CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125559Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	(electronic stamp)
From	James P. Smith, MD, MS
Subject	Deputy Division Director Summary Review
BLA #	125559
Applicant Name	Sanofi-Aventis U.S., LLC
Date of Submission	24 November 2014
PDUFA Goal Date	24 July 2015
Proprietary Name / Established (USAN) Name	PRALUENT / alirocumab
Dosage Forms / Strength	Solution for injection; 75mg/mL and 150 mg/mL pre-filled syringe and pre-filled pen
Indication originally sought by applicant (see page 31 for final)	• PRALUENT is indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo A-1). • PRALUENT is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT). • PRALUENT is indicated as monotherapy, or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.
Recommended Action	*Approval*

Material Reviewed/Consulted	**Reviewers**
Medical Officer Review	Julie Golden, MD (efficacy) & Mary Roberts, MD (safety)
Statistical Review	Bradley W. McEvoy, DrPH
Pharmacology/Toxicology Reviews	C. Lee Elmore, PhD; Timothy J. McGovern, PhD
Clinical Pharmacology Review	Sang M. Chung, PhD; Justin Earp, PhD
OBP CMC Review	Richard Ledwidge, PhD
Microbiology Reviews	Colleen Thomas, PhD (drug product); Ryes Candau-Chacon, PhD (drug substance)
OBP Immunogenicity Risk Assessments (2)	Amy Rosenberg, MD
OPQ Facility Review	Michael R. Shanks
CDRH/ODE Consult	Janice Polacek, RN, BSN, CRNI
OC/CDRH Review	LT Viky Verna
OSI Clinical Inspection Summary	Cynthia F. Kleppinger, MD
Patient Labeling Review	Twanda Scales, RN, BSM, MSN/Ed. (DMPP) and Ankur

Material Reviewed/Consulted	Reviewers
	Kalola, Pharm.D. (OPDP)
Human Factors/Labeling Review (OSE/DMEPA)	Mishale Mistry, Pharm.D., MPH
Proprietary Name Memorandum (OSE/DMEPA)	Mishale Mistry, Pharm.D., MPH
OPDP Labeling Consult	Ankur Kalola, PharmD
Consult, Division of Neurology Products	Kenneth Bergmann, MD
OSE Consult, Hepatology	John R. Senior, MD
Memorandum to File, Maternal Health Team	Christos Mastroyannis, MD
OSE/DRISK REMS Review	Amarylis Vega, MD, MPH

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 alirocumab as a first-in-class biologic for the following proposed indications:

> PRALUENT is indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo A-1).
>
> PRALUENT is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT).
>
> PRALUENT is indicated as monotherapy, or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.

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 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. Alirocumab is a human IgG1 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

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

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

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.

Dr. Roberts and Golden summarize the regulatory history of alirocumab in Table 3 of the clinical review. At the 21 February 2012 end-of-phase 2 (EOP2) meeting, the Division noted experience with drugs that induce favorable changes in lipid parameters yet do not always translate into the expected cardiovascular benefit when tested in controlled clinical trials. Furthermore, the Division noted the experience of Zetia (approved in 2002) and Vytorin (approved in 2004), which were approved on the basis of changes in LDL-C but results (for ezetimibe) regarding effects on cardiovascular outcomes were still awaited, even though the efficacy and safety of ezetimibe had been called into question by many in the scientific community on the basis of clinical trials in 2008-2009 (discussed later in this memo). Thus, the Division informed the sponsor that if their BLA was first-in-class, an advisory committee would be asked whether or not their product should be approved before their CVOT (which they had proposed to initiate during phase 3) was completed. In addition, the Division noted that the results of the then-ongoing IMPROVE-IT trial, [5] which was studying the effect of adding ezetimibe to simvastatin on cardiovascular outcomes, could influence the decision to base approval on a surrogate (LDL-C). At the time of this writing, the Division has not yet conducted an independent review of the IMPROVE-IT trial.

It is also relevant to note that, as early as the EOP2 meeting, the Division "confirmed that they would not add the LDL-C lowering of [alirocumab] vs. ezetimibe or vs. statin up-titration to the label until the CVOT [cardiovascular outcomes trial] was reviewed and represented in the label. FDA did not believe that a trial of LDL-lowering of several weeks duration is adequate to claim superiority when compared to an agent that has proven cardiac risk reduction."[6] Furthermore, the Division noted that "[i]n placebo-controlled studies, patients are expected to be receiving intensive background therapy, including a maximum tolerated dose of statin with or without other lipid-modifying agents." Last, there was considerable discussion regarding how to identify and study patients with purported "statin intolerance" in a clinical trial. The Division and sponsor did reach agreement on a definition of "statin intolerance" and study design for the purpose of conducting a clinical trial; however, the sponsor was informed that it would be a review issue whether data from such a trial would be included in labeling before their CV outcomes trial was completed and provided a robust assessment of long-term safety and efficacy.[7]

3. CMC/DEVICE

CMC

Dr. Richard Ledwidge reviewed the data for the drug substance and drug product for this BLA. The Office of Biotechnology Products recommends approval of alirocumab. In addition, OBP recommends

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[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.

[5] Cannon CP, et al. *N Engl J Med* 2015;372:2387-97.

[6] IND 105574, EOP2 Meeting Minutes, 09 March 2012.

[7] IND 105574, Advice Letter, 27 April 2012.

approval of the proposed lot release/stability specifications and stability protocols for alirocumab drug substance and drug product. The recommended expiry period is (b) (4) months for the drug substance (when stored at (b) (4) and 18 months for the drug product (when stored at 2-8°C). I concur that there are no issues related to the drug substance or drug product that would preclude approval.

Drug Substance

Alirocumab is a fully humanized antibody generated by standard monoclonal antibody techniques and expressed in Chinese Hamster Ovary (CHO) cells. (b) (4)

Dr. Ledwidge's review (pp. 20-21) describes the key changes in the manufacturing process that occurred during development, as well as his assessment of the relevant comparability exercises between changes in cell lines and processes; he found the data acceptable. I note that the cell line and process that were used for all phase 3 clinical trials (and some phase 1/2 clinical trials) will be used for manufacturing the commercial material.

According to Dr. Ledwidge, the applicant conducted a thorough analysis of the structure and functional properties of alirocumab that can be used in the future to assess manufacturing changes and comparability exercises. In addition, a thorough evaluation to identify and control all process-related and product-related impurities was conducted. Furthermore, the post-approval protocol and stability commitment were found to be acceptable.

Drug Product

The alirocumab drug product is a clear, colorless to pale yellow, aqueous solution pH 6.0. The 150 mg/mL solution contains the excipients 6 mM histidine, 10% (w/v) sucrose, 0.01% polysorbate 20, and water for injection; the 75 mg/mL solution varies only in the concentration of histidine (8 mM) with regard to excipients. The solution is isotonic with physiologic conditions. 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

An inspection related to the drug substance was conducted 30 March-03 April 2015; a one-item FDA Form 483 was issued with an initial recommendation of VAI. An inspection related to the drug product was conducted 07-14 April 2015; a two-item FDA Form 483 was issued with an initial recommendation of VAI. As noted in the review by Dr. Michael Shanks (OPQ), the facility descriptions submitted in this BLA have been reviewed and found to be adequate to support the manufacture of alirocumab drug substance and drug product.

Device

CDRH was consulted to review the device constituent part of this combination product, which consists of a pre-filled syringe (PFS) and a pre-filled pen (PFP, or auto-injector) designed to deliver a liquid

formulation of alirocumab at concentrations of 75 and 150 mg/mL for subcutaneous injection. Two PFP presentation were developed: one for the 75 mg dose and another for the 150 mg dose. The fill volumes are the same (1 mL). The PFPs are (b) (4) and contain a PFS component that is identical to the stand-alone PFS presentation with the exception of the absence of the PFS plunger rod. See the CDRH review for full details.

There was considerable discussion during the review, including with the applicant, regarding a change in the 75 mg PFP and subsequent implementation of (b) (4) process controls on syringe (b) (4). To summarize briefly, it was noted in engineering performance studies that (b) (4) (b) (4) with the 75 mg PFP. (b) (4) and although they defer clinical acceptability to clinical reviewers and DMEPA, they note the following: (1) the clinical trial used injectors that were representative of the to-be-marketed product, and thus efficacy results seen within the trial included the presence of long injection times; (2) the pen has a reliable means of indicating to the user when the injection is complete (color change and audible feedback); (3) instructions for use for the pen state that the pen should be held against the skin for at least 20 seconds; (4) DMEPA reports that patient labeling and instructions for use has been satisfactorily validated by means of clinical simulations within human factors studies; (5) DMEPA and the sponsor report that users who exhibited difficulty completing an injection time for their novel dose were able to successfully complete subsequent doses; and (6) the drug product is not representative of an "emergency use" or "rescue" medication, and therefore long injections leading to partial doses are more tolerable.

It is possible that the changes to the 75mg PFP might lead to increased injection site pain or leakage. Only clinical experience will inform this, and I do not believe that this requires additional clinical testing before approval, especially given that the same injection time specifications were used for the devices manufactured for use in clinical trials. As Dr. Roberts notes in her clinical safety review, device-related adverse events will be monitored as a part of routine post-marketing surveillance.

Human Factors Review

Mishale Mistry (DMEPA) reviewed this BLA from a human factors standpoint. She concluded that "[t]he Human Factors studies for the Praluent pre-filled syringe and autoinjector demonstrated that end users (patients, caregivers, and healthcare professionals) are able to use the product safely and effectively when used with the availability of formal training and/or training materials (Instructions for Use)." Recommendations were provided and implemented for proposed labels and labeling for areas of vulnerability that may lead to medication errors.

Facilities Review/Inspection

The Office of Compliance at CDRH recommended a pre-approval inspection for Sanofi Winthrop Industrie in Le Trait, France. This inspection was performed 07-09 April 2015 and was classified as NAI; therefore, OC/CDRH recommends approval of this BLA 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. He notes that reproductive toxicity, comprising increased maternal deaths in rats and decreased humoral immunity in infant monkeys, can be addressed in product labeling.

The applicant identified the rat and monkey as pharmacologically relevant species for toxicology testing with alirocumab. Alirocumab was well tolerated by rats and monkeys in toxicology studies of up to 6 months with weekly subcutaneous (SC) dosing that provide exposure multiples of up to 11-fold in rats and up to 103-fold in monkeys compared to the maximum recommended human dose (MRHD) of 150 mg alirocumab Q2W, based on plasma exposure. Reductions in LDL-C of up to 75% and 80% were observed in rats and monkeys, respectively. In addition, alirocumab (at 100-fold MRHD) was administered SC once weekly along with oral atorvastatin once daily (at 8-fold MRHD) to monkeys for 3 months. Although there was an additive effect of the two drugs on the reduction of LDL-C (up to 99%), as well as an unexpected reduction in HDL-C (up to 71%), there were no additive or synergistic effects on the statin-induced toxicities observed. The combination exaggerated pharmacologic changes consisting of moderate to markedly decreased adrenal vacuolation, but Dr. Elmore states that these findings were not toxicologically significant and were reversible. He also notes that the adrenal findings in monkeys were associated with significant reductions in HDL-C, which has not been observed in humans.

