CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125522Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	(electronic stamp)
From	James P. Smith, MD, MS
Subject	Deputy Division Director Summary Review
BLA #	125522
Applicant Name	Amgen Inc.
Date of Submission	27 August 2014
PDUFA Goal Date	27 August 2015
Proprietary Name / Established (USAN) Name	REPATHA / evolocumab
Dosage Forms / Strength	Solution for subcutaneous injection (140 mg/mL); 140 mg single-use pre-filled syringe, and 140 mg single-use pre-filled autoinjector
Indication originally sought by applicant (see page 34 for final)	• Primary Hyperlipidemia and Mixed Dyslipidemia REPATHA is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1: o in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or o alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or o alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. • Homozygous Familial Hypercholesterolemia REPATHA is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).
Recommended Action	*Approval*

Material Reviewed/Consulted	**Primary Reviewers**
Medical Officer Review	Eileen M. Craig, MD
Statistical Review	Shuxian Z. Sinks, PhD
Pharmacology/Toxicology Review	C. Lee Elmore, PhD
Clinical Pharmacology Review	Suryanarayana Sista, PhD & Justin Earp, PhD
OBP CMC Review	Bazzarragchaa Damdinsuren, MD, PhD (drug substance) &

Material Reviewed/Consulted	Primary Reviewers
	Sang Bong Lee, PhD (drug product)
Microbiology Reviews	Michael R. Shanks (drug substance) & Lakshmi Rani Narasimhan, PhD (drug product)
CDRH/ODE Consult (2)	Lana Shiu, MD
OC/CDRH Review	Crystal Lewis
OSI Clinical Inspection Summary	Cynthia Kleppinger, MD
Patient Labeling Review	Sharon W. Williams, MSN, BSN, RN (DMPP) & Ankur Kalola, PharmD (OPDP)
Human Factors/Labeling Review (OSE/DMEPA)	Mishale Mistry, PharmD, MPH
Proprietary Name Memorandum (OSE/DMEPA)	Mishale Mistry, PharmD, MPH
OPDP Labeling Consult	Ankur Kalola, PharmD
OBP Labeling Review	Jibril Abdus-Samad, PharmD
Carton Labeling Review (OSE/DMEPA)	Mishale Mistry, PharmD, MPH
Consult, Controlled Substance Staff	Jovita Randall-Thompson, PhD
Consult, Maternal Health Team	Christos Mastroyannis, MD
OSE/DRISK REMS Review	Joyce Weaver, PharmD

OBP Office of Biotechnology Products; CMC: Chemistry, Manufacturing, and Controls; CDRH: Center for Devices and Radiological Health; ODE: Office of Device Evaluation; OSI: Office of Scientific Investigations; OC: Office of Compliance; DMPP: Division of Medical Policy Programs; OPDP: Office of Prescription Drug Promotion; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; DRISK: Division of Risk Management; REMS: Risk Evaluation and Mitigation Strategy

1. INTRODUCTION

In the present application, the applicant is seeking approval of evolocumab for the following proposed indications:

- Primary Hyperlipidemia and Mixed Dyslipidemia

  REPATHA is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

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

- Homozygous Familial Hypercholesterolemia

  REPATHA is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

This review summarizes the conclusions and regulatory recommendations of the review disciplines assigned to review this application.[1] I am not aware of any disagreements within or between the

[1] This review also serves as a Cross-Disciplinary Team Leader review.

review disciplines regarding final recommendations; all have recommended approval, albeit with substantial modifications to the proposed labeling, including the indicated population.

2. BACKGROUND

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a freely circulating proprotein convertase, which has the ability to bind LDL receptors (LDLR), initiating internalization and lysosomal degradation of the LDLR/PCSK9 complex. Evolocumab is a human IgG2 monoclonal antibody that binds to human PCSK9 with high affinity, ultimately removing it from circulation, leading to an upregulation of LDLR on the surface of cells (especially hepatocytes) with consequent reduction of circulating LDL-C.

The relationship between PCSK9 and LDLR was discovered by Marianne Abifadel and colleagues, who identified gain-of-function mutations in *PCSK9* that cause heterozygous familial hypercholesterolemia (HeFH).[2] Subsequently, the converse was discovered by Cohen and Hobbs: they found that loss-of-function mutations in *PCSK9* were associated with lower levels of LDL-C.[3] These authors also reported that loss-of-function sequence variants appear to reduce the risk of coronary heart disease based on data from the observational ARIC study,[4] making PCSK9 an attractive pharmaceutical target for CV risk reduction via modulation of LDL, since cardiovascular disease remains the leading cause of death in the United States despite available therapies. The first PCSK9 inhibitor was approved in the United States approximately one month ago; Praluent (alirocumab) was approved "as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C."

Dr. Craig comprehensively summarizes the regulatory history of evolocumab in Section 2.5 (pp. 32-41) of her clinical review, so I will not reiterate it here. I will only note that the applicant was informed, as early as the 10 July 2012 end-of-phase 2 (EOP2) discussion, that monotherapy and superiority to ezetimibe/statin claims would likely require cardiovascular outcomes trial (CVOT) data. The Division also did not agree with Amgen's proposed definition of statin-intolerance of failing 1 or more statins, and concerns were expressed with some of the proposed study populations who may not be taking the maximum tolerated dose of statin. The Division expected that placebo-controlled studies would enroll patients who are not at goal despite taking maximally tolerated doses of statin, with or without other lipid-modulating agents. At a 10 April 2014 pre-BLA meeting, the Division reiterated that it would be unlikely that a monotherapy indication or an indication explicitly referencing "statin-intolerant" patients would be approved without positive data from a CVOT, and that the approvability of a PCSK9 inhibitor in the absence of outcomes data would be a topic for discussion with an advisory committee.

3. CMC/DEVICE

CMC

Dr. Bazarragchaa Damdinsuren and Dr. Sang Bong Lee reviewed the data for the drug substance and drug product, respectively, for this BLA. The Office of Biotechnology Products recommends approval

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[2] Abifadel M, et al. *Nature Genetics* 2003;34:154-156.

[3] Cohen J, et al. *Nature Genetics* 2005;37:161-165; and Kotowski IK, et al. *Am J Hum Genet* 2006;78:410-422.

[4] Cohen JC, et al. *N Engl J Med* 2006;354:1264-72.

of evolocumab. I concur that there are no issues related to the drug substance or drug product that would preclude approval.

Drug Substance

Evolocumab is a human monoclonal IgG2 that specifically binds to human PCSK9 with picomolar affinity and prevents its interaction with the LDLR. The epitope targeted by evolocumab spans the interaction domain of PCSK9 with repeat A of the epidermal growth factor homology (EGF-A) domain of the LDLR. The OBP review comprehensively describes the (b) (4)

The OBP review describes the key changes in the process development history. "Process 1" was used in early phase clinical studies as well as the HoFH trials (20110233 and 20110271) and the 52-week double-blind, placebo-controlled trial to support persistence of efficacy and "long-term" safety. Process 1 was also used in open-label extension studies until the availability of Process 2. "Process 2," which is the to-be-marketed product, was used for the other phase 3 trials. Differences between Process 1 and Process 2 are shown in the table below, taken from the OBP review. Dr. Damdinsuren concluded that the process development changes were described sufficiently.

Table 2. Drug Substance Formulation Changes

Parameter	Process 1[a]	Process 2[a]
Drug substance concentration (g/L)	70	140
(b) (4) excipient	(b) (4)	(b) (4) mM proline, (b) mM acetate, pH (b) (4)
Final pH of drug substance		5.0
(b) (4)		-
Polysorbate 80 (% w/v)		0.01

[a] Operational parameter set points are presented

Because the use of Process 1 drug substance contributes substantially to the evaluation of the safety of evolocumab in this BLA, the OBP review carefully reviewed analytical comparability between Process 1 and 2 "with the viewpoint of ensuring that the clinical data supporting safety and efficacy can be pooled." The OBP reviewer did not identify differences that would be expected to influence either safety or efficacy.

Drug Product

The drug product is a sterile, single-use, preservative-free solution for subcutaneous injection that contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab in 220 mM proline (25 mg), 20 mM acetate ((b) (4) mg), 0.01% polysorbate 80 (0.1 mg), pH 5.0. (b) (4) The data supporting the development of the formulation was found to be acceptable. Real-time stability data support the recommended expiry. The post-approval protocol and stability commitment were found to be acceptable.

Facilities Review/Inspection

There was one pre-license inspection at the evolocumab drug substance manufacturing facility (b) (4), which was conducted (b) (4). There was also one pre-license inspection at the evolocumab drug product manufacturing site (Amgen Thousand Oaks), which was conducted 4-22 May 2015. All inspections were ultimately found satisfactory.

Device

CDRH was consulted to review the device constituent part of this combination product, which consists of a pre-filled syringe (PFS) and an auto-injector.

The evolocumab auto-injector is a pre-filled syringe (PFS) presentation that is administered via the functional secondary packaging (auto-injector) that serves as a drug delivery system for the product. The auto-injector (AI)/pen is a single use, disposable, drug product in which the functional secondary packaging components are integrated with the current evolocumab PFS, which is the primary container closure system. The AI/pen is a modified version of the SureClick auto-injector, which is currently approved and marketed for use with Enbrel (BLA 103795; sponsor: Amgen).

The evolocumab AI/pen 1.0 (used in clinical studies and formative human factors studies) and the AI/pen 1.5 (used in summative human factors studies; commercial configuration) were developed on the basis of the existing SureClick AI/Pen, differing by color, (b) (4) and to implement a change from clinical to commercial colors, with the final device identified as AI/pen 1.5.

The CDRH reviewer concluded: "CDRH engineering review of the AI and its associated performance testing on the bench appears to be adequate (dose accuracy (b) (4) mL of drug product delivered under the specified time which is less than 15 sec with a mean time of delivery of (b) (4) sec). AI 1.0 was used during clinical trial and AI 1.5 will [be] the commercially distributed device constituent. They appear to differ in color (b) (4) Although the engineer specifications for the (b) (4) are fine and the performance testing on the bench is also adequate, but the final validation testing is actually in the hands of the users. So I would defer to Human Factors/DMEPA review for the final safety and effectiveness determination."

Human Factors Review

Mishale Mistry (DMEPA) reviewed this BLA from a human factors standpoint. She concluded that "[t]he Human Factors studies for Repatha prefilled syringe and Repatha SureClick autoinjector demonstrated that end users (patients, caregivers, and health care professionals) are able to use the product safely and effectively when used with the availability of formal training and/or training materials (i.e., Instructions for Use)." Recommendations were provided and implemented for proposed labels and labeling to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate confusion, and to clarify information.

Facilities Review/Inspection

The Office of Compliance at CDRH determined that pre-approval inspections were not necessary for this application. Upon review of the information in the BLA, they recommended approval on 13 August 2015 from the standpoint of device compliance.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. C. Lee Elmore reviewed this BLA and recommended approval from a pharmacology/toxicology perspective. See his review for complete details.

The applicant identified the hamster and monkey as pharmacologically relevant species for toxicology testing with evolocumab. Evolocumab was subcutaneously administered to monkeys in a 6-month

chronic toxicity study; this study also included fertility assessments. The tumorigenic potential of evolocumab was assessed in a lifetime hamster carcinogenicity assay. Fertility and early embryonic assessments were conducted in hamsters. Evaluation of evolocumab during the periods of embryofetal and pre/postnatal development was conducted in monkeys. Dr. Elmore notes that overall, the toxicology program was appropriately designed to evaluate the clinical risks associated with chronic administration of evolocumab per Agency guidance. Low incidences of anti-drug antibody production, combined with robust pharmacodynamic reductions in mean plasma cholesterol and other lipid parameters, indicate that anti-drug antibodies did not compromise interpretation of study results. Notably, evolocumab was observed to have similar or greater LDL-C-lowering potency in hamsters and monkeys compared with humans.

Evolocumab was well tolerated by hamsters in a 3-month toxicology study with dosing up to 112- , 48-, and 20-fold compared with the proposed human doses of 140 mg Q2W, 420 mg QM, and 420 mg Q2W, respectively. Evolocumab was also well tolerated by monkeys in toxicology studies of up to 6 months' duration, providing exposure multiples up to 744-, 300-, and 134-fold the aforementioned clinical doses. In a 3-month combination toxicity study with statin, no additive or synergistic toxicity was observed; rosuvastatin was not administered at a dose that caused any statin-related toxicity in monkeys.

