13	-1	-59 (-69,-49)	63	-0	-57 (-61,-53)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	24	-59		129	-55	
PLACEBO SC QM + EZETIMIBE QD 10 MG	17	-14	-45 (-55,-35)	60	-20	-36 (-40,-31)
PLACEBO SC QM + PLACEBO QD	15	-5	-54 (-64,-44)	63	-0	-55 (-59,-51)
20110116						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	9	-41		94	-57	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	2	-23	-18 (-52,17)	49	-17	-40 (-45,-35)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	4	-48		98	-54	
PLACEBO SC QM + EZETIMIBE QD 10 MG	5	-13	-35 (-66,-4)	46	-16	-37 (-42,-32)
20110117						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	11	-69		99	-59	
PLACEBO SC Q2W	4	-4	-64 (-78,-51)	50	-1	-59 (-66,-51)
Monthly (QM)						
AMG 145 SC QM 420 MG	12	-61		98	-56	
PLACEBO SC QM	6	-4	-57 (-70,-45)	49	6	-61 (-69,-54)

Table 26 Subgroup Analysis by Region (North America vs other)

	North America			Other		
	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)
20110109						
Monthly (QM)						
AMG 145 SC QM 420 MG	344	-52		255	-47	
PLACEBO SC QM	177	8	-61 (-66,-55)	125	6	-52 (-59,-46)
20110114						

	North America			Other		
	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)	N	LS Means: % Change	Difference: Evolocumab - Control(95% CI)
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	88	-58		65	-56	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	43	-17	-42 (-47,-37)	34	-19	-36 (-42,-31)
PLACEBO SC Q2W + PLACEBO QD	39	-1	-58 (-63,-52)	37	1	-57 (-62,-51)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	92	-57		61	-55	
PLACEBO SC QM + EZETIMIBE QD 10 MG	44	-17	-40 (-45,-35)	33	-20	-34 (-40,-28)
PLACEBO SC QM + PLACEBO QD	45	-3	-54 (-59,-49)	33	1	-56 (-62,-50)
20110116						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	33	-57		70	-55	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	22	-14	-42 (-49,-36)	29	-20	-35 (-42,-28)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	37	-55		65	-52	
PLACEBO SC QM + EZETIMIBE QD 10 MG	20	-15	-40 (-47,-33)	31	-17	-36 (-43,-28)
20110117						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	28	-60		82	-61	
PLACEBO SC Q2W	15	7	-66 (-80,-53)	39	-4	-57 (-65,-49)
Monthly (QM)						
AMG 145 SC QM 420 MG	24	-62		86	-55	
PLACEBO SC QM	7	8	-70 (-91,-49)	48	5	-60 (-67,-53)

Table 27 Subgroup Analysis by Region for Study 20110115

	NORTH AMERICA			OTHER		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
20110115--ATORVASTATIN 10MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	45	-61		65	-62	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	20	-18	-42 (-53,-32)	36	-24	-38 (-47,-30)
PLACEBO SC Q2W + PLACEBO QD	21	11	-71 (-82,-61)	35	9	-71 (-80,-63)

	NORTH AMERICA			OTHER		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	41	-56		69	-59	
PLACEBO SC QM + EZETIMIBE QD 10 MG	18	-18	-37 (-48,-26)	37	-16	-43 (-51,-35)
PLACEBO SC QM + PLACEBO QD	16	2	-58 (-69,-46)	39	1	-60 (-68,-52)
20110115--ATORVASTATIN 80MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG + PLACEBO QD	45	-62		64	-61	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	21	-14	-48 (-63,-33)	35	-15	-46 (-59,-33)
PLACEBO SC Q2W + PLACEBO QD	21	15	-77 (-93,-61)	34	13	-74 (-87,-61)
Monthly (QM)						
AMG 145 SC QM 420 MG + PLACEBO QD	46	-61		64	-57	
PLACEBO SC QM + EZETIMIBE QD 10 MG	21	-25	-35 (-51,-20)	33	-16	-40 (-53,-27)
PLACEBO SC QM + PLACEBO QD	28	20	-80 (-95,-66)	27	5	-62 (-76,-49)
20110115--ROSUVASTATIN 40MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	43	-52		59	-61	
PLACEBO SC Q2W	13	5	-57 (-72,-42)	40	13	-74 (-87,-60)
Monthly (QM)						
AMG 145 SC QM 420 MG	38	-50		66	-55	
PLACEBO SC QM	16	2	-52 (-66,-38)	35	2	-57 (-71,-43)
20110115--ROSUVASTATIN 5MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	52	-59		61	-61	
PLACEBO SC Q2W	20	6	-65 (-76,-53)	38	10	-70 (-78,-62)
Monthly (QM)						
AMG 145 SC QM 420 MG	42	-56		73	-62	
PLACEBO SC QM	21	2	-58 (-70,-47)	36	7	-68 (-76,-61)
20110115--SIMVASTATIN 40MG						
Every 2 weeks (Q2W)						
AMG 145 SC Q2W 140 MG	42	-64		56	-66	
PLACEBO SC Q2W	19	7	-70 (-84,-57)	30	4	-69 (-79,-60)
Monthly (QM)						

	NORTH AMERICA			OTHER		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
AMG 145 SC QM 420 MG	36	-58		63	-55	
PLACEBO SC QM	20	20	-78 (-92,-64)	29	-7	-48 (-57,-39)

Table 28 Subgroup analysis by Diabetes (Metabolic Syndrome; T2DM; Neither)