In studies of up to 6 months' duration in rats and monkeys, no preneoplastic or neoplastic lesions were observed. Furthermore, alirocumab is not expected to interact directly with DNA, so mutagenicity studies were not conducted. Thus, based on the weight of evidence approach outlined in the ICH-S6 guidance, alirocumab was not tested in an animal model for carcinogenesis.

In his review, Dr. Elmore also addresses theoretical concerns related to the administration of alirocumab and/or the marked lowering of plasma LDL-C that can be attained with its use, including increased intestinal bile acids, hepatitis C infectivity, effects on hormones derived from the adrenal cortex, impaired liver regeneration, immune modulation in adults, insulin sensitivity, and potential effects on neurocognition. In short, the available nonclinical evidence does not suggest that alirocumab would be expected to have adverse clinical effects related to these potential risks (see summary on pp. 137-140 of Dr. Elmore's review).

Regarding reproductive toxicology, no effects of alirocumab on fertility endpoints were observed in the 6-month monkey toxicity study. When tested in pregnant rats during the period of embryofetal development (at up to 12-fold MRHD), maternal lethality (4/25 animals) was observed; no toxicity was observed at a lower dose that provides a 2.6-fold safety margin, however. When tested in pregnant monkeys during the period of embryofetal development through infancy (at up to 81-fold MRHD), no deaths and no significant toxicity were observed. In offspring of these treated pregnant monkeys, dose-related decreases in T-cell dependent antibody response to a known antigen were observed during the period of 120 to 180 days after birth. This suggests that exposure to alirocumab in utero suppressed adaptive immunity in these infant monkeys; immune suppression was statistically significant at high dose ($p<0.01$) but approached statistical significance at low dose as well ($p=0.06$). A dose level that did not suppress humoral immunity in infant monkeys was not identified. Dr. Elmore notes that it is unclear what level of humoral immune suppression would be acceptable in human infants, and notes that administration of alirocumab to pregnant women should only be considered when benefits outweigh the potential risks.

Late in the review cycle, there was considerable discussion regarding the potential clinical significance of this signal. The Division of Pediatric and Maternal Health "determined that the signal of humoral immune suppression, demonstrated in the offspring of pregnant cynomolgus monkeys administered alirocumab, identifies a potential safety concern for neonates and infants when a pregnant woman is administered Praluent…. Further assessment of this potential safety concern is necessary to monitor for adverse neonatal and infant outcomes (i.e., recurrent infections with encapsulated bacteria, lifethreatening enterovirus infections, failure to respond to appropriate antibiotic therapy). In addition, due to the lack of adequate safety information on the use of Praluent … in pregnant women, assessment of pregnancy outcomes and embryo-fetal growth and development are recommended. DPMH has proposed a trial should be conducted to evaluate adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant outcomes related to humoral immune suppression. The study may be conducted as a pregnancy pharmacovigilance program." In multi-disciplinary follow-up discussions between DPMH, the Division of Epidemiology, the Division of Pharmacovigilance, and DMEP's nonclinical reviewers, it was ultimately determined that this signal would be evaluated as a post-marketing requirement (PMR). A variety of possible PMR study designs were discussed and considered; ultimately, there was alignment on a prospective observational study of pregnant women exposed to Praluent to evaluate fetal, infant, and childhood outcomes 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.

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

5. CLINICAL PHARMACOLOGY

Drs. Sang Chung and Justin Earp reviewed this BLA from a clinical pharmacology/pharmacometrics perspective. The Office of Clinical Pharmacology recommends approval of both 75 mg and 150 mg doses administered once every two weeks (Q2W). They recommend that patients be initiated at 75 mg Q2W, titrating up to 150 mg Q2W after 8 weeks (since this was evaluated in pivotal phase 3 trials) in patients who need additional LDL-C-lowering. Alternatively, they suggest that the dose could be titrated after 4 weeks, since the maximum LDL-C reduction was attained in 2-3 weeks following an injection of alirocumab and because LDL-C reduction reached apparent steady-state after the first dose.

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

Although there were significant changes with cell lines, manufacturing processes, and formulations during clinical development, the final formulations and presentations of devices were evaluated in the pivotal trials. The applicant provided adequate PK/PD bridging for the major changes, where appropriate.

Data from phase 2 trials informed the applicant's dose selection for phase 3. In phase 2, the 150 mg Q2W regimen yielded the largest decrease in LDL-C among those tested (i.e., 50, 100, and 150 mg Q2W; 150, 200, and 300 mg Q4W added to atorvastatin) as shown in the figure below, excerpted from the clinical pharmacology review (Figure 7, p. 22). Although the 300 mg Q4W provided the same total dose as 150 mg Q2W during a 4-week dosing interval, the maximum treatment effect was not maintained during the interval. Using data from phase 2, the sponsor selected 75 mg Q2W as a second dose to study in phase 3 based on dose-response modeling; they anticipated that this dose would yield ~50% reduction in LDL-C.

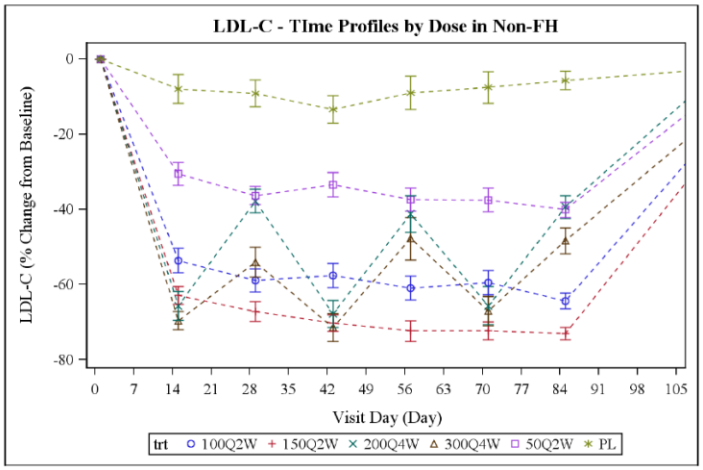


Figure 7 Mean (SE) LDL-C (% change from baseline) – time profiles by dosing regimen (Study DFI11565-Phase 2 trial)

The efficacy of 75 mg Q2W vs. 150 mg Q2W, with regard to effects on LDL-C, is discussed in Section 7, below.

Alirocumab exhibits typical PK characteristics of a monoclonal antibody. The median T_{max} is 3-7 days, and steady-state is reached after 2-3 doses with an accumulation ratio of approximately 2-fold. There were no apparent differences in alirocumab PK among the injection sites studied (i.e., upper arm, abdomen, and thigh). The mean Vd was 0.04-0.05 L/kg, supporting a distribution limited to the circulatory system.

Data from a single-dose PK study (CL-902) provide evidence of target-mediated elimination, which saturated at doses of approximately ≥3 mg/kg following intravenous administration. After subcutaneous administration in healthy subjects (study CL-0904), free PCSK9 concentrations were completely depleted during the initial period of alirocumab administration; total PCSK9 concentrations (free + alirocumab-bound) reached maximum ~14 days after alirocumab administration, and the increase in C_{max} (of total PCSK9) was dose-dependent. According to the applicant's estimation, both target-mediated and typical IgG elimination mechanisms contribute similarly to overall clearance in the typical C_{trough} range after 75 mg Q2W, whereas the typical IgG elimination pathway is the major clearance mechanism after 150 mg Q2W. The median apparent effective terminal half-life ranged from 17 to 20 days, and was ~12 days in patients receiving concomitant statins (statins induce PCSK9, thereby increasing the target-mediated clearance of alirocumab).

The effects of age, race, sex, and body weight on alirocumab exposure and efficacy were evaluated using population analysis; there were no significant covariates for both alirocumab PK and efficacy for a dose adjustment.

A dedicated study to address the effect of renal function on alirocumab PK was not conducted because renal elimination is not considered a major clearance mechanism for monoclonal antibodies. The clinical pharmacology review found no apparent correlation between eGFR and alirocumab PK among 3,743 subjects with available data for both C_{trough} and eGFR at Week 24 in phase 3 studies.

The effect of hepatic function on alirocumab PK was assessed after administration of alirocumab 75 mg to healthy subjects or those with mild or moderate hepatic impairment (i.e., 3 groups of 8 subjects each; Study POP12671). The reviewers concluded that the PK and PD differences between groups were not significant enough to warrant dose adjustment.

Regarding extrinsic factors, the potential for PK drug interaction was not formally evaluated because conventional mechanisms of such interactions are known to not be involved in the elimination of IgG. Drug interactions with lipid-modifying therapy were considered, however, since such therapy can increase PCSK9 concentration, which could promote target-mediated elimination of alirocumab. Alircoumab AUC was decreased by fenofibrate (36% in healthy subjects) and atorvastatin (39% in patients), but these PK differences did not translate into meaningful clinical differences in LDL-C. Furthermore, there was no apparent clinical significance of statins on alirocumab-induced lowering of LDL-C. Taken together, the clinical pharmacology reviewers concluded that there are no dose adjustments necessary based on drug interactions with these lipid-modifying drugs.

A thorough QT study was not conducted because alirocumab is a monoclonal IgG.

I concur with the conclusions reached by the clinical pharmacology/pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. CLINICAL MICROBIOLOGY

Dr. Candau-Chacon reviewed the drug substance and Dr. Colleen Thomas reviewed the drug product with regard to microbial control and microbiology product quality. Both reviewers have recommended approval from their perspectives. Six post-marketing commitments (PMCs), which I support, have been recommended; see the quality review addendum (dated 17 July 2015) for details. 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. Julie Golden reviewed the efficacy of alirocumab from a clinical standpoint, and Dr. Bradley McEvoy conducted the statistical review. See their detailed reviews for a full discussion. Both reviewers recommend approval of alirocumab (if limited to high-risk patients on maximally tolerated statin therapy, which I will discuss later in this review).

Ten phase 3 trials were reviewed for this BLA submission, all of which were randomized, double-blind, parallel-group, placebo- or active-controlled trials with treatment periods ranging from 6 to 24 months. In total, there were 5296 patients that underwent randomization across these trials, with 3188 assigned to alirocumab. Two alirocumab treatment regimens were studied in phase 3, and each trial investigated only one of the regimens: (1) 75 mg Q2W initially followed by uptitration to 150 mg Q2W at week 12 if the LDL-C value at week 8 had not fallen below a pre-specified thresholds based on patient-specific CV risk [8 trials, contributing 49% of the patients treated with alirocumab in phase 3]; and (2) 150 mg Q2W initially and throughout the trial [2 trials].

The five placebo-controlled trials (FH I, FH II, HIGH FH, COMBO I, and LONG TERM) randomly assigned 3499 patients to alirocumab or placebo (2:1 allocation) on top of maximally tolerated background statin with or without other lipid-modifying therapies. FH I, FH II, and HIGH FH exclusively enrolled patients with HeFH and LONG TERM enrolled patients with either HeFH or non-familial hypercholesterolemia but high CV risk. LONG TERM and HIGH FH were the only trials that studied the 150 mg dose throughout the treatment period. LONG TERM was the largest trial, with 2341 patients randomized.

