CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125559Orig1s014

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA / SE8
Application Number	125559
Priority or Standard	Standard
Submit Date	24 Oct 2017
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Division / Office	DMEP / ODE2
Reviewer Name	Julie Golden, M.D.
Review Completion Date	16 Aug 2018
Established Name	Alirocumab
Trade Name	Praluent
Therapeutic Class	PCSK9 inhibitor
Applicant	Sanofi-Aventis U.S. LLC
Formulation	Solution for injection
Dosing Regimen	150 mg every 2 weeks
Indication	LDL-C-lowering (as an adjunct to diet and maximally tolerated statin therapy)
Intended Population	Adults with HeFH on LDL-C apheresis

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approving this supplement. In patients with heterozygous familial hypercholesterolemia (HeFH) on regular background apheresis and other lipid-lowering drugs, changes in LDL-C and other relevant lipid parameters were significantly greater with use of alirocumab (Praluent) versus use of placebo. This is useful information to include in Sections 2 (Dosage and Administration) and 14 (Clinical Studies) in product labeling. I do not think that language about apheresis in Section 1 (Indications and Usage) section is necessary, as alirocumab is already approved for the HeFH population.

1.2 Risk Benefit Assessment

The benefits of lowering LDL-C with alirocumab in a population of patients with HeFH on apheresis is favorable considering its acceptable safety profile.

(b) (4)

Praluent is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as 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, (b) (4)

The ESCAPE trial was a randomized, double-blind, placebo-controlled phase 3 study to compare the effect of alirocumab 150 mg every 2 weeks (Q2W) vs. placebo on the frequency of LDL apheresis treatments in patients with HeFH who were already undergoing LDL apheresis therapy every 1 or 2 weeks. The primary endpoint was the rate of apheresis treatments during the 12-week period from week 7 to week 18, normalized by the number of planned apheresis treatments according to each patient's established schedule at screening. Secondary objectives were to evaluate the effect of alirocumab vs. placebo on LDL-C, ApoB, non-HDL-C, total cholesterol, and other lipid parameters, in addition to evaluating the effect on safety and tolerability, PK, anti-alirocumab antibodies, PCSK9 levels, and quality-of-life (QOL).

The review of the primary endpoint was substantially limited by: (1) the clinical meaningfulness; i.e., it is not clear if the benefits of apheresis withdrawal – primarily related to presumed improvement in QOL – outweigh the risks of potentially less-than-optimal LDL-C control, and (2) the systematic errors and biases introduced into the trial,

primarily related to the point-of-care (POC) device for calculating LDL-C in the field as compared to the central laboratory LDL-C result. Although the primary endpoint is statistically favorable, for these reasons I believe the result is uninterpretable and not appropriate to include in product labeling.

In the first 6 weeks of the trial, prior to adjustments being made in apheresis, the mean LDL-C reductions from baseline in patients randomized to alirocumab + apheresis were greater than in those randomized to placebo + apheresis. The following table provides the results of some key lipid secondary endpoints, controlled for multiplicity, and demonstrates that the mean percent reduction in pre-apheresis LDL-C at 6 weeks in patients on their typical background apheresis schedules is significantly greater in those on alirocumab vs. placebo. Because an analysis of the time-averaged LDL-C supports these findings, I believe that changes in LDL-C (if confirmed by the FDA statistical reviewer) are appropriate to include descriptively in the clinical studies section of the Praluent label.

Table 1. Pre-Apheresis Lipid Changes at Week 6 by Treatment

Key Secondary Endpoint	Alirocumab	Placebo	P-value
LS mean percent change from baseline in LDL-C	-53.7%	1.6%	<0.0001
LS mean percent change from baseline in ApoB	-42.8%	1.2%	<0.0001
LS mean percent change from baseline in non-HDL-C	-47.1%	2.8%	<0.0001
LS mean percent change from baseline in total cholesterol	-36.4%	3.1%	<0.0001

Source: Clinical Overview, Table 3

In this relatively small trial in a population of patients with HeFH on regular LDL apheresis, the safety of alirocumab appeared generally consistent with the safety profile in other clinical trials of alirocumab.