	Metabolic Syndrome			Neither Type 2 Diabetes Mellitus nor Metabolic Syndrome			Type 2 Diabetes Mellitus		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
20110109									
Monthly (QM)									
AMG 145 SC QM 420 MG	196	-50		341	-50		62	-52	
PLACEBO SC QM	108	5	-54 (-61,-47)	152	10	-60 (-66,-55)	42	1	-53 (-64,-42)
20110114									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 M	52	-63		101	-54		-	-	
PLACEBO SC Q2W + EZETIMIBE	26	-18	-46 (-52,-40)	51	-18	-36 (-41,-32)	-	-	-
PLACEBO SC Q2W + PLACEBO	18	5	-69 (-75,-62)	58	-2	-53 (-57,-48)	-	-	-
AMG 145 SC QM 420 MG	39	-57		114	-56		-	-	
PLACEBO SC QM + EZETIMIBE	24	-17	-40 (-46,-33)	53	-19	-36 (-41,-32)	-	-	-
PLACEBO SC QM + PLACEBO	28	-1	-55 (-61,-49)	49	-0	-55 (-60,-50)	1	-	-
20110116									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 M	41	-61		42	-51		20	-53	
PLACEBO SC Q2W + EZETIMIBE	21	-20	-41 (-49,-33)	19	-15	-36 (-45,-27)	11	-15	-37 (-47,-28)
Monthly (QM)									
AMG 145 SC QM 420 MG	33	-55		54	-51		15	-53	
PLACEBO SC QM + EZETIMEBE	19	-18	-37 (-46,-28)	16	-18	-34 (-43,-25)	16	-9	-44 (-53,-35)
20110117									

	Metabolic Syndrome			Neither Type 2 Diabetes Mellitus nor Metabolic Syndrome			Type 2 Diabetes Mellitus		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 M	34	-60		71	-62		5	-49	
PLACEBO SC Q2W	10	-9	-50 (-65,-36)	40	1	-63 (-71,-56)	4	-11	-38 (-86,11)
Monthly (QM)									
AMG 145 SC QM 420 MG	34	-56		66	-58		10	-45	
PLACEBO SC QM	17	8	-65 (-77,-52)	33	4	-62 (-71,-54)	5	-1	-44 (-83,-5)

Table 29 Subgroup Analysis by Diabetes for Study 20110115

	Metabolic Syndrome			Neither Type 2 Diabetes Mellitus nor Metabolic Syndrome			Type 2 Diabetes Mellitus		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
20110115--ATORVASTATIN 10MG									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 MG + PLACEBO QD	43	-64		44	-61		23	-59	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	18	-23	-41 (-51,-31)	32	-24	-38 (-45,-30)	6	-18	-41 (-69,-14)
PLACEBO SC Q2W + PLACEBO QD	12	9	-73 (-84,-61)	35	4	-66 (-73,-58)	9	30	-89 (-111,-66)
Monthly (QM)									
AMG 145 SC QM 420 MG + PLACEBO QD	36	-62		59	-58		15	-47	
PLACEBO SC QM + EZETIMIBE QD 10 MG	14	-16	-46 (-57,-34)	30	-21	-38 (-45,-30)	11	-11	-36 (-59,-14)
PLACEBO SC QM + PLACEBO QD	18	5	-67 (-77,-56)	30	1	-59 (-67,-52)	7	-7	-40 (-66,-14)
20110115--ATORVASTATIN 80MG									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 MG + PLACEBO QD	37	-67		56	-61		16	-53	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	21	-24	-43 (-58,-29)	25	-3	-58 (-73,-43)	10	-23	-31 (-55,-6)
PLACEBO SC Q2W + PLACEBO QD	20	20	-88 (-102,-73)	28	16	-77 (-92,-63)	7	-6	-47 (-75,-19)
Monthly (QM)									
AMG 145 SC QM 420 MG + PLACEBO QD	24	-58		68	-59		18	-54	
PLACEBO SC QM + EZETIMIBE QD 10 MG	11	-21	-37 (-55,-18)	26	-14	-45 (-60,-30)	17	-26	-29 (-49,-8)

	Metabolic Syndrome			Neither Type 2 Diabetes Mellitus nor Metabolic Syndrome			Type 2 Diabetes Mellitus		
	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)	N	LS Means:% Change	Difference: Evolocumab - Control(95% CI)
PLACEBO SC QM + PLACEBO QD	11	5	-63 (-82,-44)	34	19	-78 (-91,-64)	10	-3	-51 (-74,-28)
20110115--ROSUVASTATIN 40MG									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 MG	27	-53		57	-60		18	-49	
PLACEBO SC Q2W	20	5	-58 (-71,-45)	32	14	-74 (-87,-61)	1	-7	-42 (-140,55)
Monthly (QM)									
AMG 145 SC QM 420 MG	31	-54		62	-55		11	-34	
PLACEBO SC QM	19	-1	-53 (-66,-40)	27	2	-58 (-71,-44)	5	22	-57 (-109,-5)
20110115--ROSUVASTATIN 5MG									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 MG	30	-60		57	-59		26	-63	
PLACEBO SC Q2W	20	16	-76 (-89,-64)	35	4	-63 (-71,-55)	3	3	-65 (-86,-45)
Monthly (QM)									
AMG 145 SC QM 420 MG	33	-57		70	-61		12	-60	
PLACEBO SC QM	23	-3	-53 (-65,-42)	25	17	-78 (-86,-69)	9	-6	-54 (-69,-40)
20110115--SIMVASTATIN 40MG									
Every 2 weeks (Q2W)									
AMG 145 SC Q2W 140 MG	43	-66		37	-65		18	-62	
PLACEBO SC Q2W	15	10	-76 (-88,-63)	26	-1	-63 (-74,-53)	8	16	-78 (-107,-49)
Monthly (QM)									
AMG 145 SC QM 420 MG	29	-57		59	-56		11	-57	
PLACEBO SC QM	11	-5	-52 (-67,-37)	28	1	-57 (-66,-48)	10	20	-77 (-107,-46)

Table 30 Missing Data in Study 20110114

Treatment	week	Total Missing N (%)	Missing and off-trt (SC or Oral)	Total Non-missing N (%)	Non-missing and on trt (SC and Oral) N (%)
AMG 145 SC Q2W 140 MG + PO QD	12	20 (13.1)	10	133 (86.9)	131
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	12	7 (9.1)	3	70 (90.9)	66
PLACEBO SC Q2W + PO QD	12	7 (9.2)	1	69 (90.8)	66