The five active-controlled trials (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO) each used ezetimibe 10 mg daily as a control. OPTIONS I and OPTIONS II also included statin uptitration arms (or a switch from one statin to another) as additional active control groups. Regarding patient populations, COMBO II enrolled patients with high CV risk who were taking a maximally

tolerated statin. OPTIONS I and OPTIONS II enrolled both HeFH and non-familial hypercholesterolemia with high CV risk on a less than maximal dose of statin. ALTERNATIVE enrolled patients purportedly intolerant of statins, and MONO enrolled patients at moderate CV risk (defined as a 10-year risk of fatal CVD of ≥1% to <5% using Systematic Coronary Risk Estimation [SCORE]); in both of these trials, alirocumab was studied without background statin therapy.

Five trials were completed as of the August 31, 2014, database lock for the initial BLA submission. For the ongoing trials (FH I, FH II, HIGH FH, LONG TERM, and COMBO II), all subjects had at least 12 months of follow-up.

All ten phase 3 trials used the same primary efficacy endpoint: % change in LDL-C from baseline to week 24, using calculated LDL-C (Friedewald equation). Lipid parameters included as key secondary efficacy endpoints were total cholesterol (TC), non-HDL-C, ApoB, TG, Lp(a), HDL-C, and ApoA1.

For the eight trials that used a dose-uptitration regimen at week 12, the decision to uptitrate depended on LDL-C at week 8. Patients at very high CV risk (defined as a history of coronary heart disease [CHD] or CHD risk equivalent) underwent uptitration if their LDL-C remained ≥70 mg/dL; patients at moderate or high CV risk underwent uptitration if their LDL-C remained ≥100 mg/dL.[8] Dr. Golden summarizes how these CV risk categories were defined in Table 12 of her review.

A table summarizing the study designs for the phase 3 program, excerpted from Dr. McEvoy's review, is included below.

[8] In the MONO trial, patients were uptitrated at LDL-C ≥70 mg/dL instead of the planned threshold of 100 mg/dL in error.

Table 2. Summary of study designs

Study	Population	Design	Primary Endpoint/ Treatment duration	Treatment arms (N randomized)
Background therapy: Maximally tolerated dose of statin ± other LMTs (alirocumab add-on)				
FH I* (EFC12492)	heFH	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 75 mg/150 mg Q2W (n=323) - Placebo Q2W (n=163)
FH II* (R727-CL-1112)	heFH	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 75 mg/150 mg Q2W (n=167) - Placebo Q2W (n=82)
HIGH FH* (EFC12732)	heFH with LDL-C ≥ 160 mg/dL	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 150 mg Q2W (n=72) - Placebo Q2W (n=35)
COMBO I (EFC11568)	High CV risk with hypercholesterolemia	R, DB, PC, PG	LDL-C at week 24/ 12 months	- 75 mg/150 mg Q2W (n=209) - Placebo Q2W (n=107)
LONG TERM* (LTS11717)	heFH or non-FH with hypercholesterolemia	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 150 mg Q2W (n=1553) - Placebo Q2W (n=788)
Background therapy: Maximally tolerated dose of statin alone (alirocumab add-on)				
COMBO II* (EFC11569)	High CV risk with hypercholesterolemia	R, DB, DD, AC, PG	LDL-C at week 24/ 24 months	- 75 mg/150 mg Q2W (n=479) - Ezetimibe 10 mg (n=241)
Background therapy: Less-than-maximal dose of statin (alirocumab add-on)				
OPTIONS I (R727-CL-1110)	High CV risk with non-FH or heFH	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W + atorvastatin 20 mg (n=57) - 75 mg/150 mg Q2W + atorvastatin 40 mg (n=47) - Ezetimibe 10 mg + atorvastatin 20 mg (n=55) - Ezetimibe 10 mg + atorvastatin 40 mg (n=47) - Atorvastatin 40 mg (n=57) - Atorvastatin 80 mg (n=47) - Rosuvastatin 40 mg (n=45)
OPTIONS II (R727-CL-1118)	High CV risk with non-FH or heFH	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W + rosuvastatin 10 mg (n=49) - 75 mg/150 mg Q2W + rosuvastatin 20 mg (n=54) - Ezetimibe 10 mg + rosuvastatin 10 mg (n=48) - Ezetimibe 10 mg + rosuvastatin 20 mg (n=53) - Rosuvastatin 20 mg (n=48) - Rosuvastatin 40 mg (n=53)
Background therapy: None or LMT other than statin or ezetimibe (alirocumab monotherapy or add-on)				
ALTERNATIVE (R727-CL-1119)	Hypercholesterolemia (heFH and non-FH) at moderate or high CV risk and intolerant to statins	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W (n=126) - Ezetimibe 10 mg (n=125) - Atorvastatin 20 mg (n=63)
MONO (EFC11716)	Moderate CV risk with LDL-C ≥ 100 mg/dL and ≤ 190 mg/dL	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W (n=52) - Ezetimibe 10 mg (n=51)

LMTs – Lipid-modifying therapy; FH –familial hypercholesterolemia; heFH – heterozygous familial hypercholesterolemia; CV – cardiovascular; R – randomized; DB – double-blind; PC – placebo-controlled; AC – active-controlled; PG – parallel-group; DD – double-dummy;
* Ongoing as of the August 31, 2014 data cutoff.

In most trials, the entry criterion for LDL-C was either ≥70 mg/dL and/or ≥100 mg/dL depending on the individual patient's CV risk at entry. HIGH FH was an exception; this trial enrolled patients with HeFH who had LDL-C ≥160 mg/dL despite maximally tolerated statin therapy. As noted above, in all five placebo-controlled trials, as well as in COMBO II, patients were to be on maximally tolerated doses of atorvastatin, rosuvastatin, or simvastatin, which were expected to be high doses unless issues of tolerability or local labeling prohibited use (atorva 40-80 mg, rosuva 20-40 mg, simva 80 mg). Of the

4219 patients enrolled in these six trials, 59% entered the trial on one of these statin regimens. A history of muscle symptoms and/or increases in CK contributed to the majority of reasons why some patients were on lower doses of statins.

Across the 10 phase 3 trials, patient demographics and baseline characteristics varied depending on the trial population (e.g., HeFH, a spectrum of CV risk, "statin intolerance") and the international distribution of study sites for each trial. A greater percentage of patients in COMBO I, COMBO II, and LONG TERM had a prior history of MI or stroke compared with the other trials (53% vs. 28%). The average age across trials was 60 years, with a range of 18 to 89 years. As expected, patients enrolled in trials devoted to the HeFH population were younger, on average, than those enrolled in the trials that predominantly enrolled those with (non-familial) high CV risk. Most subjects (62%) were male, 90% were white, 5% were black or African American, 2% were Asian, and 6% were of Hispanic ethnicity. Sites in the U.S. contributed 35% of subjects (38% North America, 33% Western Europe, 16% Eastern Europe, and 14% from the rest of the world [majority, South Africa]). Baseline mean LDL-C ranged from 102 mg/dL (COMBO I) to 198 mg/dL (HIGH FH) across trials. Additional demographic and baseline characteristics are summarized in Dr. Golden's and Dr. McEvoy's reviews.

The phase 3 trials that enrolled patients with HeFH used either genotype or clinical criteria to make the diagnosis of HeFH. Clinical diagnosis was based on either "definite FH" according to the Simon Broome criteria or "certain" by the WHO/Dutch Lipid Network criteria.

Considering the 10 phase 3 trials together, 5296 patients were randomized: 3188 to alirocumab, 1175 to placebo, 620 to ezetimibe, and 313 to a change in the background statin regimen. Overall, 98.6% of randomized patients were included in the ITT (primary analysis) population, and 97.8% were included in the modified ITT (mITT) population. Dr. McEvoy discusses the ITT and mITT populations, as well as an FDA-preferred analysis that he states more appropriately represents missing data for subjects that stopped treatment early. For the five completed trials, the proportion of completers ranged from 70% (ALTERNATIVE) to 85% (MONO); these proportions (as well as the reasons for not completing the treatment period) were fairly similar across treatment arms in each trial. The proportions not completing the treatment period as of August 31, 2014, for ongoing trials were also similar across arms. See Tables 8 and 9 (pp. 23-25) in Dr. McEvoy's review for further details. The amount of missing data ranged between 6% and 13% at week 24 across trials. Dr. McEvoy opines that it is unlikely that missing data could be such that it would alter the study conclusions; I agree.

The table below, excerpted from Dr. McEvoy's review (Table 13, p. 34), summarizes the results from the applicant's primary efficacy analyses for all 10 trials, which Dr. McEvoy confirmed. The FDA's preferred analysis yielded similar results (see Table 14, p. 38, of his review), with an estimated excess reduction in LDL-C ranging between 36% and 58% compared to placebo. Although I will not present both the applicant's and FDA's results here for brevity, I agree that it is preferable to include the results in labeling that we believe most appropriately reflect the effect of treatment.

The efficacy of alirocumab in HeFH was evaluated in FH I, FH II, and HIGH FH. In addition, approximately 18% of patients in LONG TERM were known to have HeFH at baseline. As shown in the table below, the treatment difference was consistent in FH I and FH II, and somewhat attenuated in HIGH FH despite all patients in this trial receiving 150 mg Q2W throughout. Interestingly, the within-group change in % LDL-C from baseline to week 24 was similar in all three trials (-49%, -49%, and -46%), yet only ~40% of patients in each of FH I and FH II were uptitrated from 75 mg to 150 mg at week 12. Dr. Golden gives several possibilities for the smaller treatment difference in HIGH FH, but the etiology remains uncertain. Regardless, there is no question that alirocumab substantially lowers LDL-C in the HeFH population as an adjunct to statin and other lipid-modifying therapy.