Evolocumab was tested in pregnant monkeys during the period of embryofetal development to parturition at doses that provide exposure multiples of 30-, 12-, and 5.(b)(4)fold the aforementioned clinical doses. Offspring were followed to 6 months of infancy. No clear drug-related toxicity was observed in maternal or infant monkeys, but no evaluation of the infant immune system was conducted. As noted in the recently approved labeling for Praluent (alirocumab), suppression of the humoral immune response was observed in infant monkeys when alirocumab was dosed during organogenesis to parturition at dose exposures 13-fold the exposure at the maximum recommended human dose (MRHD). Discussions between the nonclinical review team as well as with the Division of Pediatric and Maternal Health have led to the recommendation that the alirocumab experience be included in labeling for evolocumab, since this potential effect of fetal exposure to a PCSK9 inhibitor may be a class effect. Similar to Praluent, this potential safety signal will be evaluated as a PMR.

I concur with the conclusions reached by Dr. Elmore that there are no outstanding pharm/tox issues that preclude approval.

5. CLINICAL PHARMACOLOGY

Drs. Sury Sista and Justin Earp reviewed this BLA from a clinical pharmacology/pharmacometrics perspective. The Office of Clinical Pharmacology (OCP) recommends approval with the following comments:

> *Primary Hyperlipidemia and Mixed Dyslipidemia: The sponsor's proposed dosing of either 140 mg every two weeks or 420 mg once monthly is acceptable.*
>
> *Homozygous Familial Hypercholesterolemia: The sponsor has proposed two regimens – 420 mg once monthly or 420 mg every two weeks. The 420 mg every two weeks dose appeared to offer little additional benefit (~6% additional reduction in LDL-C). Based on the exposure-response relationship in the Heterozygous familial Hypercholesterolemia population, the exposures from the once monthly dose are already in the plateau of the response curve and dosing higher amounts will not likely provide additional benefit. Further, from a safety perspective, there may be an insufficient amount of data in patients who received 420 mg every two weeks.*

In the discussion that follows, I summarize selected portions of the clinical pharmacology review; see the review of Drs. Sista and Earp for further details.

Key pharmacokinetic and pharmacodynamic properties of evolocumab are summarized in the table below, taken from the OCP review.

As noted previously in this summary review, the drug substance used for phase 1, phase 2, and limited phase 3 studies was manufactured in a manner referred to as Process 1. Drug substance for the majority of the subsequent phase 1 and phase 3 studies used the proposed commercial manufacturing process, referred to as Process 2. Further, Process 1 was administered using vials/syringe whereas Process 2 was administered primarily using the auto-injector, with some use of the pre-filled syringe in a dedicated home-use study. Given these differences, the applicant conducted study 20110167 as a parallel-design PK/PD study to bridge both the process & administration technique. The OCP review notes that the mean serum unbound evolocumab concentration-time and LDL-C-time profiles following SC administration from either vial/syringe (Process 1) or auto-injector (Process 2) were similar.

Table 1 Highlights of Pharmacokinetics

Pharmacokinetics	
Absorption	• Non-linear pharmacokinetics up to 140 mg, and linear pharmacokinetics between 140 mg and 420 mg • Median T_{max} - 3 – 4 days • Estimated absolute bioavailability: 72%. • C_{max}: 18.6 ± 7.3 µg/mL following 140 mg dose; 59.0 ± 17.2 µg/mL following 420 mg dose • AUC_{last}: 188 ± 98.6 day·µg/mL following 140 mg dose; 924 ± 346 day·µg/mL following 420 mg dose • Mean C_{min} at weeks 12, 24, 36, and 52 were stable, and ranged between 8.23 ± 9.05 µg/mL to 10.3 ± 11.2 µg/mL following 420 mg QM over 52 weeks.
Distribution	• Mean (SD) steady-state volume of distribution estimated to be 3.3 ±0.5 L, following a single 420 mg intravenous dose, suggesting evolocumab has limited tissue distribution
Metabolism and Elimination	• Mean systemic clearance estimated to be 12 ± 2 mL/hr • An approximate two- to three-fold accumulation was observed in serum C_{min} (7.21 ± 6.6) following 140 mg doses every 2 weeks or C_{min} (11.2 ± 10.8) following 420 mg doses administered monthly; serum trough concentrations approached steady state by 12 weeks of dosing. • Estimated effective half-life of evolocumab is 11 to 17 days • As a fully human IgG2 antibody, the clearance of evolocumab is mediated by specific binding and complex formation with its target ligand, PCSK9, as well as by typical IgG clearance processes in the reticuloendothelial system. Evolocumab is expected to be degraded into small peptides and amino acids via these catabolic pathways. • An approximately 20% increase in the clearance of evolocumab was observed in patients co-administered with statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9 • Population pharmacokinetic analysis indicated no appreciable differences in evolocumab serum concentrations in hypercholesterolemic patients (non- FH or FH) taking concomitant statins
Pharmacodynamics	
Primary Hyperlipidemia and Mixed Dyslipidemia	• LDL-C reduction of approximately 55% to 75% achieved as early as 1 week Maximal response generally achieved within 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly, respectively, and maintained during long-term therapy
Homozygous Familial Hypercholesterolemia	• Approximately 20% to 30% in patients with HoFH not on apheresis and approximately 15% to 25% in patients with HoFH on apheresis showed reduction of LDL- after 12-week treatment of Evolocumab 420 mg once monthly and 420 mg once every 2 weeks • No overall differences in safety or efficacy of Evolocumab were observed between adolescents and adult patients with HoFH.

Dose selection for phase 3 was supported by results from phase 1 and phase 2 single-dose and multiple-dose studies. Dose-ranging studies in phase 2 evaluated evolocumab dosed as 70 mg, 105 mg, and 140 mg Q2W and 280 mg, 350 mg, and 420 mg QM. For both dosing frequencies, efficacy was the greatest with the highest dose (i.e., 140 mg Q2W and 420 mg QM). The applicant noted that the higher doses were not associated with increased AEs, so they proposed to carry these doses into phase 3.

The OCP review notes that there is a clear exposure-response relationship between evolocumab trough concentrations and LDL-C response at week 10/12 in phase 3 trials 20110114 and 20110115 (see figure below). The shapes of the curves for the two trials appear similar, with the nadirs occurring close to 5 µg/mL. The reviewers note that "[t]his univariate analysis would suggest that increasing the exposures may not decrease LDL-C concentrations further. The Q2W and QM regimens produce concentrations that fall near the nadir of these exposure response relationships, as seen by comparing the peaks of the orange density plots for each dosing regimen in Figure 5."

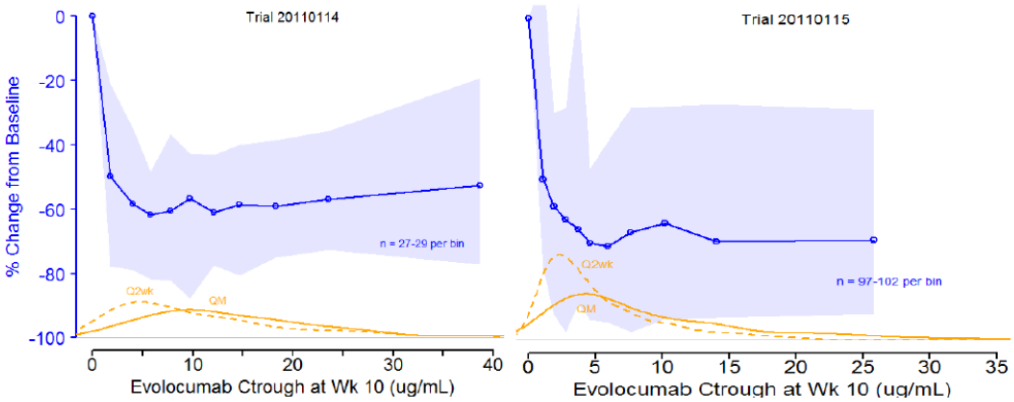


Figure 5. Exposure-response relationships for evolocumab trough concentrations at week 10 and LDL-C change from baseline in studies 20110114 (left panel) and 20110115 (right panel).

(Mean LDL-C and the range of 5th – 95th percentiles at the corresponding median C_{trough} are shown for each of 10 exposure bins in Trial 20110114 and Trial 20110115 by the blue solid lines and shaded region. Solid orange lines depict the distribution of evolocumab C_{trough} with each respective dosing regimen.)

No clinically meaningful correlations between baseline PCSK9, baseline LDL-C, age, sex, race, weight, and statin use were found to influence LDL-C for either evolocumab dosing regimen. Thus, it seems reasonable to offer both regimens as potential options for patients, with the applicant stating that patient preference would be the primary rationale for selecting one regimen over another (i.e., larger volume injections less often vs. smaller volume injections more often).

Indirect exposure-response analysis was considered as a result of a relationship between evolocumab AUC and body weight. There was a 6-7-fold change in evolocumab AUC across body weights of 40-140 kg, or a change of 2-3-fold at either end when compared to the AUC at the median weight. No clinically meaningful relationships between AE rates and body weight were identified.

A thorough QT study was not required given that evolocumab is a monoclonal antibody. ECG information from phase 3 trials did not suggest an effect of evolocumab on the QT/QTc interval.

Since renal impairment is not expected to modify the PK of a monoclonal antibody, a dedicated study to evaluate the PK of evolocumab in such patients was not conducted. Data from 243 patients were pooled from 4 studies for a population PK analysis. Based on MDRD eGFR, there were 95 patients with normal renal function (eGFR ≥90 mL/min/1.73m^2), 131 with mild renal impairment (eGFR 60-89 mL/min/1.73m^2), and 17 with moderate renal impairment (eGFR 30-59 mL/min//1.73m^2). Renal function did not appear to influence the PK of evolocumab.

In a dedicated phase 1 hepatic impairment study, following a single 140 mg subcutaneous dose of evolocumab, subjects with mild and moderate hepatic impairment had least squares mean AUC_{last} values that were 39% and 47% lower, respectively (p=0.090) and least squares mean C_{max} values that were 21% and 34% lower, respectively (p=0.18), compared with the values observed in healthy subjects. No dosage adjustments would need to be made on the basis of mild or moderate hepatic impairment; patients with severe hepatic impairment were not studied.

Study 2012033 evaluated the bioequivalence of 140 mg evolocumab delivered either via a pre-filled syringe or an auto-injector in healthy volunteers. (The auto-injector was used in phase 3 trials.) Evolocumab concentrations, PCSK9 concentrations, and LDL-C were nearly identical between the two administration techniques.

As previously noted, the OCP review notes that the 420 mg Q2W regimen appears to offer little additional benefit compared with the 420 mg QM regimen among patients with HoFH. (b) (4)

Because some patients with extremely high LDL-C may be treated with LDL apheresis (especially those with HoFH), the OCP reviewers considered the extent to which evolocumab may be cleared by LDL apheresis. The data suggest that 30-60 mg of evolocumab (i.e., 8-15% of the dose) may be cleared by the procedure, with a mean post-apheresis concentration of evolocumab that is associated with a full therapeutic effect on PCSK9 suppression. Thus, it appears that there is negligible loss of evolocumab as a result of apheresis; although not addressed by the clinical pharmacology reviewers, it would seem reasonable, therefore, to expect that the 420 mg QM dosing regimen would be an effective option even for patients receiving biweekly apheresis (b) (4)

Taken together, I concur with the conclusions reached by the clinical pharmacology/pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval of the entire application, (b) (4)

6. CLINICAL MICROBIOLOGY

Dr. Michael Shanks reviewed the drug substance and Dr. Lakshmi Narasimhan reviewed the drug product with regard to microbial control and microbiology product quality. Both reviewers have recommended approval from their perspectives. I concur with the conclusions reached by the microbiology reviewers that there are no outstanding microbiology or sterility issues that preclude approval.

7. CLINICAL/STATISTICAL-EFFICACY

Dr. Eileen Craig reviewed the efficacy of evolocumab from a clinical standpoint, and Dr. Shuxian Sinks conducted the statistical review. See their detailed reviews for a full discussion. Dr. Sinks concluded that in each of the six phase 3 pivotal trials that she reviewed, the reductions in LDL-C from baseline were statistically significant at the pre-specified alpha level for evolocumab compared with control. In trials designed to study patients with primary hyperlipidemia or mixed dyslipidemia, estimated

reductions in LDL-C on evolocumab were 55% to 76% greater than those achieved with placebo and 27% to 47% greater than those achieved with ezetimibe; in HoFH, the reduction in LDL-C was 31% greater than placebo. Dr. Sinks notes, however, that whether or not the effects 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. Dr. Craig integrated both benefit and risk considerations from a clinical standpoint, and recommended approval for both HoFH and non-HoFH, with substantial modification to the indication for the latter (i.e., limiting to high-risk patients on maximally tolerated statin therapy, which I will discuss later in this review).