Treatment	week	Total Missing N (%)	Missing and off-trt (SC or Oral)	Total Non-missing N (%)	Non-missing and on trt (SC and Oral) N (%)
AMG 145 SC QM 420 MG + PO QD	12	17 (11.1)	3	136 (88.9)	133
PLACEBO SC QM + EZETIMIBE QD 10 MG	12	8 (10.4)	3	69 (89.6)	66
PLACEBO SC QM + PO QD	12	8 (10.3)	4	70 (89.7)	68

Table 31 Missing Data in Study 20110116

Treatment	week	Total Missing N (%)	Missing and off-trt (SC or Oral)	Total Non-missing N (%)	Non-missing and on trt (SC and Oral) N (%)
AMG 145 SC Q2W 140 MG + PO QD	12	5 (4.9)	2	98 (95.1)	93
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	12	2 (3.9)	1	49 (96.1)	46
AMG 145 SC QM 420 MG + PO QD	12	6 (5.9)	2	96 (94.1)	86
PLACEBO SC QM + EZETIMIBE QD 10 MG	12	6 (11.8)	4	45 (88.2)	38

Table 32 Missing Data in Study 20110109

Treatment	week	Total Missing N (%)	Missing and off-trt (SC)	Total Non-missing N (%)	Non-missing and on trt (SC) N
AMG 145 SC QM 420 MG	52	57 (9.5)	47	542 (90.5)	516
PLACEBO SC QM	52	38 (12.6)	19	264 (87.4)	255

Table 33 Missing Data in Study 20110117

Treatment	week	Total Missing N (%)	Missing and off-trt (SC) N	Total Non-missing N (%)	Non-missing and on trt (SC) N
AMG 145 SC Q2W 140 MG	12	6 (5.5)	1	104 (94.5)	104
PLACEBO SC Q2W	12	3 (5.6)	1	51 (94.4)	51
AMG 145 SC QM 420 MG	12	7 (6.4)	2	103 (93.6)	103
PLACEBO SC QM	12	9 (16.4)	1	46 (83.6)	46

Table 34 Missing Data in Study 20110115

Treatment	week	Total Missing N (%)	Missing and off-trt (SC or Oral)	Total Non-missing N (%)	Non-missing and on trt (SC and Oral) N (%)
Atorvastatin add-on					
AMG 145 SC Q2W 140 MG + PO QD	12	14 (6.4)	5	205 (93.6)	197
AMG 145 SC QM 420 MG + PO QD	12	19 (8.6)	7	201 (91.4)	195

Treatment	week	Total Missing N (%)	Missing and off-trt (SC or Oral)	Total Non-missing N (%)	Non-missing and on trt (SC and Oral) N (%)
Atorvastatin add-on					
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	12	13 (11.6)	8	99 (88.4)	96
PLACEBO SC Q2W + PO QD	12	14 (12.6)	8	97 (87.4)	96
PLACEBO SC QM + EZETIMIBE QD 10 MG	12	5 (4.6)	1	104 (95.4)	100
PLACEBO SC QM + PO QD	12	8 (7.3)	3	102 (92.7)	98
Rosuvastatin or Simvastatin add-on					
AMG 145 SC Q2W 140 MG	12	24 (7.1)	24	312 (92.9)	312
AMG 145 SC QM 420 MG	12	29 (8.5)	29	313 (91.5)	309
PLACEBO SC Q2W	12	13 (7.6)	13	157 (92.4)	156
PLACEBO SC QM	12	15 (9.0)	15	152 (91.0)	150

Table 35 Missing Data in Study 20110233

Treatment	week	Total Missing N (%)	Missing and off-trt (SC) N	Total Non-missing N (%)	Non-missing and on trt (SC) N (%)
AMG 145 SC QM 420 MG	12	4 (12.1)	2	29 (87.9)	29
PLACEBO SC QM	12	1 (6.3)	0	15 (93.8)	15

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/s/

SHUXIAN Z SINKS
06/19/2015

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06/22/2015

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

BLA Number:	BLA 125,522
Drug Name:	AMG 145 (Evolocumab)
Indication(s):	104 Week Carcinogenicity Study in Hamster
Applicant:	**Sponsor:** Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA 91320-1799
	Performing Laboratory: (b) (4)
Documents Reviewed:	Electronic report submission: Dated August 27, 2014
	Electronic data submission: Dated August 27, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Reviewing Pharmacologist:	Calvin Elmore (Lee), Ph.D.
Project Manager:	Kati Johnson
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1. Background

In this submission the sponsor included a report of an animal carcinogenicity study in hamster. This study was intended to assess the carcinogenic potential of AMG 145 (Evolocumab) in hamsters when administered subcutaneously once every 2 weeks at appropriate drug levels for up to 105 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Elmore.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Design

Two separate experiments were conducted, one in male and one in female hamsters. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:LVG[SYR] Golden Syrian hamsters of each sex were assigned to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 10, 30, and 100 mg/kg. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The animals in control group received the placebo article (b) (4)

During the study period female hamster survival across all dose groups (including controls) was very low. As a result the surviving females in all treatment groups were terminally sacrificed on Week 86 when the number of surviving females in the control group met the FDA criteria for early termination.

All animals were checked twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were conducted for each animal twice during the predose phase and prior to dosing on Study Day 1 and weekly throughout the dosing phase. Detailed observations were also collected on the days of scheduled euthanasia. Beginning Study Week 12, appearance, and progression of grossly visible or palpable masses were recorded weekly.