Overall, more adverse events (AEs) of fatigue, myalgia, and diarrhea were reported in the alirocumab group versus the placebo group during the double-blind period. In the open-label period in a subgroup of patients, the only preferred term reported in more than 1 patient was anemia (2/29, 6.9%).

No deaths occurred during the ESCAPE trial. A total of 4 patients on alirocumab (9.8%) and 2 patients on placebo (9.5%) had at least 1 SAE during the double-blind treatment period, and 1 patient had 2 SAEs during the open-label portion of the trial. The relationship to alirocumab of an SAE of muscle rupture with compartment syndrome during the double-blind period could not be confirmed or dismissed by this reviewer. The other SAEs that occurred in alirocumab-treated patients seemed unlikely related to drug.

Two patients in the alirocumab group (4.9%) and 1 patient in the placebo group (4.8%) experienced AEs that led to study drug discontinuation during the double-blind period. No patients discontinued due to an AE during the open-label period.

No new concerns were identified in AEs of special interest, such as injection site reaction and potential allergy AEs, increases of ALT, hemolytic anemia, neurocognitive or neurological events, ophthalmologic disorders, very low LDL-C, hepatitis C seroconversion, or anti-drug antibodies (ADAs). There were too few cardiovascular events to draw any conclusions in this small trial.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). The drug product as used in the trial described in this supplement was presented as a subcutaneous injection at doses of 150 mg/mL solution for injection in a single-use pre-filled pen. This is an approved product.

2.2 Currently Available Treatments for Proposed Indications

The sponsor is proposing adding the following information to the currently approved Praluent indication (new language underlined):

Praluent is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as 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 (b) (4)

While evolocumab, the other PCSK9 inhibitor approved in the U.S., does not have an identical indication, evolocumab is approved to treat patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other therapies including apheresis.

2.3 Availability of Proposed Active Ingredient in the United States

Alirocumab is currently marketed in the U.S. with the tradename 'Praluent' in doses of 75 mg every 2 weeks (Q2W), 150 mg Q2W, and 300 mg every 4 weeks (Q4W).

2.4 Important Safety Issues With Consideration to Related Drugs

Known safety concerns with the class include hypersensitivity/allergic reactions and injection site reactions. Additional potential safety concerns that continue to be followed post-marketing include cataracts, immunogenicity, hepatitis C seroconversion, development of diabetes mellitus, and potential concerns associated with very low LDL-C, including hemolytic anemia and neurologic/neurocognitive events. As of May 1, 2018, psychiatric events, and as of July 19, 2018, influenza-like illness were being followed by FDA as Tracked Safety Issues [TSIs]). The psychiatric events TSI was closed as of August 6, 2018.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2. Chronology of Prior Substantive Communications Relevant to the sBLA

Topic	Date	Type of Interaction	Key Outcome(s)
Discussion on the design and patient population for the ODYSSEY ESCAPE (R727-CL-1216) study	25 Sep 2014 (IND 105574, SN#0315)	Protocol Amendment – new protocol submission	Submission of the ODYSSEY ESCAPE (R727-CL-1216) original protocol, dated 28 Aug 2014.
	06 Oct 2014	FDA Advice Letter	Agency provided the following comments and recommendations: • Based on the references noted in the submission, apheresis can reduce LDL-C by approximately 50-60%, therefore the Agency did not agree with the proposed threshold of 30% to withhold LDL-C. • The Agency noted that it believed that 40-50% reduction was more reasonable threshold to withhold apheresis. • The trial as designed did not present any worrisome safety concerns, however it would not support any efficacy claim or support a justification (b) (4) (b) (4)
	23 Apr 2015 (IND 105574, SN#0378)	Protocol Amendment – change in protocol submission	Submission of the ODYSSEY ESCAPE (R727-CL-1216) amended protocol version 1, dated 15 Apr 2015.
	8 Jul 2015 (IND 105574, SN#0395)	Protocol Amendment – change in protocol submission	Submission of the ODYSSEY ESCAPE (R727-CL-1216) amended protocol version 2, dated 06 Jul 2015.
	29 Sep 2015 (IND 105574, SN#0413)	Protocol Amendment – change in protocol submission	Submission of the ODYSSEY ESCAPE (R727-CL-1216) amended protocol version 3, dated 22 Sep 2015.
Submission of the Statistical Analysis Plan (SAP) for ESCAPE	19 Feb 2016 (IND 105574, SN#0439)	Statistical Analysis Plan for R727-CL-1216 submission	Submission of the ODYSSEY ESCAPE (R272-CL-1216) SAP, version 1, dated 03 Feb 2016. • The SAP was consistent with rules and conventions already included in the SAPs for all seven of the Phase 3a studies previously submitted to the Agency, except for the differences driven by the specific study design.