For the non-HoFH population (also referred to as the "primary hyperlipidemia" population), the efficacy of evolocumab was assessed in four double-blind, randomized, placebo- or ezetimibe-controlled, 12-week phase 3 trials and one 52-week placebo-controlled trial. The 12-week trials studied different patient populations and uses: (1) as monotherapy in a population at low CV risk (10-year Framingham risk score ≤10%) (trial 20110114); (2) in combination with statins, with the background statin therapy being randomly assigned as part of the protocol (trial 20110115); (3) in "statin-intolerant" patients (trial 20110116); and (4) in HeFH (trial 20110117). The 52-week trial stabilized patients on one of four background therapies based upon their background CV risk (ATP III risk category) and LDL-C; once background therapy was considered appropriate per protocol, evolocumab or placebo was added for 52 weeks (trial 20110109).

For the HoFH population, efficacy was primarily assessed in a 49-patient, double-blind, randomized, placebo-controlled, 12-week trial (trial 20110233). This trial studied the efficacy and safety of evolocumab 420 mg QM in non-apheresis patients only; the data (b) (4) to support increasing the dose to 420 mg Q2W (for HoFH) (b) (4) derive from the open-label trial 20110271.

The co-primary endpoints for trials '114, '115, '116, and '117 were the mean % change in reflexive LDL-C from baseline to week 12 or to the mean of weeks 10 and 12.[5,6] The primary endpoints for the 52-week trial '109 and the HoFH trial '233 were the mean % change in directly measured LDL-C at weeks 52 and 12, respectively. Secondary endpoints included absolute change from baseline in LDL-C and % change from baseline in several lipid parameters, including non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1 ratio, Lp(a), TG, HDL-C, and VLDL-C.

A table summarizing the study designs for the phase 3 program, excerpted from Dr. Sinks's review, is included below. See Dr. Craig's review for an expanded table that includes both phase 2 and phase 3 trials relevant to the evaluation of both safety and efficacy of evolocumab (Table 3, Section 5.1 of her review). In addition, Dr. Craig compares and contrasts the designs of the four 12-week phase 3 trials (non-HoFH) in Section 6.1.1 of her review, and discusses the design and results of 52-week trial '109 at length in Section 5.3.1.

[5] Reflexive LDL-C = directly measured (ultracentrifugation) LDL-C if calculated LDL-C (Friedewald) <40 mg/dL or if TG >400 mg/dL, otherwise calculated LDL-C.

[6] The applicant contends that the mean of weeks 10 and 12 during a 4-week dosing interval (i.e., weeks 8 to 12) better reflects the time-averaged LDL-C reduction for both the QM and Q2W doses.

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

Across the non-HoFH phase 3 trials, patient demographics and baseline characteristics varied depending on the trial population (e.g., HeFH, a spectrum of CV risk, "statin intolerance"). Overall, the average age across trials was 58 years, with approximately 30% of patients being ≥65 years, and 49% were female, 92% were white, 4% were black, 3% were Asian, and 5% were of Hispanic ethnicity. Sites in North America contributed 40% of patients, with 52% coming from Europe and 8% from Asia Pacific. The regional distribution varied substantially by trial, with the U.S. contributing 50% and 41% of subjects for the monotherapy ('114) and 52-week trial ('109), respectively, but only 6% and 4% of the HeFH ('117) and HoFH ('233) trials. For the HoFH trial, the mean age was 31 years (10 patients ≥13 to <18 years at baseline), 51% were men, and 90% were white.

Overall, in the non-HoFH trials, approximately 33% of patients were taking high-intensity statins per the ACC/AHA definition (atorva 40-80 mg or rosuva 20-40 mg daily), but baseline statin use was heterogeneous across trials because of trial design. No patients were receiving statin therapy at baseline in the monotherapy trial ('114) by design, and the majority (82%) of patients were not receiving a statin at baseline in the "statin-intolerant" trial ('116). In trial '115, patients were randomly assigned to a statin regimen at the beginning of the trial; prior to enrollment, however, 29% had been receiving intensive statin therapy and 30% had not been receiving a statin. In the HeFH trial ('117), the majority of patients (76%) were receiving high-intensity statins at baseline.

Baseline mean LDL-C ranged from 100 mg/dL in the 52-week trial ('109) to 193 mg/dL in the "statin-intolerant" trial ('116) in the non-HoFH populations. For the patients with HoFH in trial '233, baseline mean LDL-C was 349 mg/dL, despite all of these patients being on statins at baseline. Additional demographic and baseline characteristics are summarized in Dr. Craig's and Dr. Sinks's reviews.

Considering the 4 non-HoFH, 12-week phase 3 trials together, 3152 patients were randomized: 1848 to evolocumab (921 evolocumab 140 mg Q2W; 927 evolocumab 420 mg QM), 821 to placebo, and 477 to ezetimibe. Overall, 3026 (96.0%) of patients completed the trial, and 3005 (95.3%) completed investigational product. Trial '109 was intended to support safety and efficacy of evolocumab to one year of exposure. In this trial, 1485 patients entered the lipid stabilization period where a background therapy (diet alone; atorva 10; atorva 80; or atorva 80 + ezetimibe 10) was assigned based on baseline characteristics such as CV risk, LDL-C, and pre-enrollment statin. Of these 1485 patients, 905 (61%) were randomized to evolocumab or placebo (2:1) for the 52-week treatment period; the majority (69%) of the remaining 580 subjects were excluded because of a fasting LDL-C <75 mg/dL at the end of the lipid stabilization period. Of the 905 randomized patients, 901 received at least 1 dose of investigational product, 800 (89%) of whom completed treatment.

Dr. Sinks notes that 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. The applicant's primary analysis (MMRM) assumes that the missing data were missing at random (MAR); however, Dr. Sinks opines that the estimand of interest is the ITT effect (i.e., the difference in LDL-C reduction between treatment arms regardless of adherence to treatment). Since the majority of patients with missing data were no longer on treatment (in contrast to the majority with available data being on treatment), she concluded that the MAR assumption is likely not plausible. Thus, the FDA's approach to handle missing data used different imputation strategies depending on whether the patient with missing data was on or off treatment; see her review for details. Regardless of approach, the results are qualitatively similar (FDA's approach generally attenuates the applicant's treatment effect by 1 to 3 percentage points).

Table 3 and Table 4 in Dr. Sinks's review summarize the results of evolocumab on LDL-C from baseline to week 12 in each arm of each of the four 12-week phase 3 trials in non-HoFH populations. Taken together, based on the applicant's primary analysis, the estimated mean reduction in LDL-C for evolocumab ranged from 55% to 76% compared with placebo (and from 37% to 47% compared with ezetimibe). The effect of evolocumab 140 mg Q2W appears similar to 420 mg QM on LDL-C at week 12 (or at the mean of weeks 10 and 12; see Appendix of statistical review). Figure 1, below, summarizes the primary analysis results of each trial with the treatment arms grouped by evolocumab dosing regimen and comparator.

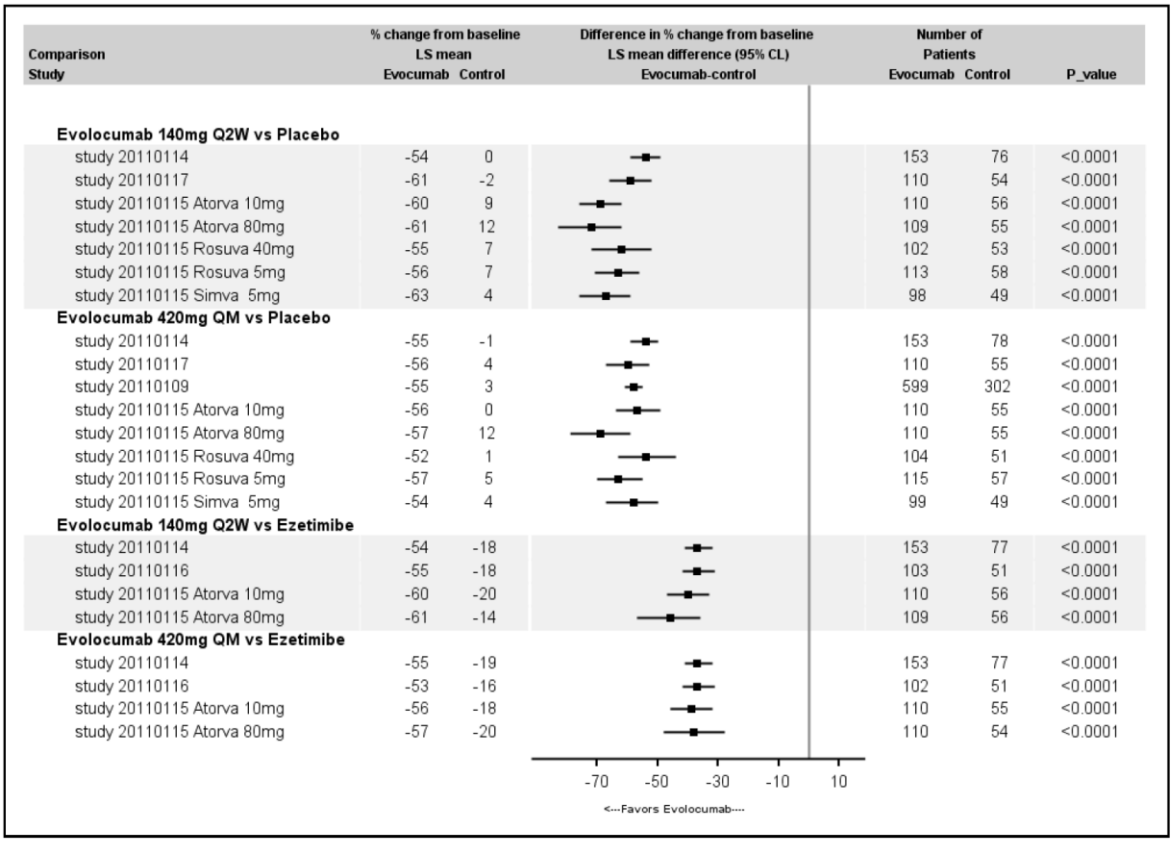
I will note that trial '117 specifically supported efficacy for patients with HeFH[7] on a stable dose of a statin. At week 12, compared with placebo, evolocumab 140 mg Q2W reduced LDL-C by 59% (95% CI, 53% to 65%) and evolocumab 420 mg QM reduced LDL-C by 61% (95% CI, 55% to 69%).[8]

Trial '109 supports a persistent treatment effect of evolocumab 420 mg QM to 52 weeks. According to the applicant's analysis, the treatment difference (evolocumab 420 mg QM vs. placebo) with regard to LDL-C reduction was -58% at week 12 and -57% at week 52.

[7] 78% had "definite" HeFH by Simon Broome Register Group clinical criteria.

[8] This is qualitatively similar to the result observed in phase 2 trial 20090158, which also enrolled patients with HeFH. In that trial, the mean change in LDL-C from baseline to week 12 was -55% for evolocumab 420 mg Q4W (n=56) and +1% for placebo Q4W (n=56), yielding a treatment difference of -56% (95% CI, -64% to -49%), according to the clinical study report (Table 9-1, p. 92).