Body weights were recorded for all animals once during the predose phase, before dosing on Study Day 1, and weekly thereafter.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor estimated the proportions of mortalities in all four treatment groups using the Kaplan-Meier product limit method and presented them graphically for male and female hamsters separately. The sponsor analyzed the mortality data for dose response relationship and pairwise comparisons of treated groups with control using the Cox-Tarone binary regression test and the Gehan-Breslow nonparametric test on life tables. All tests were performed at two-tailed 0.05 level of significance.

Sponsor's findings: Sponsor's estimate showed 53.3%, 50.0%, 51.7%, and 60.0% mortality in control, low, medium, and high dose groups, respectively in male hamsters; and 66.7%, 60.0%, 70.0%, and 70.0% mortality in control, low, medium, and high dose groups, respectively in female hamsters. The sponsor's analysis did not showed statistically significant dose response relationship across treatment groups or difference in survival in any of the treated groups compared to the control in either sex. On the point of higher mortalities of female hamsters in all treatment groups compared to male hamsters, the sponsor commented that this observed sex difference was consistent with gender-specific mortality rates reported previously for hamsters in long-term studies and was unrelated to AMG 145. The sponsor further commented that the most commonly identified cause of death in both sexes was atrial thrombosis in the heart, which occurred with a similar incidence across all dose groups, including controls.

2.1.2. Tumor data analysis

The sponsor analyzed the tumor data using the survival adjusted methodologies proposed by Peto et al. (1980). For incidental tumors, the intervals used were 0 - 52, 53 - 78, 79 - 92, 93 to before terminal sacrifice, and terminal sacrifice for male hamsters; and 0 - 52, 53 - 78, 79 to before terminal sacrifice, and terminal sacrifice for female hamsters. The nominal dose levels of 0, 10, 30, and 100 were used as scores. For dose response relationship tests when the total tumor incidences were <12 in all groups combined, the exact form of the test was used. For pairwise tests when the total tumor incidences were <12 in the two corresponding groups, the exact test was also used. Fatal, observable, or palpable tumors were analyzed by the Cox-Tarone binary regression method using the death time or the first palpation time as a surrogate for the tumor onset time.

When biologically relevant, benign and malignant neoplastic incidences were evaluated separately and combined on a per animal basis. The criterion for combination of tumors and preneoplastic changes was based on published literature (McConnell et al., 1986 and Boorman et al. 2003) and determined by the principal investigator for anatomic pathology. Each diagnosed tumor type was analyzed separately in regards to its primary cell of origin. Tumor metastasis and tumor multiplicity was assessed by animal regardless of number of organs affected or number of the same tumor type present in the animal.

Adjustment for multiple testing: One-sided positive dose response relationship in common (background incidence rate > 1%) and rare (background incidence rate < 1%) tumors were evaluated at the 0.005 and 0.025 significance levels, respectively. Pairwise comparisons of high dose group with control in common and rare tumors were evaluated at the 0.01 and 0.05 significance levels. Other intermediate (low and mid dose vs. control), pairwise comparison were evaluated at the 0.05 significance level for both common and rare tumors.

Reviewer's comment: *It should be noted that the above test levels i.e. 0.005 for common and 0.025 for rare tumors for dose response relationships and 0.01 for common and 0.05 for rare tumors for pairwise comparisons are the recommended test levels for the adjustment of multiple testing in long term rat and mouse carcinogenicity studies (FDA guidance for statistical design and analysis of carcinogenicity studies).*

Sponsor's findings: The sponsor's analysis did not show statistically significant dose response relationship or increased incidence of the tested tumor types in any of the treated groups compared to the control. The sponsor concluded that there were no statistically significant increases in tumor incidences in either sex at any dose level of AMG 145.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female hamsters, respectively. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female hamsters, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female hamsters, respectively.

Reviewer's findings: This reviewer's estimate showed 53.33%, 50.00%, 51.67%, and 60.00% mortality of male hamsters in control, low, medium, and high dose groups, respectively and 65.00%, 56.67%, 66.67, and 70.00% mortality of female hamsters in control, low, medium, and high dose groups, respectively. This reviewer's analysis did not show statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the control in either sex.

Reviewer's comment: *The sponsor's analysis showed 66.7%, 60.0%, and 70.0% mortalities in female control, low, and medium dose groups, respectively, while this reviewer's analysis showed 65.00%, 56.67%, and 66.67% mortalities in them. These differences are due to the facts that there was one female hamster in control group (#D04090), two female hamsters in low dose group (#D04164, #D04176), and two female hamsters in medium dose group (#D04236, #D04263) that died naturally during their terminal sacrifice weeks. The sponsor classified these animals as dead, while this reviewer classified them as survivors.*

2.2.2. Tumor data analysis

The tumor data were analyzed for positive dose response relationships and pairwise comparisons of each of the treated groups with control for increased incidence. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a

score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as $N^* = \Sigma s_h$. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size N^* is equal to N (the original group size) if all animals either live up to the end of the study or dies before the terminal sacrifice developing at least one tumor of the type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. Further research showed that the Poly-k test may not be too sensitive on the value of k. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female hamsters, respectively.

As mentioned earlier that all female hamsters were sacrificed on Week 86. Based on the principle of intent to treat (ITT) principle the length of the study was considered 105 weeks. Therefore, animals that were sacrificed on Week 86 got a score of 86/105=0.82. However, to see the implication of considering the female hamster study as a short study of length 86, the data were reanalyzed assuming a study of length 86 weeks. In this case all animals that were sacrificed on Week 86 got a score of 86/86=1.00.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels of α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level of α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For pairwise comparisons of treated group with control the FDA guidance suggests the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's comment: *It should be noted that the above adjustment rules are recommended for rat and mouse studies. Mathematically the rule is based on the number of tumor types generally found in rat and mouse studies. In general this number is over 30 and can go as high as 70/80 per experiment (study/species/sex). The present hamster study showed more than 60 tumor types per experiment. Hence, this reviewer reckons that the above adjustment methods, recommended for rats and mice, are also applicable in the present hamster study.*

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed above, the dose response relationship for none of the observed tumor types was considered to have statistically significant dose response relationship. The pairwise comparisons also did not show statistically significant increased incidences in any of the observed tumor types in any of the treated groups compared to the control. The reanalysis of female hamster tumor data, considering it as a study of length 86 weeks also did not show any statistically significant findings.