Table 13. % LDL-C change at week 24 by trial (ITT population; applicants' primary efficacy analysis)

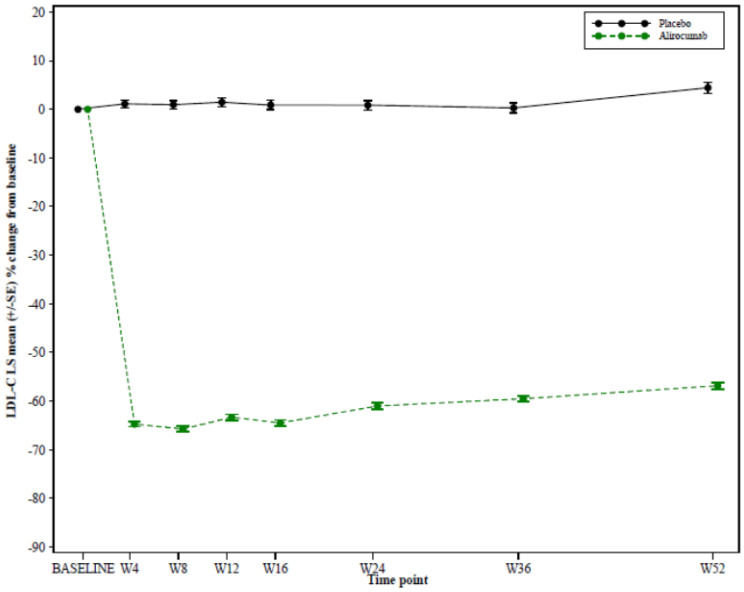
	n*	Baseline (mg/dL)	LS Mean: % Change	Difference: Alirocumab - Control (95%† CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	290	145	-49%	
Placebo (N=163)	149	144	9%	-58% (-63, -53)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	157	135	-49%	
Placebo (N=82)	78	134	3%	-51% (-58, -45)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	63	196	-46%	
Placebo (N=35)	33	201	-7%	-39% (-51, -27)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	189	100	-48%	
Placebo (N=107)	97	105	-2%	-46% (-52, -39)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	1386	123	-61%	
Placebo (N=788)	708	122	1%	-62% (-64, -59)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	428	108	-51%	
Ezetimibe (N=241)	221	104	-21%	-30% (-34, -25)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	50	103	-44%	
Atorvastatin 40mg (N=57)	50	101	-5%	-39% (-56, -22)
Ezetimibe + Atorvastatin 20mg (N=55)	43	101	-20%	-24% (-40, -7)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	41	117	-54%	
Atorvastatin 80mg (N=47)	42	109	-5%	-49% (-65, -34)
Ezetimibe + Atorvastatin 40mg (N=47)	44	99	-23%	-31% (-47, -16)
Rosuvastatin 40mg (N=45)	44	110	-21%	-33% (-48, -17)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	42	108	-51%	
Rosuvastatin 20mg (N=48)	45	106	-16%	-34% (-49, -19)
Ezetimibe + Rosuvastatin 10mg (N=48)	37	102	-14%	-36% (-52, -21)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	45	118	-36%	
Rosuvastatin 40mg (N=53)	48	114	-16%	-20% (-46, 6)
Ezetimibe + Rosuvastatin 20mg (N=53)	47	119	-11%	-25% (-51, 1)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	115	191	-45%	
Ezetimibe (N=125)	108	194	-15%	-30% (-36, -24)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	49	141	-47%	
Ezetimibe (N=51)	46	138	-16%	-32% (-40, -23)

† 99% CI for OPTIONS I and 98.75% CI for OPTIONS II; * N with baseline and week 24 data

The efficacy of alirocumab in patients at high CV risk with hypercholesterolemia not thought to be adequately controlled (LDL-C ≥70 or ≥100 mg/dL depending on trial and medical history), despite maximally tolerated statin therapy and/or other lipid-modifying therapy, was studied in LONG TERM, COMBO I, and COMBO II. The LDL-C reduction at week 24 in LONG TERM (~60%) was the largest observed in the placebo-controlled trials. Although this trial only used the 150 mg Q2W regimen, one cannot assume that the higher dose drove the larger treatment effect; after all, the HIGH FH trial only used this dose as well, yet the estimated treatment difference was much less. COMBO I provides placebo-controlled efficacy data for those with non-familial hypercholesterolemia on maximally

tolerated statin. COMBO II was ezetimibe-controlled, which I do not believe provides additional useful information regarding the LDL-C-lowering effect of alirocumab.

The six trials just described also provided data to support the persistence of efficacy to week 52. Dr. Golden summarizes the results for LDL-C at week 12, 24, and 52 in these trials, showing that the treatment effect is sustained. A representative figure from LONG TERM is shown below.



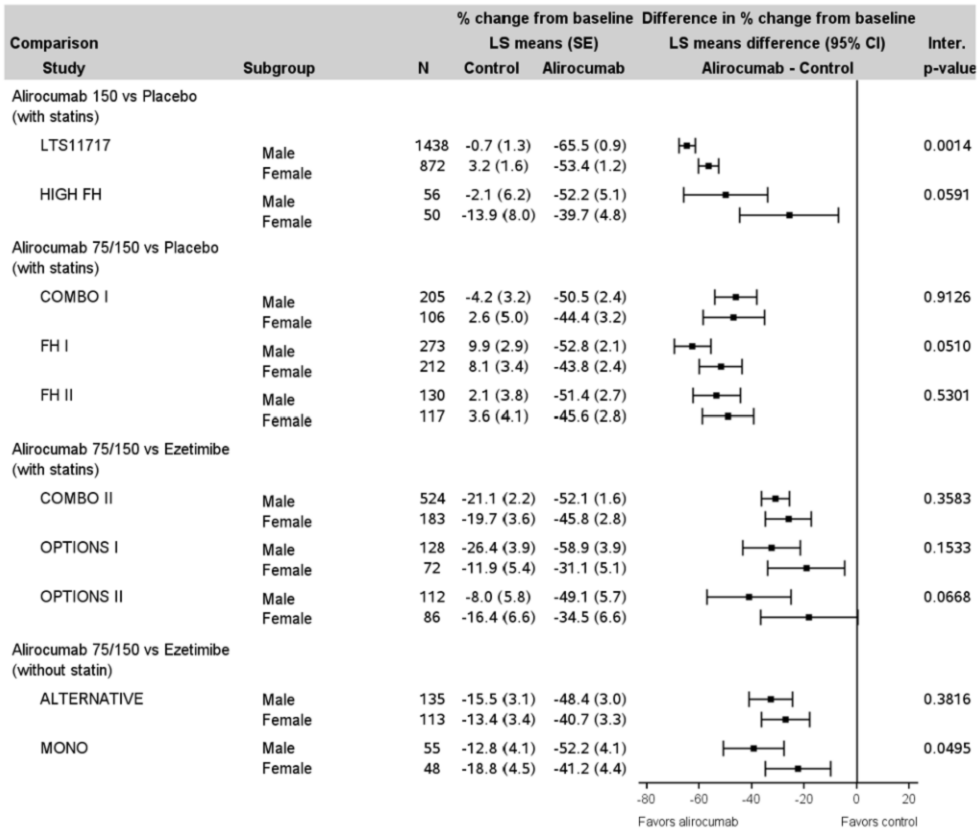
Two trials were conducted in patients not taking statins: MONO and ALTERNATIVE. MONO was conducted in patients with moderate CV risk and LDL-C between 100 and 190 mg/dL who were not on background lipid-modifying therapy. ALTERNATIVE enrolled patients who were purportedly intolerant of statins. Both trials support the LDL-C-lowering efficacy of alirocumab. Regarding MONO, Dr. Golden believes that "it is premature to conclude that monotherapy with alirocumab (i.e., first-line therapy in a moderate-risk population) is appropriate in the absence of CV outcomes data. Note that the mean percent change in LDL-C from baseline for rosuvastatin in a hyperlipidemia patient population ranges from 45% (5 mg) to 63% (40 mg), as compared to 7% for placebo." I agree, and will discuss this further later in this summary review.

ALTERNATIVE enrolled patients who were purportedly intolerant of statins, which was defined as the inability to tolerate at least two statins (one statin at the lowest daily starting dose and another statin at any dose) as a result of skeletal muscle-related symptoms, other than those due to strain or trauma, that began or increased during statin therapy and stopped when statin therapy was discontinued (see full definition in the clinical review, p. 63). Of 361 patients who were screened, 47 (13%) dropped out during a 4-week single-blind placebo run-in period, 23 of whom reported at least one skeletal muscle adverse event during the run-in period. The remaining 314 patients were randomly assigned to alirocumab (titration regimen), ezetimibe, or atorvastatin 20 mg daily (2:2:1 allocation) in a double-blind, double-dummy fashion. Dr. Golden notes that 70% of these purportedly "statin-intolerant" patients who were treated with atorvastatin 20 mg in this trial completed the double-blind 24-week portion of this trial; the proportions of completers in the ezetimibe and alirocumab groups were 70% and 81%, respectively. She notes that although this is a select statin-intolerant population (i.e., these are patients who agreed to be randomized to a statin), it is instructive that a majority of these patients were able to tolerate statin therapy, at least for the duration of the trial. I agree that this trial emphasizes the difficulty in identifying a patient population who is truly intolerant to statins as a pharmacologic class.

Drs. Golden and McEvoy reviewed the OPTIONS I and OPTIONS II trials, and I will not discuss them at any length. These trials intentionally enrolled patients who were not on less than maximally tolerated doses of statins to determine whether adding alirocumab would yield greater LDL-C-lowering than various regimens of statin uptitration or switches. Regarding both trials, Dr. Golden comments that "[a]lthough alirocumab demonstrates numeric ± statistical improvement in LDL-C as compared to other regimens tested, the clinical significance (in terms of CV benefit) has yet to be settled. Higher doses of statins and higher potency statins have demonstrated CV benefit or a trend toward benefit as compared to lower doses of or a lower potency statin. Furthermore,…preliminary data suggest that may be a benefit to the addition of ezetimibe to statin in patients with acute coronary syndrome (ACS). Therefore, in the efficacy reviewer's opinion, superiority claims to these alternative regimens in the absence of CV outcomes data would be inappropriate" (p. 90 of clinical review). Dr. McEvoy notes that OPTIONS II included the only two primary efficacy results that failed to reach statistical significance on the basis of the pre-specified strategy to control type I error. The two non-statistically significant comparisons were tested at the two-sided 1.25% alpha level: adding alirocumab (uptitration regimen) to rosuvastatin 20 mg was not shown to be significantly different than either uptitrating rousvastatin 20 mg to 40 mg (difference, -20%; 98.75% CI, -46, 6; p=0.045) or to adding ezetimibe (difference, -25%, 98.75% CI, -51, +1; p=0.014).

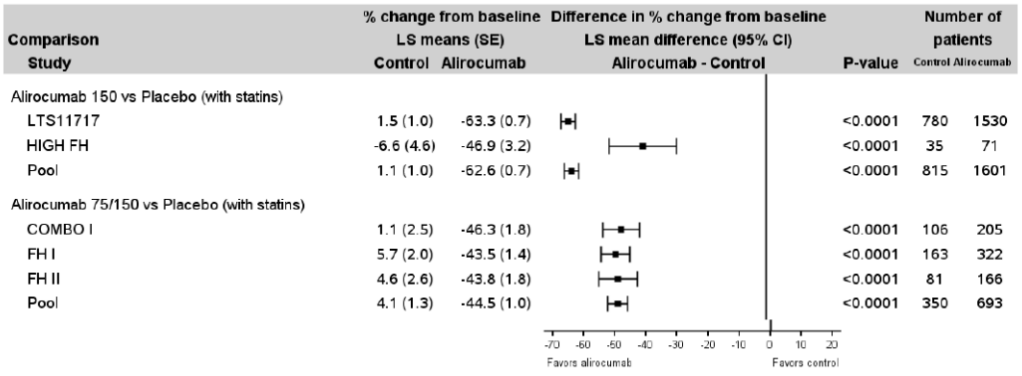
A multitude of secondary endpoints (primarily, hypotheses related to lipid parameters other than LDL-C at various timepoints) were analyzed across trials. Drs. Golden and McEvoy discuss these results in their reviews, and I will not repeat them here. Not surprisingly, given the drug's mechanism of action and its effect on LDL-C, alirocumab reduced total cholesterol, non-HDL-C, and Apo B. Alirocumab also led to statistically significant reductions in Lp(a), ranging from 15% to 26% compared with placebo when added to maximally tolerated statin. Dr. Golden notes that epidemiological studies suggest that Lp(a) levels are independently associated with atherosclerotic disease, but it is unclear if modifying Lp(a), per se, with alirocumab would reduce cardiovascular risk among patients with well-controlled LDL-C but elevated Lp(a). The effects of alirocumab on TG were not statistically significant across all placebo-controlled trials and the observed effects on HDL-C (ranging from 4% to 8%, with the 4% observed in HIGH FH not being statistically significant); the clinical relevance of these changes is uncertain.