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



For HoFH, efficacy is primarily supported by the double-blind, placebo-controlled portion of trial '233 (i.e., "part B"). In this trial 50 patients were randomly assigned to evolocumab 420 mg QM (n=33) or placebo (n=17); one patient assigned to placebo did not receive study drug; all 49 patients who received study drug completed the study, and all but 3 continued into the open-label extension trial 2011271 ('271). Overall, according to the applicant's analysis, the mean change in LDL-C from baseline to week 12 was -23% for evolocumab and +8% for placebo, yielding a treatment difference of -31% (95% CI, -44% to -18%). Regarding *LDLR* genotype, only one patient was identified as LDLR-negative (both alleles); this patient did not exhibit LDL-C reduction from baseline. The 28 patients who were considered LDLR-defective in one or both alleles appeared to have a larger treatment effect than those who were LDLR-indeterminate or LDLR-negative, as summarized in Table 8 from Dr. Sinks's review, shown below. This is biologically consistent with the mechanism of action of PCSK9 inhibition; given that PCSK9 inhibition upregulates LDLR, those HoFH patients with mutations yielding greater LDLR dysfunction would be expected to have less of a response to drug. Since statins also upregulate LDLR, I would not be surprised if HoFH patients who are observed to have a greater response to statins would be the same patients who would be expected to have a greater response to PCSK9 inhibition, but the applicant has not provided data in this regard. Conversely, I would not expect a patient to respond robustly to a PCSK9 inhibitor who had already failed to respond to a statin (e.g., LDLR-negative patients). Taken together, it is likely that the mean treatment effect among patients with HoFH is highly dependent on the mix of *LDLR* mutations, and their functional consequence, in any given sample of patients. In practice, since LDL-C is routinely measured, clinicians will quickly have a sense with regard to their patients' responses to therapy.

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

	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)
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

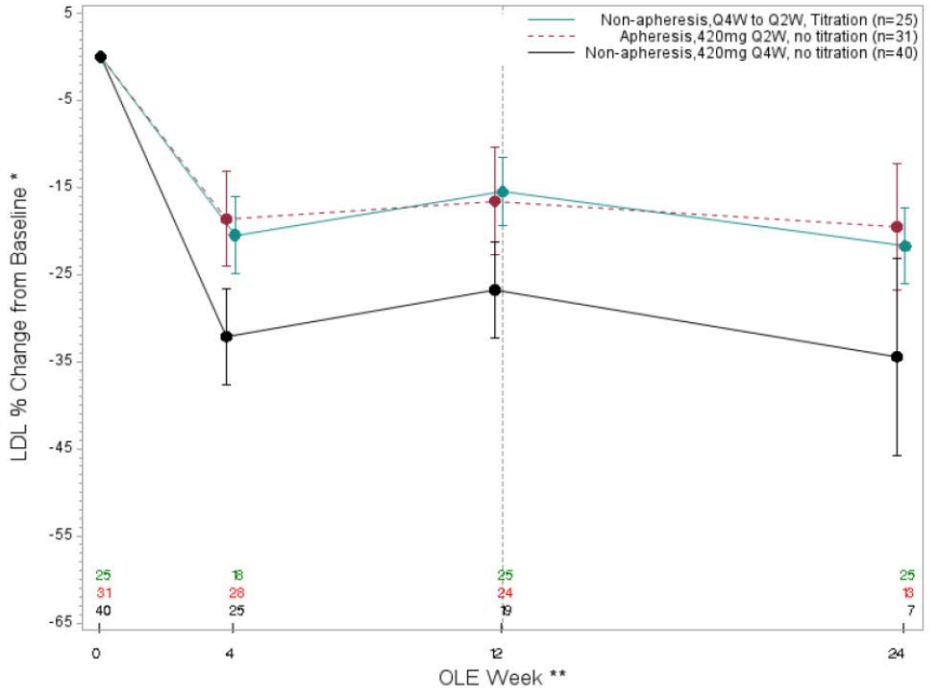
The applicant also proposed the use of evolocumab 420 mg Q2W in the HoFH population, either as an option for uptitration from 420 mg QM or as an alternative starting dosage for patients on apheresis "to correspond with their apheresis schedule." The data supporting this dosage are extremely limited; it was only evaluated in trial 20110271 ('271), an ongoing phase 2/3, open-label extension trial comprising patients with FH (including, but not limited to, HoFH). As of the 01 April 2014 data cutoff, 96 patients with HoFH had received at least 1 dose of evolocumab in this trial. Two groups of patients received the evolocumab 420 mg Q2W dosage at some point: (1) non-apheresis participants who began the study on 420 mg QM and could be uptitrated to 420 mg Q2W at week 12, essentially at investigator discretion;[9] and (2) apheresis participants who began with 420 mg Q2W. Dr. Sinks notes that the trend over time among 25 patients who titrated from 420 mg QM to 420 mg Q2W at week 12 suggests a slightly greater mean LDL-C reduction at week 24 than week 12, but (b) (4) [redacted]. The pharmacometric review states, "There was a mild numerical lowering (6%) in the mean LDL-C concentrations in patients who up-titrated…. At the individual level there was a sustaining of effect, but not much improvement. Further, exposure-response data were not available in the HoFH

[9] As part of a 16 March 2015 response to a clinical information request, the applicant states, "Per the study protocol, (b) (4) [redacted] (emphasis added).

populations. However, the relationship in the HeFH population suggests that the exposures from the QM dose are already in the plateau of the response curve and that dosing higher amounts will not likely provide additional benefit."

Regarding use of evolocumab as an adjunct to apheresis, the 13 apheresis patients with data at week 24 had LDL-C values that were 20% lower at week 24 than their baseline. (b) (4)

(b) (4)



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

(b) (4)

Multiple secondary endpoints (primarily, hypotheses related to lipid parameters other than LDL-C at various timepoints) were analyzed across trials. Drs. Craig and Sinks discuss these results in their reviews, and I will not repeat them here. Not surprisingly, given the drug's mechanism of action and its effect on LDL-C, evolocumab reduced total cholesterol, non-HDL-C, and Apo B. Evolocumab also led to statistically significant mean reductions in Lp(a) of approximately 25-30%, compared with

placebo. Although epidemiological studies suggest that Lp(a) levels are independently associated with atherosclerotic disease, it is unclear if modifying Lp(a), per se, with evolocumab would reduce cardiovascular risk among patients with well-controlled LDL-C but elevated Lp(a). Dr. Craig also notes that it is unclear whether the modest changes in TG and HDL-C observed are clinically meaningful.

Drs. Craig and Sinks both evaluated results from the analysis of the primary efficacy endpoint across multiple subgroups (e.g., age, sex, race, region, diabetes status, statin use or intensity) in individual trials and in an integrated pool of the phase 3 12-week trials. Taken together, there is no evidence of any qualitative interactions; i.e., evolocumab appears to lower LDL-C in all subgroups evaluated.

Last, I will note that the effect of evolocumab on cardiovascular outcomes has not been determined since far too few major adverse cardiovascular events occurred in this program to provide a reliable assessment of this effect. See Dr. Craig's review for further details (Section 7.3.4).

8. SAFETY

Dr. Eileen Craig reviewed the safety of evolocumab. Unless otherwise noted, the discussions that follow only include the non-HoFH population; the latter will be discussed briefly at the end of this section.

To support an indication in the non-HoFH population, the applicant crudely pooled 12 phase 2 and phase 3 trials of varying patient populations, control groups, allocation ratios, trial durations, and formulations (Process 1 [phase 2] and Process 2 [phase 3 and trial '109]). This "Integrated Parent Analysis Set (IPAS)" comprised 6026 patients: 3946 who received any dose of evolocumab (3201 at to-be-marketed doses) and 2080 who received "any control" (placebo or ezetimibe). Eight of the trials were 12 weeks in duration, with similar (although not identical) patient populations and study designs in the four phase 2 and four phase 3 trials: monotherapy in low CV risk (20101154 and trial '114), combination with statins (20101155 and trial '115), "statin intolerance" (20090159 and trial '116), and HeFH (20090158 and trial '117). In addition, a 12-week, randomized, double-blind, placebo-controlled phase 2 trial in Japanese subjects was included (20110231). Other than these nine 12-week controlled trials, the pool also included the 52-week trial '109 as well as two device home-use studies (20120348, which included a 4-week treatment period; and 20120356, which included a 12-week treatment period). The phase 2 trials used equal allocation and the phase 3 trials generally employed 2:1 allocation. Taken together, 73.5% of patients in this pool were from the combination therapy trials, 18.8% from the monotherapy (low CV risk) trials, and 7.7% from the statin-intolerant trials.

Dr. Craig notes several limitations to the applicant's chosen pooling strategy. She notes that combining the 52-week trial with the rest of the short-term trials is suboptimal, especially since the applicant focuses on subject incidence (and not incidence rate); she reviewed the 52-week trial separately and requested that this trial be removed from the above pool (summarized in Appendix 9.5 of her review). In addition, she notes that the ezetimibe-controlled "statin-intolerant" trials had higher AE rates, regardless of treatment assignment (evolocumab or ezetimibe); therefore, patients from these trials are included in the combined evolocumab groups but *not* in the combined placebo groups, potentially biasing against evolocumab if only comparing to placebo. The applicant attempts to address this by offering "Any Control" as another comparator, but note that this group includes *both* placebo- and ezetimibe-treated patients. Sometimes "ezetimibe" is presented as a separate control group, but this includes two disparate populations: low CV risk (Framingham risk score ≤10%) + "statin-intolerant" patients, the latter being much higher risk with more comorbidity, making this group difficult to interpret. Finally, crude pooling of trials with varying allocation ratios can also lead to confounding by trial (i.e., Simpson's paradox). As part of a 16 December 2014 response to a 06 November 2014

information request, the applicant provided additional AE tables that examined the 12-week phase 2 and phase 3 trials separately, including stratified risk differences by trial. In the same response, the applicant provided AE tables grouped by each of the four patient populations described in the previous paragraph. The general safety profile was rather consistent using these various approaches; therefore, I will limit my description here to the applicant's pre-specified approach, despite its limitations.

Patients who completed one of the phase 2 or phase 3 parent trials were eligible to enroll into open-label extension study 20110110 (OLE '110) or 20120138 (OLE '138), respectively. Upon entering an OLE, patients were *re-randomized* 2:1 to either evolocumab or standard of care (SoC) for the first year. In OLE '110, only evolocumab 420 mg QM was used (Process 1 via vials/syringe initially, switched to Process 2 via auto-injector when available at each site); in OLE '138, patients randomly assigned to evolocumab could select between the 140 mg Q2W and 420 mg QM regimens. The data cutoff for these trials was 01 April 2014 for the BLA submission; both trials are ongoing. Collectively, the Year 1 SoC-Controlled period included 4252 patients: 2833 treated with evolocumab + SoC and 1419 treated with SoC alone during the first year of the OLE.

Following the first year of the OLE, all patients who had been assigned to SoC were switched to evolocumab. Combining the OLE studies, 954 patients were included in this "Year 2+" pool.

Overall, the phase 2/3 program (excluding HoFH trial '233 and OLE '271) included a total of 4783 patients exposed to to-be-marketed doses of evolocumab as of 01 April 2014, including 3276 for at least 6 months and 1760 for at least 12 months. As noted previously, however, the majority of this exposure occurred in open-label studies. The only 52-week, placebo-controlled trial ('109) included 599 patients exposed to evolocumab. OLE studies are subject to bias with regard to AE reporting, and only patients who tolerate study drug (evolocumab or control) during the parent trial are likely to enroll in an extension study.[10] In addition, note that the applicant treated the parent trial period, year 1 of the OLE (SoC-controlled period), and year 2+ of the OLE as three distinct phases when reporting AE incidences, etc. Thus, an event reported in the year 2+ pool is conditional on the patient remaining on study through year 1 and proceeding into year 2. In addition, patients in the year 2+ pool could have quite heterogeneous exposures to evolocumab, since some would be treatment-naïve (on placebo during the parent trial and SoC during year 1 of the OLE), and others would have already been exposed for up to 2 years (i.e., evolocumab-treated patients in '109 who are then randomized to evolocumab during year 1 of the OLE) at the time that they begin contributing time-at-risk to the year 2+ pool. Thus, I consider the OLE safety data from these studies to serve primarily as a screen for serious and infrequent adverse events; (b) (4)

As shown in Table 48 in Dr. Craig's review, the median exposure to study drug was 2.8 months in the pool of parent trials (although exposure for the QM regimen was skewed by the inclusion of '109, with a mean exposure of approximately 5 months). Because the OLE studies were ongoing, AE incidences in the "Year 1 SoC-controlled" cohort do not reflect one-year exposure; in fact, the median exposure *during this period* was 7.3 months at the time of the original data cutoff. For the patients who progressed into year 2 of the OLE, the median exposure from OLE year 2 onward was 12.9 months.

[10] In phase 2, 79% of patients treated with study drug during a parent trial were randomized in OLE '110 (range, 71% to 88% across parent trials). In phase 3, 72% of patients treated with study drug during a parent trial (including the device home-use studies and '109) were randomized in OLE '138 (range, 62% to 89%). In both phase 2 and 3, patients in the HeFH trials were most likely to continue into the OLE.