3. Evaluation of the validity of design

The tests did not show statistically significant positive dose response relationship or increased incidence in the treated groups compared to their respective control in any of the observed tumor types in either sex. However, before drawing any conclusion regarding the non-carcinogenic or carcinogenic potential of the study drug in hamster, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with about fifty to sixty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field.

Reviewer's comment: *It is important to note that these rules were suggested particularly for long term rat and mouse carcinogenicity studies. Therefore, their application to hamster carcinogenicity studies may not be completely suitable. However, in order to get an understanding, this reviewer applied these rules to evaluate this hamster study.*

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the AMG 145 hamster carcinogenicity study in the light of the above guidelines.

The following is the summary of survival data of hamsters in the high dose group:

Percentage of Survival in the High Dose Group at the End of Weeks 52, 78, and 91 in Hamster

	_____Percentage of Survival_____		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	95%	85%	40%
Female	80%	53%	30%*

***Up to the end of Week 85**

Based on the survival criterion Haseman and Chu et al., it may be concluded that enough male hamsters were exposed to the high dose for a sufficient amount of time. However, according to Haseman's criteria enough female hamsters might not have been exposed to the high dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain from the concurrent control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Controls in Rats

Male			Female		
Low	Medium	High	Low	Medium	High
6.58	9.21	7.89	0.00	-9.72	-3.89

Source: Table 8.5 Summary of Body Weight

Therefore, relative to the control the male hamsters in high dose group had about 8% increment in their body weight gains, while the female hamsters had about 4% decrements in their body weight gains.
The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment in Hamsters

	Control	Low	Medium	High
Male	53.33%	50.00%	51.67%	60.00%
Female	65.00%	56.67%	66.67%	70.00%

The above data show that the morality rates in the high dose group was 6.67% and 5.00% higher in male and female hamsters than their respective controls.

Thus, from the mortality and the body weight gain data it can be concluded that the used high dose level might have reached the MTD in female hamsters. From the mortality data it can be concluded that the used high dose level in male hamsters might have also reached the MTD, however the bodyweight data does not support it. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4. Summary

In this submission the sponsor included a report of an animal carcinogenicity study in hamster. This study was intended to assess the carcinogenic potential of AMG 145 (Evolocumab) in hamster when administered subcutaneously once every 2 weeks at appropriate drug levels for up to 105 weeks.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Design: Two separate experiments were conducted, one in male and one in female hamsters. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:LVG[SYR] Golden Syrian hamsters of each sex were assigned to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 10, 30, and 100 mg/kg. The animals in control group received the placebo article (b) (4).

During the study period female hamster survival across all dose groups (including controls) was lower than males. The surviving females in all treatment groups were terminally sacrificed on Week 86 when the number of surviving females in the control group met the FDA criteria for early termination. The sponsor commented that this observed sex difference was consistent with gender-specific mortality rates reported previously for hamsters in long-term studies and was unrelated to AMG 145. Surviving males continued to be administered vehicle control or AMG 145 up to week 105.

All animals were checked twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were conducted for each animal twice during the predose phase and prior to dosing on Study Day 1 and weekly throughout the dosing phase. Detailed observations were also collected on the days of scheduled euthanasia. Beginning Study Week 12, appearance and

progression of grossly visible or palpable masses were recorded weekly. Body weights were recorded for all animals once during the predose phase, before dosing on Study Day 1, and weekly thereafter.

The tests did not show statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the control in either sex. The tests did not show statistically significant dose response relationship in any of the observed tumor types in either sex. The pairwise comparisons also did not show statistically significant increased incidences in any of the observed tumor types in any of the treated groups compared to the control in either sex.

From the mortality and the body weight gain data it can be concluded that the used high dose level might have reached the MTD in female hamsters. From the mortality data it can be concluded that the used high dose level in male hamsters might have also reached the MTD, however the bodyweight data does not support it. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival BLA 125,522

Dr. Elmore
Ms. Johnson

Dr. Tsong
Dr. Lin
Dr. Rahman
Ms. Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Hamsters

Week	0 mg|kg|day No. of Death	Cum. %	10 mg|kg|day No. of Death	Cum. %	30 mg|kg|day No. of Death	Cum. %	100 mg|kg|day No. of Death	Cum. %
0 - 52	4	6.67	6	10.00	4	6.67	3	5.00
53 - 78	4	13.33	3	15.00	8	20.00	6	15.00
79 - 91	10	30.00	3	20.00	8	33.33	9	30.00
92 - 104	14	53.33	18	50.00	11	51.67	18	60.00
Ter. Sac.	28	46.67	30	50.00	29	48.33	24	40.00
Total	N=60		N=60		N=60		N=60	

Table 1B: Intercurrent Mortality Rate
Female Hamsters

Week	0 mg|kg|day No. of Death	Cum. %	10 mg|kg|day No. of Death	Cum. %	30 mg|kg|day No. of Death	Cum. %	100 mg|kg|day No. of Death	Cum. %
0 - 52	13	21.67	6	10.00	9	15.00	12	20.00
53 - 78	16	48.33	21	45.00	19	46.67	16	46.67
79 - 85	10	65.00	7	56.67	12	66.67	14	70.00
Ter. Sac.	21	35.00	26	43.33	20	33.33	18	30.00
Total	N=60		N=60		N=60		N=69	

Table 2A: Intercurrent Mortality Comparison
Male Hamsters

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.3873
Homogeneity	Log-Rank	0.7769

Table 2B: Intercurrent Mortality Comparison
Female Hamsters

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.3827
Homogeneity	Log-Rank	0.5676