Drs. Golden and McEvoy both evaluated results from the analysis of the primary efficacy endpoint across multiple subgroups (e.g., age, sex, race, ethnicity, region, BMI, diabetes, HeFH, statin use or intensity, baseline LDL-C and other lipid parameter thresholds, baseline total and free PCSK9 levels, CrCl thresholds) in individual trials that could support an analysis of a particular subgroup of interest. Taken together, there is no evidence of any qualitative interactions; i.e., alirocumab appears to lower LDL-C in all subgroups evaluated. Drs. Golden and McEvoy both note that there appears to be a quantitative interaction for sex: the estimated effect on LDL-C was larger for males than females in all 10 trials (see figure below from the clinical review, p. 111). The etiology of this observation remains uncertain.



A major limitation of the designs of trials in this development program is that they provide no data to directly compare the effect of the 75 mg Q2W regimen with the 150 mg Q2W regimen without relying on post-randomization factors or cross-trial comparisons. Regarding cross-trial comparisons, the week 12 results from COMBO I, FH I, and FH II provide data for the effect of 75 mg Q2W compared with placebo, and the week 12 results from LONG TERM and HIGH FH provide data for the effect of 150 mg Q2W compared with placebo. (As noted previously, the latter two trials yielded quite disparate results with regard to LDL-C lowering for unclear reasons.) These results are summarized in the figure below.

Figure 20. Percent Change in LDL-C from Baseline at Week 12, Phase 3 Placebo-Controlled Trials



Note: LTS11717 = LONG TERM
Source: SCE, Figure 20

Examining LDL-C profiles over time from individual trials also suggests that additional LDL-C lowering was associated with the increase in dose (see Figure 6, p. 28, of Dr. McEvoy's review), although Dr. McEvoy notes that this was not consistently observed in every trial. Although patients who required uptitration had higher levels of baseline LDL-C, the applicant has not provided evidence that there exists some LDL-C cutoff at which one should initiate therapy with 150 mg Q2W. Similarly, because 75 mg Q2W and 150 mg Q2W were not studied in a parallel-group trial, we cannot estimate an average treatment effect for each dose, which could potentially guide dosing instructions (e.g., if a patient requires LDL-C reduction exceeding some percentage, they ought to start with the 150 mg Q2W dose). In fact, Figure 16 (p. 55) in Dr. McEvoy's review shows that there were a substantial number of patients with substantially elevated baseline LDL-C values that did not uptitrate, suggesting that they achieved "goal" while using the 75 mg Q2W regimen. Taken together, I believe that given the data provided at this time, it is rational to recommend initiating all patients with 75 mg Q2W with an instruction to assess LDL-C within 4-8 weeks to guide dosage adjustments. It should also be noted that since some patients may achieve maximal reduction on this regimen, it ought to be recommended to check LDL-C again after uptitration so that the provider can assess whether doubling the dose appeared to provide any additional benefit.

Last, I will note that the effect of alirocumab on cardiovascular outcomes has not been determined since too few major adverse cardiovascular events (93 adjudicated MACE total in the 10 phase 3 trials) occurred in this program to provide a reliable assessment of this effect. I will briefly discuss the available data in the safety section of this review.

8. SAFETY

Dr. Mary Roberts reviewed the safety of alirocumab; she recommends approval if limited to high-risk patients on maximally tolerated statin therapy (discussed later in this review).

The safety of alirocumab was evaluated in four phase 2 trials and ten phase 3 trials that included a total of 3340 patients exposed to alirocumab as of August 31, 2014. The phase 2 trials were short (one 8-week and three 12-week) compared to the phase 3 trials, but they only contributed 158 (4.7%) of the alirocumab-treated patients in the phase 2/3 safety database. Various safety pools were analyzed: a placebo-controlled pool that combines nine trials (four phase 2, five phase 3), a placebo-controlled pool limited to the five phase 3 trials; an ezetimibe-controlled pool (five phase 3 trials), a phase 3 pool (ten trials), and a "global" pool (14 phase 2/3 trials).

In the placebo-controlled pool, 2476 patients were treated with alirocumab and 1276 with placebo. The median duration of injection exposure was 65 weeks in both groups, with ~80% in each group exposed for at least 52 weeks, providing 2759 patient-years of exposure to alirocumab and 1408 patient-years of exposure to placebo (all five phase 3 placebo-controlled trials used 2:1 allocation). In the ezetimibe-controlled pool, 864 patients were treated with alirocumab and 618 with ezetimibe. The median duration of injection exposure was 27 and 24 weeks, respectively, providing 692 patient-years of exposure to alirocumab and 419 patient-years of exposure to placebo.

As noted previously, no trial studied 75 mg Q2W and 150 mg Q2W in a parallel-group fashion; therefore, there are no head-to-head safety data comparing these two doses. Of the 3188 patients randomized to alirocumab in phase 3 trials, approximately half participated in the 8 trials that used an uptitration scheme. Dr. Roberts agreed with the applicant, however, that it was reasonable to pool safety data from both doses for the main safety analyses after considering exploratory analyses that compared adverse event (AE) incidences between those who uptitrated and those who did not, as well as cross-trial comparisons. Although this is suboptimal, the trial designs simply do not allow

randomized comparisons by dose. In the placebo-controlled pool, the exposure to the 75 mg Q2W and 150 mg Q2W doses were 535 and 2224 patient-years, respectively; in contrast, in the ezetimibe-controlled pool, the exposures to these doses were 595 and 97 patient-years, respectively.

Because of the longer duration of exposure, the greater proportion of exposure to the 150 mg Q2W dose, the consistency of study designs, the use of maximally tolerated statin therapy, and the preference for a placebo control when describing safety data, I will primarily focus on the placebo-controlled pool in this summary review; see Dr. Roberts's review for additional results. In this pool, the mean age was 59 years, 40% were women, 90% were white, 4% were black, and 6% were Hispanic. Overall, 64% had known coronary heart disease [CHD], 8% had a history of ischemic stroke/TIA, 19% were current smokers, 31% had diabetes, mean BMI was 30 kg/m^2, and 16% had eGFR 30 to <60 mL/min/1.73m^2.

Multiple adverse events of interest were pre-specified based on nonclinical findings or theoretical risks: local injection site reactions, general allergic events, neurological events (focusing on myelin-sheath related disorders), neurocognitive disorders, musculoskeletal-related disorders (for ALTERNATIVE), diabetes mellitus, hepatic disorders, ophthalmologic events, and adjudicated CV events. For most of these categories, MedDRA SMQs (or company queries, CMQs) were used to identify potentially related events. For each, the applicant provided incidence, incidence rate, hazard ratio using a Cox model stratified on study, an assessment of treatment effect across studies, assessment of risk over time using study-adjusted Kaplan-Meier estimates, and treatment effect across subgroups.

Deaths, SAEs, AEs Leading to Discontinuation

The overall safety findings from the placebo- and ezetimibe-controlled pools are shown in the following table from Dr. Roberts's review. Overall, the proportions of patients who experienced any AE, SAE, or AE leading to treatment discontinuation were very similar between the alirocumab and control groups.

Table 75. Overview of TEAE (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Patients with any TEAE	975 (76.4)	1876 (75.8)	421 (68.1)	607 (70.3)
Patients with any treatment emergent SAE	182 (14.3)	340 (13.7)	69 (11.2)	113 (13.1)
Patients with any TEAE leading to death	11 (0.9)	13 (0.5)	7 (1.1)	2 (0.2)
Patients with any TEAE leading to treatment discontinuation	65 (5.1)	131 (5.3)	60 (9.7)	76 (8.8)

Source: ISS Table 14
Placebo-controlled studies phase 3: LONG TERM, FH I, FH II, HIGH FH, COMBO I; phase 2 DFI11565, DFI 11566, CL-1003, DFI12361
Ezetimibe-controlled studies phase 3: COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE

No patients died in phase 1 or phase 2 studies. In the global pool of phase 3 studies, there were 37 deaths on study: 20 (0.6%) of 3182 alirocumab-treated patients and 17 (0.9%) of 1792 control-treated patients. The majority were blindly adjudicated as being cardiovascular in nature (15 [0.5%] vs. 11 [0.6%] for alirocumab and control, respectively). Dr. Roberts reviewed the narratives of alirocumab-treated patients who died and did not find any that strongly suggested a causal relationship between alirocumab and the fatal event.

The incidence of SAEs (fatal and nonfatal combined) in the placebo-controlled pool was 13.7% and 14.3% for alirocumab and placebo, respectively. At the system organ class (SOC) level, the largest contributor of SAEs was *Cardiac disorders*; however, the incidence of any event in this SOC was similar

between treatment groups (4.4% alirocumab, 4.5% placebo). With the exception of the SOCs of *Nervous system disorders* (47 [1.9%] vs. 19 [1.5%] for alirocumab and placebo, respectively), *Investigations* (7 [0.3%] vs. 1 [<0.1%]), *Reproductive system and breast disorders* (4 [0.2%] vs. 1 [<0.1%]), *Skin and subcutaneous tissue disorders* (2 [<0.1%] vs. 0), *Endocrine disorders* (1 alircoumab), and *Social circumstances* (1 alirocumab), the proportion of SAEs occurring in the alirocumab treatment group was the same or slightly lower than the proportion occurring in the placebo treatment group at the SOC level. Individual preferred terms for SAEs that occurred in ≥0.5% of patients, and more commonly in the alirocumab group than placebo, included unstable angina (1.0% vs. 0.7%), angina pectoris (0.6% vs. 0.5%), coronary artery disease (0.6% vs. 0.2%), and noncardiac chest pain (0.6% vs. 0.5%). Although this list may seem to suggest that several CV-related SAEs favor placebo, the absolute risk differences for these events are very small and, not unexpectedly, Dr. Roberts notes that several others favor alirocumab. In sum, I agree that there is no signal of cardiovascular risk in the current safety database based on these SAEs. Dr. Roberts did not identify any other topics of specific concern based on the reported SAEs; I will summarize incidences when relevant in the subsequent discussion.

In the placebo-controlled pool, 5.3% and 5.1% of alirocumab- and placebo-treated patients permanently discontinued therapy because of a nonfatal TEAE. Ten (0.4%) alirocumab-treated patients and no placebo-treated patients discontinued treatment as a result of an AE in the *Skin and subcutaneous disorders* SOC, most commonly pruritus and rash-related events. The most frequently reported individual preferred terms for TEAEs leading to discontinuation of alirocumab, and occurring at a higher incidence than placebo, were increased ALT and myalgia (n=4 [0.2%] for each) and anemia, vertigo, and pruritus (n=3 [0.1%] each).

Selected AEs of Interest

Dr. Roberts comprehensively reviews the safety data related to multiple potential adverse consequences of the drug; see her review for full details. I will limit my discussion to the results related to allergic reactions/hypersensitivity and injection site reactions, neurologic/neurocognitive events, diabetes, liver-related safety, cardiovascular safety, and her exploration for adverse events related to very low LDL-C.