Dr. Craig noted similar incidences of AEs, SAEs, and AEs leading to discontinuation between evolocumab 420 mg QM and 140 mg Q2W; therefore, in this summary review, I will only present data for "evolocumab," referencing the pool of to-be-marketed doses.

Deaths, SAEs, AEs Leading to Discontinuation

The overall safety findings are shown in the following tables from Dr. Craig's review, which show both the pooled results from the parent trials as well as the trial-level summaries from the pivotal phase 3 trials. Overall, the proportions of patients who experienced any AE, SAE, or AE leading to treatment discontinuation were very similar between the evolocumab and control groups.

Table 66: Summary of Subject Incidence of Adverse Events During the Parent Studies by Combined Treatment Groups (Integrated Parent Analysis Set)

	Any Placebo (N = 1526) n (%)	**Any Control (N = 2080) n (%)**	**EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)**	**Any EvoMab (N = 3946) n (%)**
Adverse Events*	753 (49.3)	1031 (49.6)	1599 (50.0)	2016 (51.1)
Grade ≥ 2	367 (24.0)	487 (23.4)	713 (22.3)	878 (22.3)
Grade ≥ 3	54 (3.5)	66 (3.2)	125 (3.9)	147 (3.7)
Grade ≥ 4	6 (0.4)	6 (0.3)	20 (0.6)	24 (0.6)
SAEs	36 (2.4)	43 (2.1)	95 (3.0)	110 (2.8)
AEs that led to D/C of IP	24 (1.6)	48 (2.3)	71 (2.2)	75 (1.9)
Serious	4 (0.3)	4 (0.2)	16 (0.5)	16 (0.4)
Non-serious	21 (1.4)	45 (2.2)	59 (1.8)	63 (1.6)
Fatal AEs	1 (0.1)	1 (<0.1)	3 (0.1)	3 (0.1)

*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117,
20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab (AMG 145).
IP=investigational product
Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects.
Any EvoMab includes any subject with EvoMab as a component of investigational product.
Coded using MedDRA version 17.0.
Source: modified from ISS Table 14-6.1.2.

Table 64: Summary of Subject Incidence of Adverse Events in the Phase 3 Trials

	20110114 (Monotherapy)			**20110115 (Statin Combination)**			**20110116 (Statin-Intolerant)**		**20110117 (HeFH)**		**20110109**	
	12 week (N = 614)			12 week (N = 1896)			12 week (N=307)		12 week (N=329)		52 week (N=601)	
	Pbo	Eze.	EvoMab	Pbo	Eze	EvoMab	Eze	EvoMab	Pbo	EvoMab	Pbo	EvoMab
	N=154	N=154	N=306	N=558	N=221	N=1117	N=102	N=205	N=109	N=220	N=302	N=599
AEs*, %	44	46	44	39	40	36	73	66	49	56	74	75
SAEs, %	<1	<1	1	2	<1	2	4	3	5	3	4	6
AEs that led to D/C of IP, %	4	3	2	2	2	2	13	8	0	0	1	2
Fatal AEs, %	0	0	0	<1	0	0	0	0	0	0	0	<1

	20110114 (Monotherapy)	20110115 (Statin Combination)	20110116 (Statin-Intolerant)	20110117 (HeFH)	20110109
	12 week (N = 614)	12 week (N = 1896)	12 week (N=307)	12 week (N=329)	52 week (N=601)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab; Eze=ezetimibe; IP=investigational product
*These are treatment emergent adverse events which are adverse events occurring between the first dose of Investigational Product and End of Study.
Source: modified from CSR 20110114: Table 12-1; CSR 20110115: Tables 14-6.1.1., 14-6.1.3., 14-6.1.2.; CSR 20110116: Table 12-1.; CSR 20110117: Table 12-1.

There were 15 deaths reported in the clinical program. Four deaths occurred during the parent trials (1 [0.05%] of 2080 control vs. 3 [0.08%] of 3946 evolocumab), seven during year 1 of the OLEs (4 [0.3%] SoC vs. 3 [0.1%] evolocumab), 2 deaths occurred during year 2+ of the OLEs, and 2 occurred after the end of study. Eleven of the deaths were adjudicated to be cardiovascular in nature. Dr. Craig reviewed the narratives of evolocumab-treated patients who died and did not find any that strongly suggested a causal relationship between evolocumab and the fatal event.

In the parent trials, nonfatal SAEs were reported by 95 (3.0%) patients treated with evolocumab Q2W/QM, 36 (2.4%) treated with placebo, and 43 (2.1%) treated with any control (i.e., placebo or ezetimibe). The most common SAEs were myocardial infarction (0.1% and 0% for evolocumab and control, respectively), angina pectoris (0.1% for both groups), and pneumonia (0.1% vs. 0%). Dr. Craig notes that although the numbers were small, there were numerically more SAEs in evolocumab-treated patients for cardiac disorders, pancreatitis, appendicitis, pneumonia, and back pain.

Regarding AEs leading to discontinuation of study drug, the overall incidence of such events was slightly higher for evolocumab than placebo for both dosing frequencies (Q2W: 2.3% vs. 1.7%; QM: 2.1% vs. 1.5%). Once again, both the incidence and risk differences for AEs leading to discontinuation were extremely small. Comparing evolocumab to any control, Dr. Craig notes numerically higher incidences for evolocumab for cardiac disorders (4 [0.1%] events vs. 1 [<0.1%] event), CPK increased (4 [0.1%] vs. 1 [<0.1%]), and nausea (6 [0.2%] vs. 3 [0.1%]).

Selected AEs of Interest

Dr. Craig comprehensively reviews the safety data related to multiple potential adverse consequences of the drug; see her review for full details.

Hypersensitivity & Injection Site Reactions

The incidence of potential hypersensitivity events, identified with the Hypersensitivity SMQ, was modestly higher among patients treated with evolocumab than placebo (or any control). Using the narrow SMQ, the incidence was 3.2% for evolocumab, 2.4% for placebo, and 2.4% for any control in the parent trials. Using the broad SMQ, the incidence was 5.0% for evolocumab, 4.7% for placebo, and 4.7% for any control. During the clinical program, including the OLE trials, Dr. Craig notes that five patients – all treated with evolocumab – reported AEs of angioedema; review of the narratives shows that evolocumab cannot clearly be implicated as the cases have several confounding features. One case of an anaphylactic reaction has been reported, but it was temporally related to an intravenous bolus of penicillin; evolocumab was continued without further incident.

The incidence of injection site reactions was low and similar between treatment groups in the parent trials; the incidence was 3.3% for evolocumab and 3.0% for any control. During the OLEs, the incidence of injection site reactions among evolocumab-treated patients was 3.7% during year 1 and 3.1% from year 2 onward. The most common adverse reactions related to the injection site were erythema, pain,

and bruising. Nine patients discontinued evolocumab as a result of injection site reactions (5 with recurring events, 4 with single events).

Neurocognitive Events

Because the etiology of the rare post-marketing reports of cognitive impairment associated with statin use (class safety labeling change in 2012) remains uncertain, the potential for PCSK9 inhibitors to have neurocognitive effects has been a focus of attention. Notably, evolocumab should not cross the blood-brain barrier (unless the barrier is otherwise compromised, perhaps). In addition, cognitive symptoms are not a feature of patients with genetic disorders such as hypobetalipoproteinemia and have not been described in the few published case reports of individuals homozygous (or compound heterozygous) for loss-of-function *PCSK9* mutations.

A search for neurocognitive-related adverse event terms was performed using the MedDRA HLGTs *Deliria (including confusion), Cognitive and attention disorders and disturbances, Dementia and amnestic conditions, Disturbances in thinking and perception, and Mental impairment disorders.* In the parent trials, 11 patients reported such events: 6 (0.3%) in control groups and 5 (0.1%) in evolocumab groups. Of course, the exposure duration was quite short for all but one of these trials, likely limiting their usefulness to describe the incidence of an event that may depend on exposure duration. In year 1 of the OLE (which, as noted previously, had a median exposure duration of ~7 months), events in these categories were reported by 16 (0.6%) patients treated with evolocumab and 3 (0.2%) treated with SoC. Dr. Craig explored for a potential relationship between low LDL-C and these events, and there is currently no compelling evidence to suggest that very low LDL-C levels promote neurocognitive events. In addition, her review of many of these case narratives showed that many were confounded by other conditions/comorbidities or medications that could also affect cognitive function.

Table 84: Adverse Events Related to Neurocognitive Function during the Parent Studies by High Level Group Term and Preferred Term (IPAS)

High Level Group Term Preferred Term	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)	Any EvoMab (N = 3946) n (%)
Number of subjects reporting adverse events	3 (0.2)	6 (0.3)	5 (0.2)	5 (0.1)
Deliria (incl confusion)	1 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Delirium	0	0	1 (0.0)	1 (0.0)
Disorientation	1 (0.1)	2 (0.1)	1 (0.0)	1 (0.0)
Mental impairment disorders	2 (0.1)	4 (0.2)	3 (0.1)	3 (0.1)
Amnesia	0	0	2 (0.1)	2 (0.1)
Memory Impairment	1 (0.1)	1 (0.0)	1 (0.0)	1 (0.0)
Cognitive Disorder	0	1 (0.0)	0	0
Dementia With Lewy Bodies	1 (0.1)	1 (0.0)	0	0
Disturbance In Attention	0	1 (0.0)	0	0

Table 85: Adverse Events Using HLGT Related to Cognitive Function During the Extension Studies SoC-Controlled Period by High Level Group Term and Preferred Term (IECAS)

	Control in Parent Study		EvoMab in Parent Study		All	
High Level Group Term Preferred Term	SoC (N = 472) n (%)	EvoMab + SoC (N = 943) n (%)	SoC (N = 947) n (%)	EvoMab + SoC (N = 1890) n (%)	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)
Number of subjects reporting adverse events	1 (0.2)	3 (0.3)	2 (0.2)	13 (0.7)	3 (0.2)	16 (0.6)
Deliria (incl confusion)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)
Confusional State	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Disorientation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Mental impairment disorders	1 (0.2)	2 (0.2)	2 (0.2)	12 (0.6)	3 (0.2)	14 (0.5)
Memory Impairment	1 (0.2)	2 (0.2)	1 (0.1)	5 (0.3)	2 (0.1)	7 (0.2)
Amnesia	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)
Dementia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Mental Impairment	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Dementia Alzheimer's Type	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)

Because neurocognitive function/events were not prospectively assessed and queried, however, it is possible that underreporting may have occurred. Dr. Craig recommends a randomized, controlled, long-term trial that prospectively evaluates changes changes in neurocognitive function as a post-marketing requirement. I concur with her recommendation.

I note that the ongoing CVOT has included a substudy to better explore effects of evolocumab on neurocognition prospectively, and given the concern about this potential safety risk and the limitations of the current safety database, we will incorporate this into a post-marketing requirement.

Diabetes

Dr. Craig reviewed whether evolocumab may have an adverse effect on glycemic control. Since 2012, labeling for statins (except for pravastatin) note that increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, based on evidence from clinical trials and epidemiologic data. Some have suggested that upregulation of LDLR on the pancreatic beta cell may adversely impact its function, thereby worsening glycemic control.[11]

Evaluation of median changes from baseline in both plasma glucose and HbA1c in the integrated parent trials did not show consistent, meaningful changes over time. Furthermore, such measures of central tendency did not reveal a signal when examined across baseline status of glucose control (normoglycemia and/or impaired fasting glucose at baseline among non-diabetic subjects). Of course, in the parent trials, the vast majority of patients only contributed 12 weeks of data given the trial durations. Comparing changes in central tendency over time in year 1 of the OLE (SoC-controlled period) did not reveal a convincing signal, either.[12]

Dr. Craig also reviewed the incidence of new-onset diabetes (defined using a combination of data from AEs, concomitant medications, and laboratories). In the parent trials, among patients with impaired fasting glucose (IFG) at baseline (i.e., FBG 100 to <126 mg/dL), the incidence of post-baseline new-onset diabetes was 3.1% for evolocumab, 2.6% for placebo, and 1.9% for any control. (When "any post-

[11] Besseling J, et al. *JAMA* 2015;313:1029-36.