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Hamster

Organ Name	Tumor Name	0 mg Veh C N=60	10 mg Low N=60	30 mg Med N=60	100 mg High N=60	P_Value Dose Resp	P_Value L vs Veh C	P_Value M vs Veh C	P_Value H vs Veh C
Adrenal, Cortex	B-Adenoma, cortical cell	12	12	7	10	0.6251	0.5930	0.8220	0.5511
	B-Adenoma, subcapsular ce	22	18	20	23	0.2525	0.7571	0.5808	0.5000
	M-Carcinoma, cortical cel	0	2	2	1	0.4342	0.2581	0.2418	0.5000
	M-Carcinoma, subcapsular	8	8	6	7	0.5882	0.4102	0.5797	0.5000
Adrenal, Medull	B-Pheochromocytoma	0	2	0	1	0.4344	0.2581	.	0.5000
	M-Malignant pheochromocyt	1	0	1	0	0.6216	0.5106	0.7473	0.5000
Body, Whole/Cav	B-Hemangioma	1	5	4	0	0.9329	0.1118	0.1737	0.5000
	M-Hemangiosarcoma	3	3	0	4	0.2472	0.3487	0.8709	0.4878
	M-Histiocytic Sarcoma	0	0	0	1	0.2486	.	.	0.5000
	M-Lymphosarcoma	6	3	5	1	0.9506	0.7570	0.4695	0.9377
	M-Mast cell tumor	1	0	1	0	0.6216	0.5106	0.7473	0.5000
	M-Plasma cell tumor	3	0	1	0	0.9251	0.8868	0.6834	0.8791
Cecum	M-Carcinoma	0	0	1	0	0.2486	.	0.4945	.
Colon	M-Leiomyosarcoma	0	0	0	1	0.2486	.	.	0.5000
Foot	M-Fibrosarcoma	0	1	0	0	0.4919	0.5106	.	.
Harderian Gland	B-Adenoma	0	1	0	2	0.1106	0.5106	.	0.2527
Liver	B-Adenoma, hepatocellular	4	5	3	6	0.2353	0.5135	0.4754	0.3560
	M-Carcinoma, hepatocellul	1	0	1	1	0.3845	0.5106	0.7473	0.7527
Mesentery	B-Lipoma	0	0	0	1	0.2486	.	.	0.5000
Pancreas	B-Adenoma, islet cell	3	0	2	0	0.8840	0.8868	0.4895	0.8791
	M-Carcinoma, islet cell	0	0	1	0	0.2486	.	0.4945	.
Parathyroid	B-Adenoma	6	12	2	6	0.7243	0.1035	0.8520	0.6053
Penis	M-Carcinoma, squamous cel	0	1	0	0	0.4919	0.5106	.	.
Pituitary	B-Adenoma	1	1	0	1	0.5323	0.2581	0.4945	0.7527
Skin/Subcutis	B-Adenoma, sebaceous	1	0	0	0	0.7514	0.5106	0.4945	0.5000
	B-Basal cell tumor	0	1	0	0	0.4919	0.5106	.	.
	B-Melanoma	0	0	0	1	0.2486	.	.	0.5000
	B-Papilloma, squamous cel	0	0	0	1	0.2486	.	.	0.5000
	M-Fibrosarcoma	1	0	0	0	0.7514	0.5106	0.4945	0.5000
	M-Sarcoma, NOS	0	0	1	0	0.2473	.	0.5000	.
Stomach, Nongla	B-Papilloma, squamous cel	1	0	0	0	0.7514	0.5106	0.4945	0.5000
Subcutaneous In	B-Schwannoma	0	0	0	1	0.2486	.	.	0.5000
Thyroid	B-Adenoma, C-cell	3	3	4	4	0.3279	0.3592	0.5000	0.5000
	B-Adenoma, follicular cel	0	1	0	2	0.1073	0.5106	.	0.2473
	M-Carcinoma, C-cell	2	1	2	0	0.8471	0.5080	0.6750	0.7473

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Hamster

Organ Name	Tumor Name	0 mg Cont N=60	10 mg Low N=60	30 mg Med N=60	100 mg High N=60	P_Value Dose Resp	P_Value L vs Cont	P_Value M vs Cont	P_Value H vs Cont
Adrenal, Cortex	B-Adenoma, cortical cell	19	10	11	9	0.8852	0.9644	0.9220	0.9470
	B-Adenoma, subcapsular ce	12	18	15	11	0.7573	0.3021	0.4857	0.5000
	M-Carcinoma, cortical cel	0	0	1	0	0.2333	.	0.5333	.
	M-Carcinoma, subcapsular	3	0	2	2	0.4214	0.8908	0.5209	0.4782
Adrenal, Medull	B-Pheochromocytoma	3	3	0	0	0.9879	0.3951	0.8833	0.8663
	M-Malignant pheochromocyt	2	0	0	1	0.5198	0.7660	0.7556	0.4829
Body, Whole/Cav	B-Hemangioma	0	0	1	0	0.2360	.	0.5227	.
	M-Hemangiosarcoma	1	2	4	1	0.5875	0.5489	0.2305	0.7558
	M-Lymphosarcoma	2	2	4	0	0.8820	0.3369	0.3951	0.7326
	M-Plasma cell tumor	0	1	0	0	0.4944	0.5333	.	.
Cervix	B-Stromal tumor	0	1	0	0	0.4944	0.5333	.	.
	M-Adenocarcinoma	0	0	0	1	0.2444	.	.	0.5116
	M-Carcinoma	0	0	1	0	0.2333	.	0.5333	.
Harderian Gland	B-Adenoma	0	0	1	0	0.2360	.	0.5227	.
Jejunum	B-Polyp	0	0	1	0	0.2333	.	0.5333	.
Kidney	M-Nephroblastoma	0	1	0	0	0.4944	0.5333	.	.
Liver	B-Adenoma, hepatocellular	2	1	0	0	0.9397	0.5333	0.7667	0.7442
Lymph Node, Oth	M-Sarcoma, NOS	0	1	0	0	0.4889	0.5435	.	.
Mammary Gland,	B-Fibroadenoma	1	0	1	0	0.6183	0.5217	0.2667	0.4884
	M-Carcinoma	2	1	0	2	0.3341	0.5319	0.7556	0.6791
Mandibular Sali	M-Carcinoma	1	0	0	0	0.7556	0.5217	0.5111	0.4884
Ovary	B-Granulosa/theca cell tu	2	3	3	2	0.5299	0.5624	0.5426	0.6965
	B-Thecoma	0	0	1	0	0.2360	.	0.5227	.
	M-Granulosa/theca cell tu	0	0	0	1	0.2444	.	.	0.5116
	M-Leiomyosarcoma	0	0	1	0	0.2333	.	0.5333	.
Pancreas	B-Adenoma, islet cell	0	1	0	1	0.3159	0.5333	.	0.5116
	M-Carcinoma, acinar Cell	0	0	1	0	0.2333	.	0.5333	.
Parathyroid	B-Adenoma	6	8	8	7	0.4625	0.5111	0.4791	0.5345
Pituitary	B-Adenoma	6	10	8	4	0.8530	0.3286	0.4791	0.6093
	M-Carcinoma	0	0	1	1	0.1853	.	0.5333	0.5116
Skin/Subcutis	B-Adenoma, sebaceous	0	0	0	1	0.2444	.	.	0.5116
	B-Fibroma	0	1	0	0	0.4944	0.5333	.	.
	B-Lipoma	1	0	0	2	0.1439	0.5217	0.5111	0.5000
	B-Papilloma, squamous cel	0	0	0	1	0.2444	.	.	0.5116
	M-Liposarcoma	0	0	1	0	0.2333	.	0.5333	.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Hamster