General Allergic Events & Injection Site Reactions

General allergic events were identified using the SMQ "hypersensitivity," excluding preferred terms associated with local injection site reactions. A modestly higher proportion of alirocumab-treated patients compared with placebo reported a TEAE in this category (8.6% vs. 7.8%) in the placebo-controlled pool. The most commonly reported preferred term that occurred more often in alirocumab-treated patients, and also had the greatest absolute risk difference, was pruritus (1.1% vs. 0.4%); none of these events were serious and only 3 of the 28 alirocumab-treated patients who reported this AE permanently discontinued treatment because of it. The proportions of patients with SAEs potentially related to "hypersensitivity" were balanced in each group (0.4% in both alirocumab and placebo); the majority of these patients had a history of allergies or asthma. There were no cases of anaphylaxis in alirocumab-treated patients. In the 120-day safety update, there was one serious report of anaphylaxis requiring intubation in an alirocumab-treated patient at a dose of 300 mg Q4W in the CHOICE I trial (ongoing trial not included in the safety pool), approximately 1.5 years after the first dose. This patient was re-challenged with a single dose of alirocumab after recovery without signs and symptoms, but treatment was then discontinued. There have also been isolated (or very few) serious reports of leukocytoclastic vasculitis, angioedema, laryngeal edema and rash, hypersensitivity, and nummular eczema. Some cases of hypersensitivity resulted in hospitalization, and others left sequelae (e.g., post-inflammatory hyperpigmentation after a skin reaction diagnosed as nummular eczema, which began

as an allergic skin reaction on day 1 of study drug administration). Given the serious nature of the events, allergic reactions should be listed in WARNINGS AND PRECAUTIONS, and patients who experience serious hypersensitivity reactions should not restart alirocumab.

Because sham injections were included in all trials, Dr. Roberts summarized the incidence of local injection site reactions (ISRs) using the global pool of phase 2/3 studies: 6.1% with alirocumab and 4.1% with control; no ISR met criteria as an SAE; and similar proportions of patients discontinued treatment because of an ISR (0.2% alirocumab, 0.3% placebo). Although the majority of ISRs were mild, a higher proportion of alirocumab-treated patients had moderate reactions (11.2% vs. 7.7%), and the only severe reaction was in the alirocumab group. In addition, alirocumab-treated patients were more likely to have ≥1 ISR (36.1% vs. 19.2%), a reaction after first dose (22.0% vs. 15.4%), and longer duration of symptoms (15.2 vs. 11.1 days).

Neurologic & Neurocognitive Events

Neurologic events related to myelin-sheath disorders or neuropathies were collected based on the theoretical concern that low LDL-C levels may impair myelination. Using an SMQ-based approach, in the placebo-controlled pool, there were similar proportions of neurological events of interest in the alirocumab and placebo groups (3.5% in each); in the ezetimibe-controlled pool, the incidence was modestly higher with alirocumab (3.4% vs. 2.4%). Dr. Roberts summarizes the individual preferred terms for these events in Table 94 in her review. Across the phase 2/3 program, there were 7 serious neurologic SAEs identified in this manner among alirocumab-treated patients and 2 among control. Dr. Roberts discusses four notable cases at length: optic neuritis; Miller-Fisher syndrome; demyelination (suspicious of multiple sclerosis); and transverse myelitis. In addition, the Division of Neurology Products was consulted to review these seven cases. The consultant concluded that "[r]arely occurring treatment emergent neurological syndromes or adverse events cannot be completely ruled out. Miller Fisher syndrome and transverse myelitis are so rare that a single case of either is unexpected in this clinical trial population. However, none of the cases are definitive, each is lacking in important supportive clinical or laboratory findings, and there appears to be no evidence supporting a particular biological pathway that would give alirocumab a propensity to cause such side-effects. We recommend that the review division consider classifying demyelinating adverse events as Adverse Events of Special Interest, and asking for enhanced investigation and reporting of such events." I note that the ongoing CVOT has already designated Neurologic/Neurocognitive AEs as AEs of Special Interest, and we will incorporate this into a post-marketing requirement to further assess this signal. The consultant also conducted an independent review using a custom MedDRA query for potential events related to peripheral neuropathy; he did not find evidence that alirocumab increases the risk for these 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, alirocumab 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. To assess the incidence with alirocumab, AEs were identified using custom queries. The table below from Dr. Roberts's review summarizes the results. In the placebo-controlled trials, the preferred terms "confusional state" and "memory impairment" both occurred at a higher incidence in the alirocumab group (0.2% for each) than in the placebo group (<0.1% for each). There were 3 (0.1%) and 2 (0.2%) neurocognitive SAEs in the alirocumab and placebo groups, respectively.

Table 97. Number (%) of patients with Neurocognitive TEAEs of interest by CMQ and PT (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Neurocognitive disorders				
n (%)	9 (0.7)	21 (0.8)	6 (1.0)	8 (0.9)
# of pts with an event per 100 pt-yrs[1]	0.6	0.7	1.3	1.1
95% CI	0.3 to 1.2	0.5 to 1.1	0.5 to 2.8	0.5 to 2.2
HR (95% CI)[2]	1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)	
Neurocognitive disorders (CMQ)	**9 (0.7)**	**21 (0.8)**	**6 (1.0)**	**8 (0.9)**
Confusional state	1 (<0.1)	6 (0.2)	2 (0.3)	2 (0.2)
Amnesia	2 (0.2)	5 (0.2)	2 (0.3)	1 (0.1)
Memory impairment	1 (<0.1)	5 (0.2)	0	3 (0.3)
Disturbance in attention	1 (<0.1)	2 (<0.1)	2 (0.3)	0
Confusion postoperative	0	1 (<0.1)	0	0
Dementia	2 (0.2)	1 (<0.1)	0	0
Disorientation	0	1 (<0.1)	0	0
Frontotemporal dementia	0	1 (<0.1)	1 (0.2)	0
Transient global amnesia	1 (<0.1)	1 (<0.1)	1 (0.2)	0
Aphasia	0	0	0	1 (0.1)
Delirium	1 (<0.1)	0	0	0
Dementia Alzheimer's type	1 (<0.1)	0	0	1 (0.1)
Hallucination	0	0	0	1 (0.1)

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

Diabetes

Dr. Roberts devoted considerable attention to the assessment of whether alirocumab 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.[9] Thus, Dr. Roberts explored this topic in various safety pools, including stratification by baseline glycemic status defined in various ways.

Overall, identifying potential adverse events using a custom query, the proportion of patients having an AE related to the incidence of diabetes or complications of diabetes was higher for alirocumab than placebo (4.2% vs. 3.8% in the placebo-controlled pool) and lower for alirocumab than ezetimibe (2.9% vs. 3.6% in the ezetimibe-controlled pool). When restricted to patients without diabetes at baseline (per medical history), alirocumab had a lower incidence of these AEs in both pools.

Evaluation of mean changes from baseline in both fasting plasma glucose and HbA1c in the phase 3 placebo-controlled pool (only includes 52-week placebo-controlled trials) and in the ezetimibe-controlled pool (24 weeks) did not show consistent, meaningful changes over time, whether one considers changes from baseline to last on-treatment, highest on-treatment, or week 52 (placebo)/week 24 (ezetimibe). Furthermore, such measures of central tendency did not reveal a signal when examined across baseline status of glucose control (normal, impaired fasting glucose, or diabetes mellitus).

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

Because measures of central tendency can sometimes mask low-frequency outlier effects that might be potentially important, Dr. Roberts also conducted various exploratory analyses that assessed shifts in glycemic control, determined using laboratory data. Representative results are summarized below, showing that higher proportions of alirocumab-treated patients shifted to a worse glycemic category at least one time during the trial. In contrast, however, a higher proportion of patients also "improve" (i.e., shift from impaired fasting glucose (IFG) at baseline to normal throughout the rest of the trial) in the alirocumab group than the placebo group, although this was not consistent in the ezetimibe-controlled pool.

Table 114. Shifts in glucose control category during TEAE period (safety population) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1174 n/N1 (%)	Alirocumab N=2318 n/N1 (%)	Ezetimibe N=618 n/N1 (%)	Alirocumab N=864 n/N1 (%)
Total individuals with shift to worse glycemic category	**114/785 (14.5%)**	**274/1583 (17.3%)**	**50/417 (11.9%)**	**73/556 (13.1%)**
Normal to Impaired	97/365 (26.6%)	224/718 (31.2%)	42/174 (24.1%)	59/223 (26.5%)
Normal to Diabetes	1/365 (0.3%)	1/718 (0.1%)	0	1/223 (0.4%)
Impaired to Diabetes	16/420 (3.8%)	49/865 (5.7%)	8/243 (3.3%)	13/333 (3.9%)
Total individuals with shift to improved glycemic category	**76/1174 (6.5%)**	**178/2318 (7.7%)**	**77/618 (12.5%)**	**94/864 (10.9%)**
Impaired to normal	76/420 (18.1%)	178/865 (20.6%)	77/243 (31.7%)	94/333 (28.2%)

Source: ISS Appendix Table 1.5.2.2.1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period, by baseline glucose control status

I created 2x2 contingency tables using results above from the placebo-controlled pool (not shown), and I note that these differences in proportions between treatment groups are not statistically significant (Any shift to a worsening category, p=0.15; Normal at baseline to Impaired/Diabetes, p=0.13; Impaired at baseline to Diabetes, p=0.15).

In her summary of safety, Dr. Roberts states that "[i]t is uncertain whether the observed shifts represent a true risk for worsening glycemic control with alirocumab treatment. Glycemic control is monitorable and treatable, factors which should be considered when evaluating the benefits and risks associated with alirocumab." I concur. Given the lack of any signal related to changes in measures of central tendency for glucose or HbA1c combined with the modest differences in the glycemic shifts noted above, we do not have sufficient data at this time to conclude that alirocumab 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. Roberts reviewed liver-related safety using both adverse event data as well as laboratory data. The general conclusions were similar from each analysis. Higher proportions of patients treated with alirocumab, compared with placebo, reported adverse events identified using the *Hepatic disorders* SMQ (2.5% vs. 1.8%), and most of these related to laboratory abnormalities. Liver-related adverse events led to treatment discontinuation for 0.4% and 0.2% of patients treated with alirocumab and placebo, respectively. Dr. Roberts notes that positive rechallenge has been observed, suggesting that alirocumab does have the potential to cause elevated transaminases.

There was a modestly higher proportion of alirocumab-treated patients who had elevations in ALT >3x ULN, although the same pattern was not consistently observed for AST. In the ezetimibe-controlled trials, there were no patients with ALT or AST >5x ULN among ezetimibe-treated patients, but among alirocumab-treated patients, 5 (0.6%) had ALT >5x ULN and 4 (0.5%) had AST >5x ULN. These data are summarized in the table below, from Dr. Roberts's review.