[12] See 16 March 2015 response to clinical information requests, BLA 125522 (SD 30).

baseline HbA1c ≥6.5%" was added to the composite to define a new-onset diabetes event, the incidences were 4.5% for evolocumab, 5.4% for placebo, and 4.1% for any control.) Among those with baseline normoglycemia, an increase in new-onset diabetes incidence was not observed with evolocumab regardless of definition. Similarly, in year 1 of the OLE, the incidence of new-onset diabetes was higher in the evolocumab group compared with the SoC group (3.3% vs. 2.4% or 6.3% vs. 5.2% for the two definitions) among those with IFG at baseline of the parent trial but not among those with normoglycemia at baseline.

Dr. Craig concludes, "A potential signal for new onset diabetes with evolocumab use, particularly with subjects with baseline impaired fasting glucose, is possible from these analyses. This potential for an increased incidence of new onset diabetes should be explored in the on-going CVOT (FOURIER). Of note, with statins, we believe that the modest diabetogenic effect is outweighed by the CV event reduction, which has been shown in CV outcomes trials in patients with diabetes." At this time, I agree that this is a *potential* signal, but we do not have sufficient data to conclude that evolocumab has an adverse effect on glycemic control. It took years (and large randomized controlled trials, notably JUPITER) for this effect to be appreciated with statins, however; therefore, we must remain vigilant and continue to assess this prospectively. I support the recommendation to evaluate this further as a post-marketing requirement.

Liver-related Safety

Dr. Craig reviewed liver-related safety using both adverse event data as well as laboratory data. In the integrated parent trials, AEs in the Hepatobiliary Disorders SOC were reported for 13 (0.3%) patients treated with evolocumab and 9 (0.4%) treated with any control. SAEs in this SOC were reported for 4 (0.1%) patients treated with evolocumab (preferred terms: cholecystitis, cholelithiasis, and biliary tract disorder) and 2 (0.1%) patients treated with any control. In year 1 of the OLE, 15 (0.5%) and 8 (0.6%) of patients treated with evolocumab and SoC, respectively, had an AE in this SOC. Three evolocumab-treated patients had a liver-related SAE during this period (preferred terms: cholelithiasis, hepatic function abnormal, and hepatotoxicity); Dr. Craig reviewed these narratives and found them unlikely the result of evolocumab. Searches using both broad and narrow SMQs for liver-related disorders showed similar incidences of events between evolocumab and control groups.

In the integrated parent trials, 5 (0.2%) patients treated with evolocumab and 7 (0.3%) treated with either control had ALT or AST >5xULN at any postbaseline visit (see table below from Dr. Craig's review). No patient in the parent trials had both ALT or AST >3xULN + total bilirubin >2xULN (or INR >1.5) at any study visit. Three (0.1%) patients in the evolocumab group met this criterion during year 1 of the OLE, one of which had an elevated INR secondary to warfarin and another occurred a few days after the patient admitted himself for alcohol detoxification. The last case involved a patient being treated for a UTI with nitofurantoin and was also on simvastatin; a liver biopsy was consistent with drug-induced hepatitis. The elevated transaminases eventually normalized after suspending nitrofurantoin, evolocumab, simvastatin, and other medications. There have been no cases of hepatic failure.

Table 75: Participant Incidence of Liver Related Test Abnormality (Integrated Parent Analysis Set)

	CONTROL			EVOLOCUMAB				TOTAL	
	Pbo Q2W (N= 586) n (%)	Pbo QM (N =940) n (%)	Eze. (N = 554) n (%)	Other EvoMab dose (N = 715) n (%)	140 mg Q2W (N =1245) n (%)	420 mg QM (N =1956) n (%)	420 mg QM+Eze. (N = 30) n (%)	Any Control (N=2080) n (%)	EvoMab 140 Q2W or 420 mg QM (N = 3201) n (%)
Baseline									
ALT or AST > 3 x ULN	3 (0.5)	3 (0.3)	5 (0.9)	1 (0.1)	1 (0.1)	3 (0.2)	0	11 (0.5)	4 (0.1)
ALT or AST > 5 x ULN	3 (0.5)	1 (0.1)	1 (0.2)	0	0	1 (0.1)	0	5 (0.2)	1 (0.0)
Total bilirubin > 2 x ULN	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	1 (0.0)	2 (0.1)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR>1.5)	0	0	0	0	0	0	0	0	0
Any Postbaseline Visit	579	928	548	712	1227	1924	30	2055	3151
ALT or AST > 3 x ULN	6 (1.0)	9 (1.0)	5 (0.9)	4 (0.6)	5 (0.4)	8 (0.4)	0	20 (1.0)	13 (0.4)
ALT or AST > 5 x ULN	3 (0.5)	4 (0.4)	0	1 (0.1)	1 (0.1)	4 (0.2)	0	7 (0.3)	5 (0.2)
Total bilirubin > 2 x ULN	0	2 (0.2)	1 (0.2)	1 (0.1)	0	5 (0.3)	0	3 (0.1)	5 (0.2)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR>1.5)	0	0	0	0	0	0	0	0	0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR=international normalized ratio.
Any Control includes subcutaneous placebo and ezetim be with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product.
Source: Modified from ISS Tables 14-7.3.1 and 14-7.3.2

Pancreatitis

Including data from the 120-day safety update (data cut-off date 01 July 2014), Dr. Craig notes that there were 7 patients with 8 events of pancreatitis. Six events occurred while the participants were receiving evolocumab (3 events in parent trials; 2 during year 1 of OLE; 1 during year 2+). All events were serious, requiring hospitalization, and all patients recovered. Dr. Craig reviewed the narratives of these events and concluded, "the incidence of pancreatitis in the clinical development program was low overall but numerically greater in the evolocumab group in the parent studies. Cases were confounded by histories of gallstones, cholecystitis or diabetes; concomitant medications associated with pancreatitis such as valproate therapy; and alcohol use."

Renal Disease/Proteinuria

Dr. Craig notes that an imbalance was observed in cases of serious renal disorders and proteinuria in statin-intolerant and diabetic subjects. In the parent trials, SAEs were reported in 4 (0.1%) patients treated with evolocumab and no patients in the control groups. In year 1 of the OLE, 6 (0.2%) patients

reported a renal-related SAE in the evolocumab group compared with 1 patient in the SoC group; three of the 6 patients reported a renal or ureteral stone. Dr. Craig also notes a small but greater incidence of proteinuria among statin-intolerant and diabetic subjects who had no baseline proteinuria in the evolocumab group compared with the SoC group in year 1 of the OLE. I note, however, that this signal is inconsistent (see table below from Dr. Craig's review) across populations and trial periods.

Table 86: Analysis of Subject Incidence of Proteinuria in Subjects With No Baseline Proteinuria Across Therapeutic Settings

	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)
	Any Control n (%)	Any EvoMab n (%)	SoC n (%)	EvoMab + SoC n (%)	EvoMab + SoC n (%)
MONOTHERAPY	N = 480	N = 651	N = 264	N = 485	N = 258
Postbaseline proteinuria	23 (5.1)	31 (5.2)	17 (7.0)	40 (8.9)	1 (0.4)
COMBINATION THERAPY	N = 1466	N = 2965	N = 1028)	N = 2101	N = 585
Postbaseline proteinuria	72 (5.4)	151 (5.6)	85 (9.0)	146 (7.6)	1 (0.2)
STATIN INTOLERANT	N = 134	N = 330	N = 127	N = 247	N = 111
Postbaseline proteinuria	7 (5.8)	16 (5.4)	6 (5.1)	31 (14.0)	0 (0.0)

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; OLE = open-label extension; SoC = standard of care

[a] Included the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product.

[b] Includes the following studies: 20110110, 20120138

[c] Includes the following studies: 20110110, 20120138

Source: Table 88 of Summary of Clinical Safety

Musculoskeletal Events

In the integrated parent trials, AEs in the Musculoskeletal and Connective Tissue Disorders SOC were reported for 14.6% patients treated with evolocumab and 13.7% treated with any control. The incidence of markedly elevated CK was similar between evolocumab and control, with most patients with these abnormalities having confounding factors. Dr. Craig notes, however, that in the phase 1 studies, there were 3 reports of rhabdomyolysis and/or CK >10xULN in healthy individuals not on concomitant statin therapy suggesting that evolocumab may contributed to such muscle symptoms or CK increases. The narrative of the case of "rhabdoymyolysis" appears to have been an asymptomatic elevation of CK, albeit to more than 62xULN (CK 12440 IU/L). One of the cases, however, involved a healthy Caucasian subject who received a single dose of evolocumab 210 mg and had a CK 750 IU/L on day 22 that rose to 10248 IU/L (51xULN) on day 24, nearly resolving by day 36; this was considered a treatment-related AE by the investigator, and Dr. Craig agrees.

Trial '116 was conducted in patients purported to be "statin-intolerant." The applicant defined statin-intolerant subjects as those who had tried at least 2 statins and were unable to tolerate any dose or an increase in statin dose above total weekly maximum doses of statins specified in the protocol[13] due to

[13] atorvastatin 70 mg, simvastatin 140 mg, pravastatin 140 mg, rosuvastatin 35 mg, lovastatin 140 mg, or fluvastatin 280 mg, or 7 times the smallest tablet size for any other statins

intolerable myopathy, i.e., myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation); and symptoms resolved or improved when statin dose was decreased or discontinued. Dr. Craig notes that this definition did not *require* patients to have failed at least one statin at the lowest approved dose. Furthermore, trial '116 did not include a statin rechallenge arm, as the Division recommended; based on our experience with other programs (for one example, see the reviews for Praluent [alirocumab] for a discussion of the ALTERNATIVE trial), it is unlikely that most of these patients were truly intolerant to the pharmacological class. Without such an arm, one also cannot draw any conclusions about comparative tolerability or safety between evolocumab and statins.

Cardiovascular Safety

In the parent trials, AEs in the Cardiac Disorders SOC were reported for 2.4% of patients in the to-be-marketed evolocumab groups and 1.4% of patients in any control group. SAEs in this SOC were reported for 0.7% and 0.2% of these groups, respectively. Dr. Craig examined AEs by preferred term and did not find any imbalances of particular concern. Although these AEs collectively favored the control group when grouped at the SOC level in the parent trials, the pattern reversed in year 1 of the OLE, with AEs and SAEs in this SOC occurring less often with evolocumab than SoC (AEs: 2.4% vs. 2.9%; SAEs: 0.9% vs. 1.3%).

Potential CV events were adjudicated in this program, with the results summarized below (Table 73 from the clinical review). I agree with Dr. Craig that the number of adjudicated events is too small to make any reliable conclusions regarding CV risk reduction; furthermore, to what degree the open-label design following the integrated parent studies influenced the reporting of events for adjudication is unknown.

Table 73: Participant Incidence of Positively Adjudicated Cardiovascular Events and Noncoronary Revascularizations

	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)
	Any Control (N = 2080) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 655) n (%)	EvoMab + SoC (N = 1314) n (%)	EvoMab + SoC (N = 954) n (%)
Number of participants with any positively adjudicated clinical event	9 (0.4)	25 (0.6)	19 (1.3)	22 (0.8)	12 (1.3)
Death	2 (0.1)	4 (0.1)	4 (0.3)	3 (0.1)	2 (0.2)
Cardiovascular	2 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Non-cardiovascular	0	0	2 (0.1)	0	1 (0.1)
Undetermined	0	0	1 (0.1)	0	0
Myocardial infarction	2 (0.1)	8 (0.2)	5 (0.4)	6 (0.2)	3 (0.3)
Fatal	1 (0.0)	0	0	0	0
Non-fatal	1 (0.0)	8 (0.2)	5 (0.4)	6 (0.2)	3 (0.3)
Hospitalization for unstable angina	0	2 (0.1)	2 (0.1)	2 (0.1)	1 (0.1)
Coronary Revascularization	5 (0.2)	11 (0.3)	8 (0.6)	11 (0.4)	7 (0.7)
Cerebrovascular Event	3 (0.1)	5 (0.1)	5 (0.4)	3 (0.1)	3 (0.3)
Transient ischemic attack	0	2 (0.1)	4 (0.3)	1 (0.0)	1 (0.1)
Stroke (fatal and non-fatal)	3 (0.1)	3 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)
Fatal Stroke	1 (0.0)	0	0	0	0
Ischemic	0	0	0	0	0
Ischemic with hemorrhagic conversion	0	0	0	0	0
Hemorrhagic stroke	1 (0.0)	0	0	0	0
Type Undetermined	0	0	0	0	0
Non-Fatal Stroke	2 (0.1)	3 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)