Organ Name	Tumor Name	0 mg Cont N=60	10 mg Low N=60	30 mg Med N=60	100 mg High N=60	P_Value Dose Resp	P_Value L vs Cont	P_Value M vs Cont	P_Value H vs Cont
Stomach, Nongla	B-Papilloma, squamous cel	0	1	0	0	0.4944	0.5333	.	.
Subcutaneous In	B-Lipoma	0	0	0	1	0.2444	.	.	0.5116
	M-Melanoma	0	0	0	1	0.2444	.	.	0.5116
Thyroid	B-Adenoma, C-cell	3	4	2	1	0.8699	0.5713	0.5209	0.6791
	B-Adenoma, follicular cel	2	2	3	3	0.3011	0.3546	0.5426	0.5218
	M-Carcinoma, C-cell	3	0	1	0	0.9248	0.8908	0.7121	0.8663
	M-Carcinoma, follicular c	3	0	1	0	0.9248	0.8908	0.7121	0.8663
Uterus	B-Adenoma	0	0	0	1	0.2444	.	.	0.5116
	B-Papilloma	0	0	0	1	0.2444	.	.	0.5116
	B-Polyp, endometrial stro	0	2	3	1	0.4728	0.2899	0.1515	0.5116
	M-Adenocarcinoma	0	0	0	1	0.2444	.	.	0.5116
	M-Carcinoma, endometrial	0	1	0	0	0.4944	0.5333	.	.
	M-Leiomyosarcoma	0	2	3	0	0.7335	0.2899	0.1426	.
	M-Sarcoma, endometrial st	1	0	0	0	0.7556	0.5217	0.5111	0.4884
Vagina	B-Papilloma, squamous cel	1	3	2	1	0.6358	0.3546	0.5333	0.7558
	M-Adenocarcinoma	0	0	1	1	0.1840	.	0.5227	0.5116