In the BLA submission, there were three cases that met the laboratory criteria for Hy's Law, but all had alternative etiologies (hepatitis A, cholangitis, and acute cholecystitis). In addition, Dr. Roberts identified an additional apparent Hy's Law case that was submitted to IND 105574 (alirocumab) as a 15-day safety report for a patient participating in an open-label extension study who developed symptomatic severe liver injury and jaundice, leading to an urgent consultation with Drs. John Senior and Mark Avigan of the Office of Surveillance and Epidemiology. The applicant was urgently asked to provide additional information regarding this case and to query their entire safety database to identify any additional potential cases that met Hy's Law criteria in all ongoing and completed trials. We quickly learned that hepatitis E IgM were detected on 05 March 2015 for this case of liver injury and jaundice, and Drs. Senior and Avigan confirmed that the clinical syndrome was consistent with hepatitis E and unlikely to be related to drug. Furthermore, when the applicant queried their database as requested, no confirmed Hy's Law cases were found.

Table 103. Hepatic biochemistry: Categorical increase in liver enzymes (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

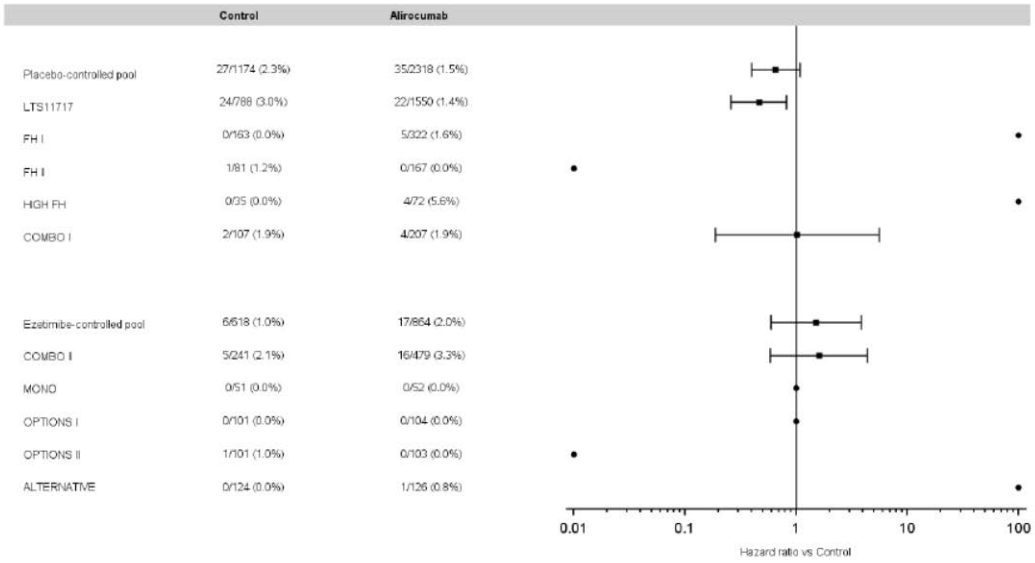
	Placebo-controlled				Ezetimibe-controlled			
	Placebo N=1276		Alirocumab N=2476		Ezetimibe N=618		Alirocumab N=864	
	n/N1	%	n/N1	%	n/N1	%	n/N1	%
ALT elevation								
≥3x ULN (if BL ALT < ULN) or ≥2x baseline (if BL ALT ≥ULN)	13/1266	1.0	34/2453	1.4	1/612	0.2	10/850	1.2
>3x ULN	18/1266	1.4	41/2455	1.7	1/612	0.2	9/850	1.1
>5X ULN	7/1266	0.6	8/2455	0.3	0	0	5/850	0.6
>10X ULN	3/1266	0.2	2/2455	<0.1	0	0	1/850	0.1
>20x ULN	1/1266	<0.1	1/2455	<0.1	0	0	1/850	0.1
AST elevation								
>3x ULN	18/1266	1.4	28/2455	1.1	0	0	10/849	1.2
>5X ULN	5/1266	0.4	7/2455	0.3	0	0	4/849	0.5
>10X ULN	3/1266	0.2	3/2455	0.1	0	0	1/849	0.1
>20x ULN	1/1266	<0.1	1/2455	<0.1	0	0	0	0
Alkaline phosphatase elevation								
>1.5x ULN	13/1266	1.0	11/2455	0.4	6/612	1.0	7/850	0.8
Bilirubin elevation								
>2x ULN	6/1266	0.5	13/2456	0.5	2/612	0.3	5/850	0.6
ALT >3x ULN and Bili >2x ULN	2/1266	0.2	1/2455	<0.1	0	0	0	0

Cardiovascular Safety

Dr. Roberts assessed cardiovascular safety by considering investigator-reported AEs/SAEs (i.e., in the *Cardiac disorders* SOC) as well as by considering analyses that only included events confirmed by a blinded adjudication committee. In the placebo-controlled pool, 199 (8.0%) and 115 (9.0%) of alirocumab- and placebo-treated patients, respectively, reported an event within the *Cardiac disorders* SOC; of these, similar proportions reported at least one cardiac SAE (4.4% alirocumab, 4.5% placebo). In the ezetimibe-controlled pool, 76 (8.8%) and 44 (7.1%) of alirocumab- and ezetimibe-treated patients, respectively, reported an event in this SOC; a slightly higher proportion of alirocumab-treated patients reported SAEs (5.6% alirocumab, 4.0% ezetimibe). Dr. Roberts summarizes the incidences of these events by high-level terms (and preferred terms within the HLT *Ischemic coronary artery disorders*); there were no striking differences that suggest a cardiovascular safety signal.

In the phase 3 trials, suspected CV events (as well as abnormal values of CK, CK-MB, and troponin I or T) and all deaths were adjudicated by a clinical events committee, managed by the Duke Clinical Research Institute, blinded to both treatment assignment and LDL-C results. Major adverse cardiovascular events (MACE) were defined as CHD death (including undetermined cause), non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization. In the applicant's on-treatment analysis (included events occurring within 70 days of last dose) of phase 3 trials, MACE occurred in 52 (1.6%) patients in the alirocumab group and 33 (1.8%) patients in the control group (HR 0.81; 95% CI, 0.52-1.25). This was primarily driven by the LONG TERM trial; estimates across trials were not consistent (see the figure below), although there were too few events to describe the effect of alirocumab on MACE with any certainty.

Figure 1. Positively adjudicated MACE, by phase 3 study



Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Studies with no event in at least one treatment group are conventionally displayed as follows:
dot at HR=1 in case of no event in both groups, dot at right extremity in case of 0 event in control arm, dot at left extremity in case of 0 event in alirocumab arm
Source: ISS, Figure 19

Dr. McEvoy conducted an ITT analysis, which identified 93 total MACE in the ten trials, 58 in the alirocumab group and 35 in the control groups. The majority of events came from LONG TERM (52 MACE) and COMBO II (21 MACE). Dr. McEvoy notes that in the placebo pool, the incidence of MACE was smaller for alirocumab than placebo (1.8% vs. 2.4%), yielding a cause-specific HR 0.74 (95% CI, 0.46, 1.19), but in the ezetimibe-controlled pool, the frequency of MACE was greater for alirocumab (1.4% vs. 1.1%), which was driven by an excess in fatal and non-fatal MI events with alirocumab (1.3% vs. 0.7%).

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.

In the global pool of phase 2 and phase 3 trials, Dr. Roberts notes that 722 and 1371 patients treated with alirocumab had at least one calculated LDL-C value <15 and <25 mg/dL. (Note that calculated LDL-C values this low usually underestimate the true LDL-C somewhat.) Furthermore, 288 and 796 patients treated with alirocumab had at least two consecutive LDL-C values <15 and <25 mg/dL, respectively. Exploring safety in the low LDL-C subgroups carries substantial limitations, as the alirocumab-treated patients who achieved LDL-C <25 mg/dL may differ with respect to important characteristics compared with alirocumab-treated patients who did not achieve LDL-C <25 mg/dL, as Dr. Roberts describes in her review.[10] Nevertheless, I note that overall, the proportions of alirocumab-treated patients with AEs, SAEs, AEs leading to treatment discontinuation, and deaths, were quite similar regardless of whether very low LDL-C levels were achieved (and even compared to control patients, although these are not randomized comparisons).

Dr. Roberts also reviewed the available data regarding hemolytic anemia (no cases), cortisol and adrenal function, gonadal hormones, and fat-soluble vitamins. 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.

Dr. Roberts concludes that the currently available data do not demonstrate a safety signal related to very low LDL-C values, although she stresses the limitations of the available analyses and notes that it is uncertain what, if any, adverse effects will result from prolonged exposure to very low levels of LDL-C. I concur that although we have not identified a specific safety concern at this time, longer-duration trials will be necessary to further inform any potential risks.

Immunogenicity

In the ten placebo- and active-controlled phase 3 trials, a treatment-emergent positive anti-drug antibody (ADA) response was detected in 147 (4.8%) and 10 (0.6%) patients treated with alirocumab and control, respectively.[11] Among alirocumab-treated patients, persistent ADA (detected in ≥2 consecutive samples at least 12 weeks apart) was identified in 39 (1.3%) patients. The median time to first occurrence of ADA was ~12 weeks. Neutralizing antibodies (NAbs) were measured after baseline in 1.2% of alirocumab-treated patients and in no control-treated patient. Only 10 (0.3%) patients had ≥2 positive samples for NAbs. Dr. Roberts reviewed the AEs occurring in patients with NAbs and did not identify a particular safety concern.

Development of ADA did not appear to affect incidence of overall AEs among alirocumab-treated patients (75.9% without a positive ADA response vs. 76.2% with a positive ADA response). I do note, however, that there was a higher incidence rate of injection site reactions among those who developed ADA (9.9 vs. 5.4 events per 100 patient-years among ADA-positive and ADA-negative, respectively).

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[10] In response to an information request, the applicant attempted to explore the potential safety of very low LDL-C using additional analytical techniques, such as a propensity score analysis. The Division of Biometrics VII was asked to comment on the applicant's analyses, and they highlight the uncertainty about the reliability of the findings given concerns with both the applicant's propensity score approach and analyses of post-randomization subgroups, in general (Statistical Memorandum by Janelle Charles, Ph.D., dated 22 June 2015).

[11] Pre-existing reactivity was observed in 1.4% and 1.1% of alirocumab- and control-treated patients, respectively. For these patients, a ≥4-fold increase in titer after baseline was required to be considered a positive treatment-emergent ADA response.

SAEs were reported for 16.3% vs. 14.1% of patients with and without a positive ADA response. There were no individual SAEs reported for >2 patients with a positive ADA response.

Dr. Golden reviewed patient-level data and found that many of the cases of ADA were transient and had no obvious effect on LDL-C. Other cases could not be interpreted, as NAbs were identified at the end of dosing. However, she did identify 8 cases of NAbs (and one case of high-titer non-NAb ADA) that appeared to be associated with loss of efficacy, including one patient who developed LDL-C concentrations above baseline in associated with NAbs. In addition, there were two cases of NAbs potentially associated with enhanced efficacy.