	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period[c] (year 2+ of OSLER1 and OSLER2)
	Any Control (N = 2080) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 655) n (%)	EvoMab + SoC (N = 1314) n (%)	EvoMab + SoC (N = 954) n (%)
Ischemic	2 (0.1)	3 (0.1)	0	1 (0.0)	2 (0.2)
Ischemic with hemorrhagic conversion	0	0	0	0	0
Hemorrhagic stroke	0	0	1 (0.1)	1 (0.0)	0
Type Undetermined	0	0	0	0	0
Heart failure event	0	3 (0.1)	1 (0.1)	0	1 (0.1)
Non-coronary revascularization	1 (0.0)	1 (0.0)	3 (0.2)	5 (0.2)	2 (0.2)

N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab; OLE = open-label extension; SoC = standard of care
a Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Any Control includes subcutaneous placebo and ezetimibe with or without subcutaneous placebo subjects. Any EvoMab includes any subject with EvoMab as a component of investigational product. Some cases from the phase 2 and phase 3 lipid lowering clinical studies had lipid values present in the adjudication package which may have led to unblinding
b Includes the following studies: 20110110, 20120138
c Includes the following studies: 20110110, 20120138
Source: Modified from Summary Clinical Safety, Table 43

Low LDL-C & Adverse Events

Very low levels of LDL-C have been achieved with the administration of PCSK9 inhibitors. The effects of chronic, pharmacologic reduction of LDL-C to very low levels have not been established. Although patients with familial hypobetalipoproteinemia and abetalipoproteinemia have difficulties with fat malabsorption resulting in fat-soluble vitamin deficiency, ophthalmologic and peripheral nerve disorders, and RBC abnormalities, these issues have not been described in the few case reports of patients homozygous or compound heterozygous for *PCSK9* loss-of-function mutations. Nevertheless, pharmacologic interventions may not always recapitulate the effects of genetic mutations. We should not assume that we understand the safety of a novel class of agents because of a few interesting case reports.

Dr. Craig considered some analyses that attempted to screen for AEs that may have occurred at higher incidence among those who achieved very low LDL-C. In the parent trials, among patients treated with evolocumab, at least one AE was reported for 51.3% of patients who achieved LDL-C <25 mg/dL, 51.0% of those who achieved LDL-C <40 mg/dL, and 52.0% of patients who had a nadir LDL-C of ≥40 mg/dL. She specifically sought an imbalance for common AEs, diabetes, eye disorders, and neurocognitive events, but no signals were detected. See her review for details, including the analogous results for the OLE periods.

Dr. Craig also reviewed the available data regarding steroid hormones and Vitamin E. See her review for details; overall, there were no particular safety concerns raised by these analyses that would warrant inclusion in labeling at this time.

Immunogenicity

Validated assays for detecting anti-drug antibodies (ADA) were used in the clinical trials. If detected (in an electrochemiluminescent bridging immunoassay), the sample was then tested for neutralizing antibodies using a receptor binding assay based on the binding of PCSK9 to LDLR. Across the phase 2/3 trials, the overall incidence of anti-drug antibodies (ADA) was 0.1% (7 of 4846 patients).

Neutralizing antibodies were not detected. Dr. Craig reviewed the individual cases and concluded that there does not appear to be a temporal correlation between the development of ADA and specific AEs, such as hypersensitivity. Given that this is a therapeutic protein and the pre-approval safety database is relatively small given the target patient population, the incidence and potential consequences of immunogenicity will be further assessed as a PMR.

Homozygous Familial Hypercholesterolemia

The HoFH safety database (both '233 and OLE '271) includes 99 patients total. Across the two HoFH trials, 81 patients receive evolocumab for at least 3 months, 56 for at least 6 months, and 23 for at least 12 months. Section 7.3.5.2 of Dr. Craig's review discusses AEs in trials '233 (part B) and the OLE '271, with updated information from the 12-day safety update discussed in Section 7.7.1. In short, she identified no important differences in AEs in the HoFH population compared with the non-HoFH population.

9. ADVISORY COMMITTEE MEETING

This BLA was discussed with the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 10 June 2015. The committee was asked to discuss the safety of evolocumab as observed in the clinical development program, to which the general consensus was that there were no serious safety signals observed with evolocumab treatment at this time. However, several members noted that the current safety database is limited with respect to both number of patients treated and duration of exposure. Some members noted that many of the studies did not enroll the type of patients who would compose the target population for the drug (i.e., high CV risk), which was viewed as a limitation. The committee generally expressed that although the lack of safety signals provided some level of reassurance, the safety database was not adequate to comfortably state that there was no reason for concern with widespread use.

The committee opined regarding the two dosage regimens proposed (for patients without HoFH) – i.e., 140 mg Q2W and 420 mg QM – since these regimens were not selected with the intent to provide healthcare providers with options related to the magnitude of LDL-C lowering. The committee had some concern with this, stating that they believed it would be inappropriate for providers to downtitrate proven background therapy (i.e., statins) if they were uncomfortable with very low LDL-C levels being achieved. Other members added that some of this concern can be mitigated by choosing appropriate patients for evolocumab therapy (i.e., those with substantially elevated LDL-C levels despite maximally tolerated statin therapy).

Regarding the 420 mg Q2W dosage for patients with HoFH, the committee generally agreed that there is insufficient evidence that this regimen provides benefit beyond 420 mg QM, although they did not have much concern about the safety of the regimen. Some felt that even a small increase in LDL-C reduction with this dosage may provide a meaningful difference to some HoFH patients.

The committee was also asked to discuss whether evolocumab-induced LDL-C lowering is sufficient to substitute for demonstrating its effect on clinical outcomes (i.e., to substitute for investigation in a CV outcomes trial) in one or more populations. Opinions varied; some stated that there is not much doubt that lowering LDL-C by a large amount will lead to a reduction in CV risk provided the drug has no off-target effects that offset this benefit. Others expressed that LDL-C is best-suited as a surrogate in diseases such as FH, which is caused by a genetic defect of LDL-C metabolism. Some found it reassuring that the mechanism of action of evolocumab is similar to statins – i.e., LDL-C is reduced by upregulation of LDLR – and because of the genetic data suggesting that PCSK9 loss-of-function mutations are associated with lower CV risk.

The committee was asked, "Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval in one or more patient populations (excluding HoFH)? We remind you that under the current regulatory pathway, it would not be required to successfully demonstrate an effect of evolocumab on CV outcomes after an approval based on changes in LDL-C." Eleven members voted "yes" and four members voted "no." In their comments, members who voted "yes" unanimously supported approval for HeFH. Several members, but not all, also believed that benefit/risk would also be favorable for patients at high or very high CV risk who have residually high levels of LDL-C despite maximally tolerated statin therapy and/or have verified statin-intolerance. Some expressed concern, however, regarding how "high risk" and "statin intolerance" would be defined or interpreted. Several members agreed that evolocumab should not be approved as monotherapy or for patient populations such as low or moderate CV risk or mixed dyslipidemia.

The four members who voted against approval cited insufficient trial durations, patient drug exposure, and number of patients with HeFH, high CV risk, and/or statin-intolerance. One member specifically stated that anti-hyperlipidemic drugs, including evolocumab, should not be approved without showing benefit in CVOTs.

The committee was separately asked whether the applicant has sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval for HoFH. The committee voted unanimously for approval. In their comments, several members stated that there is not enough evidence to suggest that the 420 mg Q2W dosage is more effective than 420 mg QM, but others stated that the potential benefit of more frequent dosing in this patient population outweighs any risk.

10. PEDIATRICS

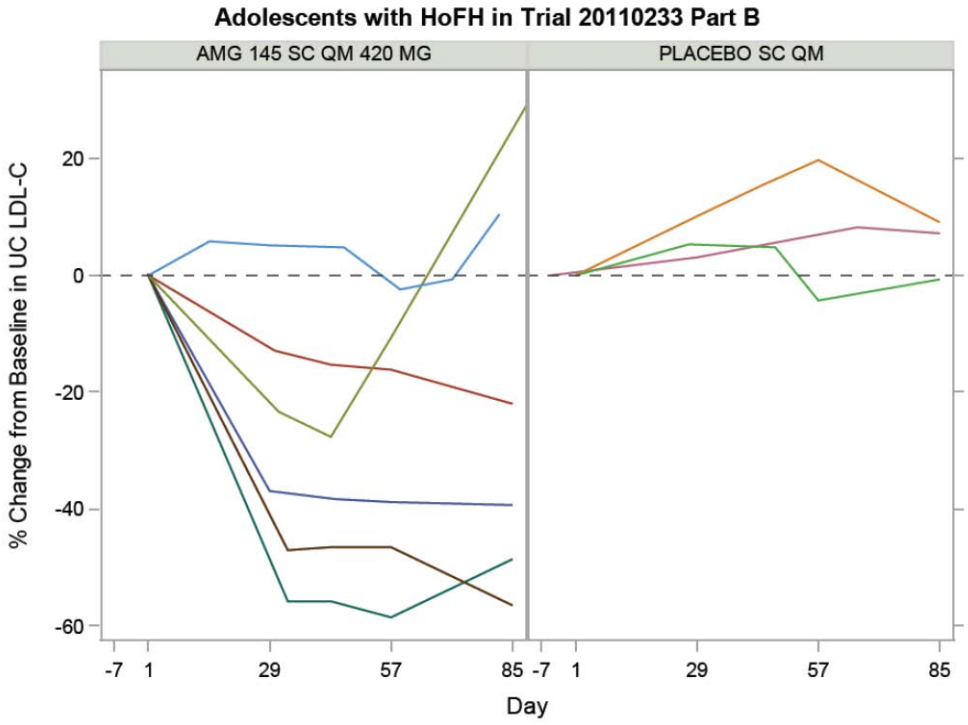
The pediatric experience with evolocumab is currently limited to HoFH. With the original BLA submission, 14 adolescents[14] had been treated with evolocumab during either trial '233 (8 total – 1 in part A, 7 in part B) and/or OLE '271 (addition of 3 patients who had received placebo in '233 + 3 evolocumab-naïve apheresis patients). Seven of the patients who received evolocumab in trial '233 also participated in the OLE.[15] The baseline ages included two age 13, five age 14, one age 15, four age 16, and two age 17. The applicant appears to have summarized exposure for trial '233 and OLE '271 separately, but I believe the combined mean and median exposures to evolocumab were 8.5 months and 9.2 months, respectively, at BLA submission, with five exposed <24 weeks, four exposed 24-52 weeks, and five exposed ≥52 weeks.

The estimated treatment difference between evolocumab and placebo in mean % change in LDL-C from baseline to Week 12 in the adolescent subgroup was -26.7% in trial '233. In the figure below, I plotted LDL-C over time for the individual subjects.[16]

[14] (b) (4)

[15] The remaining patient, a 16-y/o girl, only received one dose of evolocumab in trial '233 because her mother attributed an AE of Achilles tendonitis on day 24 to drug and did not want her child to continue.

[16] Although I cannot explain the one evolocumab-treated patient who exhibited a marked increase in LDL-C between weeks 6 and 12, I note that this patient proceeded into OLE '271 and, according to the submitted datasets, had a mean % change in LDL-C at OLE weeks 16, 20, and 24 of -26%, -31%, and -53%, respectively, relative to the '233 baseline.



Source: *adefflip.xpt*; paramcd=LDL_DRC; x=ady; y=pchg.
The one evolocumab-treated patient that does not appear in this figure is the 16-y/o girl mentioned in footnote 15.

Although the numbers are small, the safety profile among adolescents with HoFH appears similar to adults with HoFH. There were two adolescents with CK >10x ULN (22x and 64xULN), but both were apparently associated with heavy physical activity and no adverse events other than the laboratory abnormalities were reported.

This application was discussed with the PeRC on 24 June 2015. The discussion centered on the applicant's original proposed indications. Still relevant to the final agreed-upon indication, the PeRC agreed with the Division's recommendation to a waiver in patients with HeFH younger than 10 years of age because studies would be impossible or highly impractical and to the deferral of studies in patients 10 to less than 17 years of age.

11. OTHER RELEVANT REGULATORY ISSUES

Financial Disclosures

Dr. Craig noted that the applicant adequately disclosed financial interests/arrangements with clinical investigators. Disclosed interests, or lack of disclosure despite due diligence, do not raise concern regarding data integrity (pp. 49-51 of the clinical review).