Topic	Date	Type of Interaction	Key Outcome(s)
Agreement on the structure, content, and submission of the sBLA to support the 150 mg Q2W dosing regimen as an adjunct to apheresis	18 May 2017 (BLA 125559, SN#0141)	Type B Meeting Request (pre-sBLA, clinical and regulatory topics) submission	Submission of a Type B Meeting Request for a pre-sBLA meeting to discuss the content and structure of an anticipated supplemental Biologics Licensing Application. Sponsor addressed the comments and recommendations regarding study design received from the Agency 06 Oct 2014
	01 Jun 2017	FDA Meeting Request Granted	Agency grants the Sponsor a Type B pre-sBLA Meeting – A 60 minute teleconference on 27 Jul 2017 at 10:00AM eastern time.
	23 Jun 2017 (BLA 125559, SN#0149)	Type B Meeting Briefing Package (pre-sBLA, clinical and regulatory topics) submission	Submission of the Type B, pre-sBLA meeting briefing package. Sponsor's proposal for sBLA includes: • A new indication statement based on the efficacy and safety data from the ESCAPE trial • Providing modules 1 (relevant sub-sections), 2.5, 2.7.2, and the final CSR in the application
	24 Jul 2017	FDA Preliminary Meeting Comments	Agency provided the following preliminary comments: • A new indication based on the trial is unlikely as FDA does not believe that the trial describes a new use of the drug. • The Agency agrees that some information regarding the use of the drug in relation to apheresis may be helpful to providers and patients and therefore agrees that the ESCAPE trial would be adequate to support an sBLA submission. • The Agency requests several additional analyses to be included in the sBLA.
	27 Jul 2017	Type B Meeting – Teleconference (pre-sBLA, clinical and regulatory topics)	The Sponsor met with the Agency via teleconference.
	25 Aug 2017	FDA Final Meeting Minutes	The final meeting minutes were received from the Agency. • The Agency agreed that the results of the ESCAPE trial are adequate to support submission of an sBLA • The Agency reiterated that the trial would not support the new indication proposed in the briefing package, but that the Sponsor could propose alternative language for consideration. • The Agency agreed with the proposed formatting of the submission.

Source: Regulatory History (Module 1), Table 1

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

See Section 6.1.4 for a discussion of LDL-C measurement issues that were uncovered during the review that substantially impacted the interpretation of the primary endpoint as well as analyses of LDL-C during the apheresis-withholding phase of the trial. These findings are also discussed in detail in Dr. Brad McEvoy's statistics review.

A number of minor errors in the R727-CL-1216/ESCAPE CSR were also identified during review, none of which impacted the overall interpretation of the results.

The sponsor responded to information requests during the course of the review in a forthcoming and timely manner.

3.2 Compliance with Good Clinical Practices

The sponsor confirmed that the trial submitted in this supplement was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements.

The final clinical study protocol, as amended, was subject to health authority and Institutional Review Board and/or Independent Ethics Committee approval prior to initiation, as applicable, and adverse events (AEs) were reported according to local laws.

3.3 Financial Disclosures

Table 3. Summary of Financial Disclosure Information

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 51		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Source: Financial Disclosure, Summary

Clinical investigators for ESCAPE with disclosable financial interests, including equity interests in the sponsors as defined by 21 CFR 54.2(b) and significant payments of other sorts as defined by 21 CFR 54.2(f) are listed in the table below:

Table 4. Clinical Investigators with Disclosable Financial Interests

Country	Center ID	Investigator Name (Principal Investigator in bold)	Center Address	Patients Enrolled
[redacted]				(b) (6)

Source: Financial Disclosure Information (Module 1), Table 2

(b) (6) (principal investigator) received $35,299.74 for attendance at conferences, advisory panel meetings, forums, speaker programs, and honoraria from (b) (6) from March 2015 until August 2016.