Figure 1A: Kaplan-Meier Survival Functions for Male Hamster

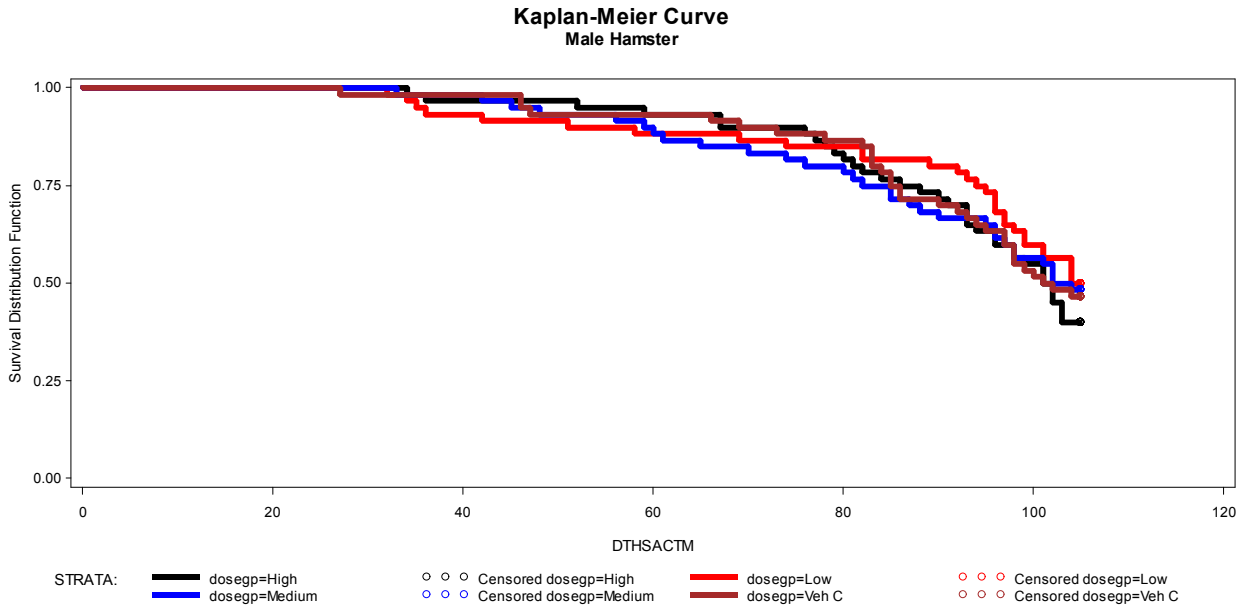
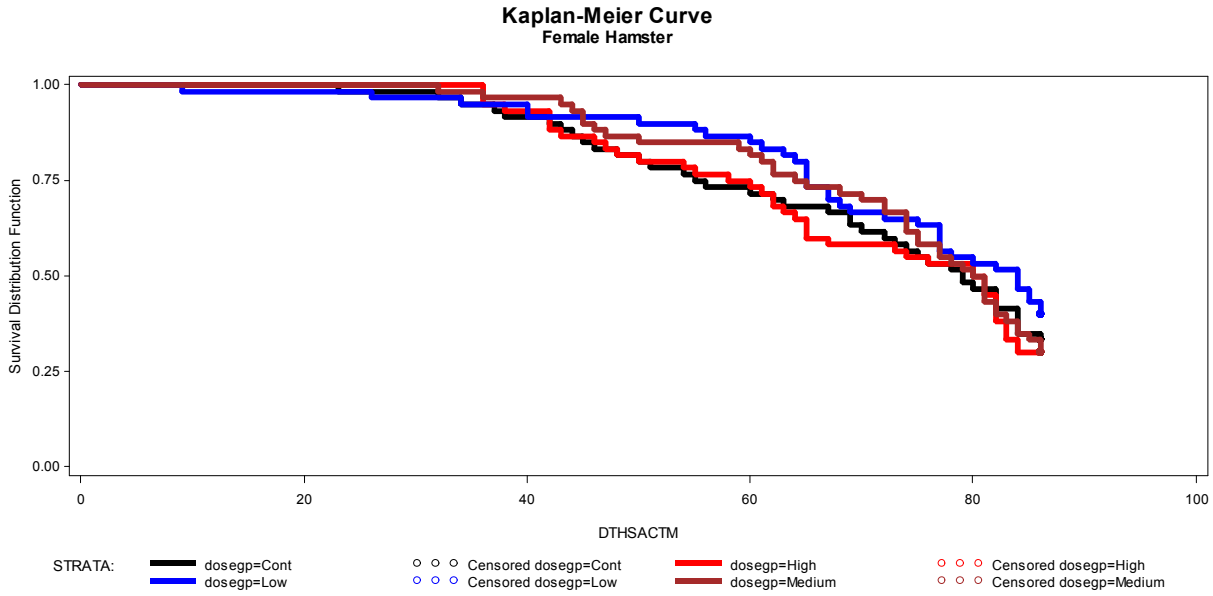


Figure 1B: Kaplan-Meier Survival Functions for Female Hamster



6. References

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/s/

MOHAMMAD A RAHMAN
12/29/2014

KARL K LIN
12/29/2014
Concur with review

STATISTICS FILING CHECKLIST FOR BLA 125522

BLA Number: 125522 **Applicant:** Amgen **Stamp Date:** August 27, 2014

Drug Name: Evolocumab **BLA Type:** NME BLA

On **initial** overview of the BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No formal interim analysis is planned
Appropriate references for novel statistical methodology (if present) are included.			X	No novel statistical methodology is applied
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Sensitivity analyses for missing data are not included in the pivotal studies.

Reference ID: 3642021

STATISTICS FILING CHECKLIST FOR BLA 125522

Brief Summary of Pivotal Studies

Study 20110114, 20110115, 20110116, and 20110117 are pivotal studies to support efficacy of evolocumab for primary hyperlipidemia and mixed dyslipidemia. The co-primary endpoints are mean percent change from baseline at weeks 10 and 12 and percent change from baseline to week 12. Evolocumab 140mg every 2 weeks (Q2W) and 420 mg monthly (QM) are focused in the studies.

Both Study 20110114 and Study 20110115 are double-blind, double-dummy, multicenter, phase III randomized, stratified, placebo and ezetimibe-controlled studies. Study 20110114 is to evaluate the efficacy and safety of 12 weeks of subcutaneous (SC) evolocumab monotherapy in subjects with hyperlipidemia and a 10-year Framingham risk score of 10% or less. Study 20110115 is to evaluate the efficacy, tolerability, and safety of 12 weeks of SC evolocumab in combination with a statin in subjects with primary hypercholesterolemia and mixed dyslipidemia.

Study 20110116 is a double-blind, multicenter, phase III randomized, active-controlled study. The study is to evaluate the efficacy and safety of 12 weeks of SC evolocumab compared with ezetimibe in subjects with hypercholesterolemia and unable to tolerate an effective dose of a statin.

Study 20110117 is a double-blind, multicenter, phase III randomized, stratified, placebo-controlled study. The study is to evaluate safety, tolerability and efficacy of 12 weeks of SC evolocumab with stable stain (with or without ezetimibe) in subjects with heterozygous familial hypercholesterolemia (HeFH).

Both Study 20110233 and study 20110271 are pivotal studies to support efficacy of evolocumab for homozygous familial hypercholesterolemia (HoFH). Study 20110233 is a phase 2/3 study: part A is a phase 2, open-label, multicenter, single arm (420mg QM) pilot HoFH study; part B is a phase 3 randomized, double-blind, multicenter, placebo-controlled study. The primary efficacy for the study is the percent change in LDL-C from baseline to week 12. Study 20110271 is an on-going phase 2/3, multicenter, open-label extension study to assess the long-term safety and tolerability of evolocumab (420mg Q2W or QM) among subjects with severe familial hypercholesterolemia.

Comments to be conveyed to the sponsor for the 74-day letter

The sponsor should provide statistical analysis to study the potential impact of missing data.

Reference ID: 3642021

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHUXIAN Z SINKS
10/09/2014

MARK D ROTHMANN
10/09/2014
I concur