Clinical Inspections

The clinical inspection for this BLA consisted of 2 domestic and 3 foreign clinical sites, representing 10 protocol sites for 3 trials (20110115, 20110109, and 20110114). The sponsor was also inspected. One clinical site representing 2 protocol sites for a single trial (20110115) was issued a Form FDA-483 citing inspectional observations with a VIA classification; the reliability of data from this site was deemed acceptable for use in support of the indication for this application. Dr. Kleppinger concludes that "…the inspectional findings support validity of data as reported by the Sponsor under this BLA."

Controlled Substance Staff Review

The Controlled Substance Staff (CSS) reviewed the AEs collected during phase 1 trials and concluded that the AE profile of evolocumab support that it has no abuse potential.

12. LABELING

DMEPA reviewed the proposed proprietary root name, Repatha, and the proposed proprietary name, Repatha SureClick, and concluded that these names are acceptable.

The labeling recommended for approval differs substantially from the labeling originally proposed by the applicant. Following the advice we obtained from the EMDAC, the review team discussed the proposed indication at length. We proposed, and the applicant ultimately accepted, modifying the indication for primary hyperlipidemia/mixed dyslipidemia to "REPATHA is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C." I will describe the basis for this recommendation in the next section of this memo.

(b) (4)

With regard to adverse events, Dr. Craig recommends largely limiting the description of adverse reactions to placebo-controlled trials. I concur, as the ezetimibe-controlled trials do not substantively add to the safety profile. (b) (4) it would be reasonable to include the broader population in Section 6 (with appropriate disclaimers) to better characterize the safety profile.

Last, efficacy results presented in labeling will be limited to LDL-C, apo B, non-HDL-C, and total cholesterol. Evolocumab is viewed as an LDL-C-lowering drug, and changes in these other parameters are highly correlated with changes in LDL-C, so it is not unreasonable to include them. Historically, with other lipid-altering drugs, many other lipid parameters have been described in Section 14. There is increasing attention, however, to limiting data presented in Section 14 to those data that support the indication, as noted above. One could argue, therefore, that the only endpoint that needs mention in

Section 14 is LDL-C itself. However, to strike a compromise with precedent, I believe that limiting the description of the results to the aforementioned parameters is appropriate and should not affect the ability of providers to use evolocumab safely and effectively.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

Risk/Benefit Assessment

There is no question that treatment with evolocumab yields a robust reduction in LDL-C, whether administered as monotherapy or as an adjunct to maximally tolerated statins with or without other lipid-modifying therapies, such as ezetimibe. For decades, the Agency has used a reduction in LDL-C as a surrogate for CV risk reduction for several lipid-altering drugs to support approval. The validity of a reduction in LDL-C as a surrogate for reduced CV risk, at least for statins, has been confirmed through numerous randomized, controlled CVOTs involving multiple drugs of the class and a variety of patient populations with varying degrees of baseline risk and LDL-C values. The plethora of evidence characterizing both benefit and risk for statins, with benefit established on the basis of improved clinical outcomes, has made statins the hegemonic class for lipid-lowering therapy and CV risk reduction in clinical practice, as exemplified by the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[17]

Prior to the approval of Praluent (alirocumab) last month, the last first-in-class LDL-C-lowering drug intended for broad use was Zetia (ezetimibe) in October 2002. The lack of data regarding CV outcomes became the subject of a great deal of controversy, fueled by the publication of the ENHANCE trial in 2008 and, six months later, the SEAS trial.[18,19] ENHANCE failed to show a reduction in the progression of carotid intima-media thickness among patients treated with ezetimibe/simvastatin vs. simvastatin alone. The fact that controversy erupted regarding the "efficacy" of ezetimibe based on results from a trial that used another surrogate endpoint (in fact, one that we would consider "non-validated") suggests just how tenuous the scientific community's confidence was in LDL-C as a surrogate for CV risk reduction by a non-statin drug. The lack of data regarding a benefit of ezetimibe on hard outcomes (e.g., MI, stroke, CV death) was further criticized when the SEAS trial raised a concern that the combination of simvastatin/ezetimibe was associated with cancer-related deaths and did not reduce the risk of a composite endpoint of CV events, compared with placebo, among patients with aortic stenosis. Even before these two trials, lipid biomarkers (especially HDL-C, but also LDL-C) had been called into question by torcetrapib, which increased the risk of CV events by 25% and increased the risk of all-cause mortality by 58% in a ~15,000-patient CV outcomes trial despite a 25% reduction in LDL-C and a 72% increase in HDL-C.[20]

Although the concern regarding the safety of ezetimibe has been quelled by additional data that have accumulated since that time, and ezetimibe has now been reported to reduce major adverse cardiovascular events following acute coronary syndrome in the IMPROVE-IT trial, I found this history informative for the approval of Praluent as well as the current application in that it emphasizes: (1) the challenges inherent to the benefit/risk assessment when benefit is characterized solely by effects on a biomarker, leaving the magnitude of the true benefit on clinical outcomes uncertain; and (2) the

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[17] Stone NJ, et al. *J Am Coll Cardiol* 2014;63:2889-934.

[18] Kastelein JJP, et al. *N Engl J Med* 2008;358:1431-43.

[19] Rossebø AB, et al. *N Engl J Med* 2008;359:1343-56.

[20] Barter PJ, et al. *N Engl J Med* 2007;357:2109-22.

influence of the availability of statins, which are known to reduce cardiovascular events, on the risk tolerance for non-statin lipid-lowering drugs. When new safety concerns arise after approval, which they inevitably do, one can only speculate about how many cardiovascular events the drug might be preventing and whether this offsets the identified risks. The ezetimibe controversy suggests that one should accept very little risk from a novel LDL-C-lowering drug when approving for a broad population only based on its effects on LDL-C.

Regarding this application, the current safety database for evolocumab is reassuring, although it is quite limited by the fact that all phase 2/3 double-blind, controlled trials – except for one – were only 12 weeks' duration. Although the applicant has accumulated substantial exposure in open-label extension studies, such designs are limited in their ability to characterize safety without concern of bias (e.g., from underreporting). Nevertheless, such studies would not be expected to miss very serious cases that could potentially preclude approval, such as fulminant hepatic failure or Stevens-Johnson syndrome, so they do provide some degree of reassurance. I agree with the Dr. Craig and the advisory committee members that there are no strong safety signals at this time. The applicant's proposed population, however, would include millions of patients for this potentially life-long therapy. I concur that some adverse events may emerge or become more clearly defined only after years of exposure to a larger number of patients, whether or not they are related to the extremely low levels of LDL-C that can be achieved with PCSK9 inhibition (at present, I find little evidence to suggest that low levels of LDL-C are unsafe, and our advisors concurred). This uncertainty regarding long-term safety contributed to the recommendation of Dr. Craig and the advisory committee members to limit approval to patients at very high cardiovascular risk, where the benefit/risk is expected to be more favorable, until we can better quantitate clinical benefit and longer-term risk through the completion of a CVOT. Risks of concern will be studied as post-marketing requirements (see below).

I believe that benefit/risk is favorable for patients with HoFH and HeFH who are already being treated with maximally tolerated statin yet still require additional LDL-C reduction (to be defined by their healthcare provider). These patients have elevated LDL-C from birth as a result of abnormal LDL metabolism, and it is clear that elevated LDL-C is the basis for their clinical phenotype of premature atherosclerosis/cardiovascular disease. As such, I do not believe that we should demand pre-approval outcomes data before allowing these patients access to evolocumab. Although FH may be underdiagnosed currently, there are various established clinical criteria that healthcare providers can apply to determine the likelihood that a patient has this condition. Educational efforts to raise awareness of FH may increase the size of the target population following this approval, and I would view this as an overall benefit to the public health. I would expect that newly identified patients would first be placed on a therapy known to reduce cardiovascular risk.

Regarding patients who do not have HoFH or HeFH, I do not believe that data have accumulated that preclude the use of LDL-C as a potential basis for approval. The torcetrapib experience illustrates, however, that reductions in LDL-C may not always yield net clinical benefit, and one might not always be able to predict when this may occur. Thus, even if we accept the "LDL hypothesis," we must remember that LDL-C remains a surrogate and not a clinical outcome that reflects how patients feel, function, or survive. This residual uncertainty, with regard to both true clinical benefit and potential long-term risks, weighed heavily on our advisory committee members during their deliberations as well as the clinical reviewers who have been involved with the applications for both evolocumab and Praluent. Dr. Craig states, "The applicant's proposed indication included evolocumab to be given in combination with statin therapy in patients with primary hyperlipidemia and mixed dyslipidemia as well as monotherapy use in patients unable to take a statin. I do not believe that the benefit-risk assessment of evolocumab supports such a broad indication in the absence of positive data from a

cardiovascular outcomes trial (CVOT). This reviewer's recommended indication targets patients in whom the benefit-risk is likely to be favorable in the absence of confirmatory CV outcomes data and a relatively limited pre-marketing safety database," specifically:

> *REPATHA is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.*

I support this revised indication, and the applicant has also agreed. I believe that it is reasonable, given the extensive data supporting statins as a class with regard to both efficacy (clinical outcomes) and safety, to indicate this first-in-class therapy to patients who are already taking maximally tolerated statin therapy. Consistent with the Division's statements to the sponsor while evolocumab was under development, I agree that an indication for monotherapy should not be granted before a CVOT has demonstrated a benefit on clinical outcomes. This does not call into question whether LDL-C lowering is beneficial, but rather should discourage physicians from concluding that evolocumab is superior to certain statins (or doses of statins) on the basis of LDL-C comparisons alone until the quantitative relationship between LDL-C reduction and CV risk reduction is understood for evolocumab. This indication also supports the use of statins as first-line therapy, which is consistent with contemporary clinical practice and treatment guidelines. Some patients will not tolerate statins, and I would not exclude such patients from treatment; [redacted] (b) (4)

Furthermore, I agree with Dr. Craig that benefit/risk is favorable for patients with clinical atherosclerotic cardiovascular disease (ASCVD), a term that is used throughout the 2013 ACC/AHA cholesterol guidelines and defined by the inclusion criteria for secondary prevention statin RCTs.[21] These patients, by definition, already have serious disease and are at high risk for a recurrent atherosclerotic event that could be fatal. As such, given the wealth of data supporting a causal role for LDL-C in atherosclerotic disease, as well as the expectation that the mechanism of action of evolocumab would be expected to have a low propensity for off-target effects, I believe that evolocumab ought to be a treatment option for such patients at this time. For use in the much larger primary prevention population, however, I believe we need to accrue additional long-term safety data from both post-marketing pharmacovigilance and additional clinical trials, such as the applicant's ongoing CVOT. Certainly, determining the magnitude of benefit on cardiovascular outcomes would help inform the benefit/risk assessment [redacted] (b) (4).

Last, regarding the 420 mg Q2W regimen proposed as an alternative for HoFH, Dr. Craig notes that some members of the EMDAC stated "that the potential cardiovascular benefit from this 420 mg Q2W dose may outweigh the risk in this HoFH population who do not achieve adequate LDL-C lowering with the 420 mg every 4 week dose." In her assessment, however, "the limited amount of safety and efficacy data provided in this submission for the 420 mg every 2 week dose is insufficient to support approval at this time, especially as this dosing regimen could be used in children." I concur that the current data [redacted] (b) (4)

[21] Acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

(b) (4)

Recommended Regulatory Action

- Approval, pending successful negotiation of labeling with the applicant, for the following indications:
    - REPATHA is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
    - REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Recommendations for Risk Evaluation and Mitigation Strategies

- None. This recommendation is supported by OSE/DRISK (see Dr. Joyce Weaver's review).

Recommendations for Post-marketing Requirements and Commitments

I recommend that the following safety-based PMRs be included in the approval letter (see approval letter for additional details):

- Conduct a prospective observational study of pregnant women exposed to evolocumab to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab and their liveborn offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression.
- A large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination with evolocumab treatment will be evaluated.[22]
- A randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with evolocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.[23]

In addition, there will be five post-marketing commitments requested by OBP, which I support.

[22] It is expected that the applicant's ongoing cardiovascular outcomes trial should provide a sufficient platform to evaluate these safety signals, but the applicant will need to submit an analysis plan to confirm that the data being collected would be suitable to fulfill this PMR.

[23] The applicant notes that they already have an ongoing substudy of their CVOT to evaluate neurocognitive function prospectively. The Division will have the opportunity to review whether this substudy would be sufficient to fulfill the PMR.

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/s/

JAMES P SMITH
08/25/2015