(b) (6) (principal investigator) received $30,193.32 for attendance at conferences, advisory board meetings, consulting services, and honoraria from (b) (6) from March 2015 until August 2016.

(b) (6) (sub-investigator) received $27,800.12 for attendance at conferences, advisory board meetings, consulting services, speaker programs, and honoraria from (b) (6) from March 2015 until August 2016.

(b) (6) (principal investigator) received $64,439.80 for attendance at conferences, advisory board meetings, consulting services, speaker programs, and honoraria from (b) (6) from March 2015 until August 2016.

Of note, the 17 patients impacted by investigators with financial disclosures is 17 out of a total of 62 patients (27.4%) randomized in the trial.

The sponsor states that bias has been minimized due to the following:

- The trial employed double-blind masking for the collection of safety and efficacy data
- Patients were randomly assigned to treatment arms
- The quality of data reported by investigators and the adherence to the protocol were followed during the course of the studies by the central clinical team blinded to treatment arm

Reviewer comment: I agree that although the study was small and therefore a small number of potential conflicted investigators could have proportionally more

influence than in larger trials, the ESCAPE trial was designed in such a way that such conflicts should have been minimized to the extent possible. Importantly, investigators were blinded to subjects' LDL-C values during the double-blinded portion of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new chemistry information was provided in this submission.

4.2 Clinical Microbiology

No new microbiology information was provided in this submission.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was provided in this submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

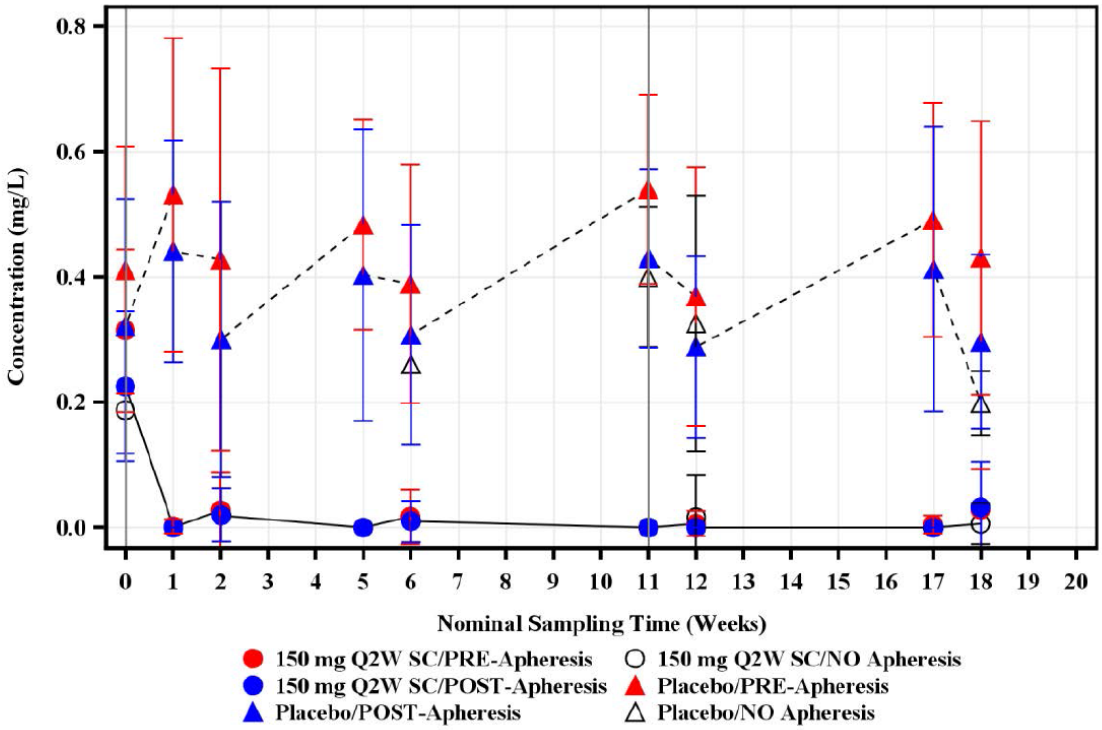
No new information was provided in this submission regarding the mechanism of action of alirocumab.