Dr. Amy Rosenberg, Director of the Division of Biotechnology Review and Research III, also provided assessments related to immunogenicity. Regarding potential effects on efficacy, she described the same cases that Dr. Golden reviewed and reached similar conclusions that ADA might lead either to loss of efficacy or, less frequently, enhanced efficacy. Dr. Rosenberg recommended a few post-marketing commitments related to the further assessment of the consequences of developing ADA and NAbs with prolonged treatment. In a separate memo, Dr. Rosenberg provided an immunogenicity evaluation from a safety perspective. She notes that two patients with ADA discontinued treatment because of generalized hypersensitivity responses, but the etiology of these reactions is not well-understood since isotype analysis or skin testing was not performed; she recommended post-marketing commitments to further evaluate the nature of such reactions and how they might be mitigated. In addition, she raises the concern that a hypothetical concern remains that if dosing were to continue in the presence of a robust antibody response, delayed (type III) hypersensitivity responses could occur, causing immune complex diseases. Such reactions have not been observed in clinical trials to date.

During the review cycle, there was much internal discussion between the clinical review team and the OBP reviewers, including Dr. Rosenberg, regarding potential immunogenicity-related PMRs/PMCs. Ultimately, the clinical reviewers recommended that the incidence and severity of injection site reactions, hypersensitivity, and immunogenicity be evaluated in a large, randomized, controlled, long-term trial as a post-marketing requirement. In addition, they recommended a post-marketing commitment related to developing an algorithm for decision-making in the face of loss of efficacy due to antibody response. Although Dr. Rosenberg also wanted a commitment for the company to take responsibility, as long as the product is marketed, for testing for ADA in cases of hypersensitivity or loss of efficacy, the Division did not believe this would be warranted as a PMC based on the data observed to date with their product. This could certainly be reconsidered, of course, if additional safety and immunogenicity data accrued in the required long-term trial produce concerns that would support such a commitment.

9. ADVISORY COMMITTEE MEETING

This BLA was discussed with the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 9 June 2015. The committee was asked to discuss the safety of alirocumab as observed in the clinical development program, to which the general consensus was that there were no serious safety signals observed with alirocumab treatment at this time. However, several members noted that the current safety database is limited to a relatively short duration of exposure and small number of patients relative to the very large target population (estimated in the millions) that the applicant had proposed for approval. It was noted that some adverse events may emerge or become more clearly defined only after several years of exposure; therefore, the applicant's ongoing CVOT was considered very important to help inform benefit/risk. The panel did acknowledge that there is little evidence, at present, to suggest that very low levels of LDL-C are harmful. The concern was raised, however, that

physicians may respond to such levels by lowering or discontinuing statins, which have more safety data and demonstrated CV benefit.

The committee was also asked to discuss whether alirocumab-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. In general, the committee expressed uncertainty regarding whether changes in LDL-C are sufficient to substitute for an effect on clinical outcomes, especially given that alirocumab is a new class of drug. Many agreed, however, that an effect on LDL-C may be sufficient to substitute for an effect on CV outcomes in specific patient populations, such as those with a phenotype that results from abnormal LDL metabolism (e.g., familial hypercholesterolemia). In addition, some members appeared to find the mechanism of action of alirocumab reassuring, as it is a targeted therapy that results in upregulation of LDLR, similar to statins; the Mendelian randomization studies that suggest a cardioprotective effect of *PCSK9* loss-of-function were also cited as supportive.

The committee was asked, "Has the applicant sufficiently established that the LDL-C-lowering benefit of alirocumab exceeds its risks to support approval in one or more patient populations? We remind you that under the current regulatory pathway, it would not be required to successfully demonstrate an effect of alirocumab on CV outcomes after an approval based on changes in LDL-C." Thirteen members voted "yes" and three members voted "no." In their comments, members who voted "yes" unanimously supported approval for HeFH. Some, but not all, believed that benefit/risk would also be favorable for patients at high CV risk whose LDL-C is not adequately controlled with maximally tolerated (or high-dose) statin, or in the setting of secondary prevention with insufficient response to maximally tolerated statin. These members generally agreed that alirocumab should not be approved for a broad, primary prevention population, including patients identified only as having mixed dyslipidemia or diabetes, until a benefit on CV outcomes has been established.

The three members who voted against approval stated that this drug should not be approved until a CVOT establishes benefit. Concern was also expressed that approval prior to the completion of the ongoing CVOT could lead to patients prematurely discontinuing study medication in the trial.

10. PEDIATRICS

This application was discussed with the PeRC on 27 May 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 (b) (4) years of age because studies would be impossible or highly impractical and to the deferral of studies in patients (b) (4) to less than 17 years of age. The (b) (4) years had been suggested by the applicant based on study design considerations influenced by the European Medicines Agency. Upon further consideration during the review cycle, however, the Division believed that it would be more appropriate to waive studies for children with HeFH younger than 10 years, since alirocumab will be approved as an adjunct to maximally tolerated statin therapy. Except for pravastatin, which is labeled for pediatric HeFH down to 8 years, all other statins that include an indication for pediatric HeFH are labeled for ≥10 years. Thus, to be consistent with alirocumab's position as an add-on to statin therapy, we will require a dose-finding study and an efficacy/safety study in patients 10 to <18 years with HeFH, but we will state that if children younger than age 10 are included in the protocol, the eligibility criteria should ensure that other available interventions to lower LDL-C have been insufficient. Furthermore, because the final agreed-upon indication references treatment of patients with clinical atherosclerotic cardiovascular disease, we will waive pediatric studies in this population because they would be impossible or highly impractical as this condition rarely occurs in pediatric patients. I

discussed these changes with Dr. Lynne Yao, Director (acting) of the Division of Pediatric and Maternal Health, and she agreed with this approach.

11. OTHER RELEVANT REGULATORY ISSUES

Financial Disclosures

The clinical reviewers 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 (p. 42 and Appendix 9.6 of the clinical review).

Clinical Inspections

The clinical inspection for this BLA consisted of 7 domestic and 7 foreign clinical sites, representing 16 sites (four each from LONG TERM, FH I, COMBO II, and ALTERNATIVE) as well as the sponsor and clinical research organization (b) (4) Four clinical sites were issued a Form FDA-483; preliminary classifications for each were VAI. Dr. Kleppinger concluded, however, that the violations were unlikely to significantly impact primary safety and efficacy analyses; therefore, the data from these sites are considered acceptable for use in supporting this application. The remaining 10 clinical sites, the CRO, and the sponsor were not issued a Form FDA-483. Dr. Kleppinger concluded "…the inspectional findings support validity of data as reported by the Sponsor under this BLA."

12. LABELING

DMEPA reviewed the proposed proprietary name, Praluent, and concluded that it is 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 to "PRALUENT is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C." I will describe the basis for this recommendation in the next section of this memo.

Regarding Dosing & Administration, the applicant proposed various ways to suggest that the starting dose of Praluent could be either 75 mg or 150 mg Q2W, (b) (4) As I have discussed in the efficacy section of this review, the applicant has not studied these two dosing regimens in a parallel-group trial, and the protocols that studied 75 mg/150 mg used an efficacy criterion (i.e., LDL-C value) to determine whether the dose should be up-titrated. Thus, we do not have a well-characterized estimate of the treatment effect of each dose in the same population. We do not know what would have happened to LDL-C had alirocumab been up-titrated in the patients who had achieved their "target" LDL-C on the 75 mg dose (and, therefore, remained on this dose for the duration of the trial). Given that the LDL-C reduction in response to alirocumab occurs quickly, LDL-C is routinely measured in clinical practice, and LDL-C does not need to be emergently lowered to optimum levels, I believe that it is rational to recommend an initial dose of 75 mg Q2W followed by subsequent up-titration in the event of an inadequate response. Providers would, of course, have the information from the CLINICAL STUDIES section that 150 mg Q2W has been used as a starting dose in clinical trials (i.e., LONG TERM and HIGH FH). Nevertheless, the logic of initiating with the lower dose could be articulated with language such as, "The recommended starting dose of PRALUENT is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve

sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Measure LDL-C levels within 4 to 8 weeks of initiating or titrating PRALUENT to assess response and adjust the dose, if needed."

With regard to adverse events, the clinical reviewers have recommended largely limiting the description of adverse reactions to the placebo-controlled pool. I concur.

The clinical reviewers recommend only including the descriptions of the five phase 3 placebo-controlled trials in the CLINICAL STUDIES section (LONG TERM, COMBO I, FH I, FH II, HIGH FH). I agree that these trials would support the indication described above, and the patients in these trials were all taking maximally tolerated statin therapy. Given the similarity in study designs and populations, it is reasonable to pool FH I and FH II. I also agree with the reviewers that the (b) (4) [redacted] recognize that some patients will be unable to take statins for a variety of reasons. Section 12.3 notes the lack of a clinically meaningful drug-drug interaction between statins and alirocumab that would impact dosing recommendations; therefore, it ought to be apparent to prescribers that alirocumab would be prescribed similarly to patients who are not taking statins, if clinically appropriate. Last, the ALTERNATIVE trial highlights the challenges of identifying patients who are truly intolerant of statins. Although I certainly applaud the applicant taking on the challenge of conducting such a trial with a double-blind, statin re-challenge arm, its results do not provide additional information important to the safe and effective use of alirocumab. Prescribers may be interested in whether alirocumab is better tolerated than atorvastatin in this population, but this trial does not provide substantive evidence to support such claims.

Last, the clinical reviewers recommend limiting the efficacy results presented in labeling to LDL-C, apo B, non-HDL-C, and total cholesterol. Alirocumab 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. 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 as the clinical reviewers have recommended is appropriate and should not affect the ability of providers to use alirocumab safely and effectively.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

Risk/Benefit Assessment

There is no question that treatment with alirocumab 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.[12]

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.[13,14] 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.[15]

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 find this history informative and relevant to 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 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 alirocumab is reassuring. Although there have been some serious hypersensitivity events that warrant labeling as Warnings & Precautions, I agree with the clinical reviewers and 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; not unexpectedly, the current safety database is relatively small and short duration in comparison. I concur with the reviewers and advisors that some adverse events may emerge or become more clearly defined only after years of exposure to a larger number of patients; such events may or may not be 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

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

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

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

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

recommendation of the clinical reviewers and 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. Identified risks of concern will be studied as post-marketing requirements (see below).

I believe that benefit/risk is favorable for patients with 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 alirocumab. Although HeFH 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 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. The clinical reviewers' 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:

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

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 alirocumab 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 alirocumab 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 alirocumab. 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; I do not believe, however, that using terms such as "statin-intolerant" in labeling, when it remains unclear how to identify patients who are truly intolerant of the pharmacological class, is necessary and may be counterproductive.

Furthermore, I agree with the clinical reviewers 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.[16] 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 alirocumab would be expected to have a low propensity for off-target effects, I believe that alirocumab 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 for a future approval in a broader patient population.

Recommended Regulatory Action

- Approval

Recommendations for Risk Evaluation and Mitigation Strategies

- None. This recommendation is supported by OSE/DRISK (see Dr. Amarilys Vega'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 alirocumab to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to alirocumab 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 alirocumab treatment will be evaluated.[17]
- A randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with alirocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

Regarding PMCs, the applicant will be asked to commit to developing an algorithm for decision-making in the face of loss of efficacy due to antibody response. In addition, microbiology has recommended several PMCs, which I support.

[16] 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.

[17] 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.

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/s/

JAMES P SMITH
07/24/2015