4.4.2 Pharmacodynamics

The pharmacodynamics (PD) of alirocumab was described in the original BLA review. This section will focus on PD information relevant to utilizing alirocumab with apheresis. PD results were presented as the concentrations of total and free PCSK9.

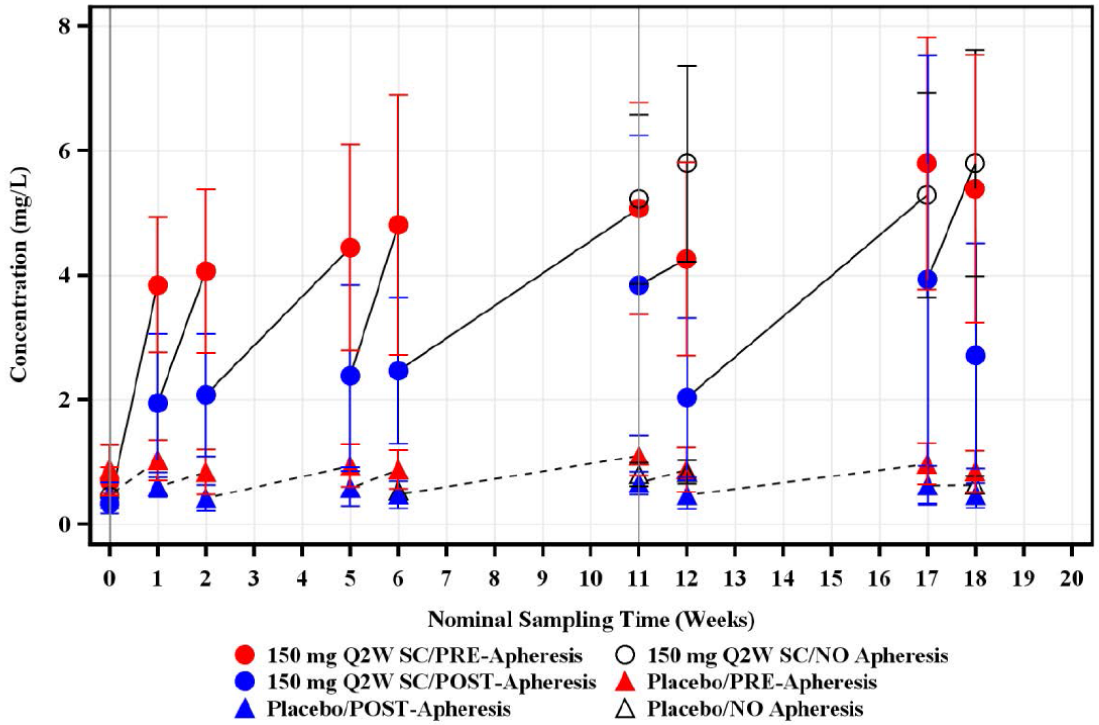
In patients receiving alirocumab, free PCSK9 concentrations were reduced below the level of quantitation regardless of whether patients received apheresis. The following figure illustrates mean free PCSK9 concentrations in patients treated with alirocumab vs. placebo in the ESCAPE trial.

Figure 1. Mean (±SD) Free PCSK9 Concentrations Obtained Pre- and Post-Apheresis or Without Apheresis vs. Nominal Time by Treatment Group



Note: BLQs were set to 0. Week 11 (vertical line) is the first sampling when apheresis schedules were no longer fixed and some patients did not receive apheresis.
Source: Clinical Pharmacology Report, Figure 5

In patients receiving alirocumab, total PCSK9 concentrations were increased from baseline and remained relatively stable, consistent with sustained target saturation. Concentrations of total PCSK9 post-apheresis were lower by approximately 40% to 50% compared to pre-apheresis concentrations.



Note: BLQs were set to 0. Week 11 (vertical line) is the first sampling when apheresis schedules were no longer fixed and some patients did not receive apheresis.

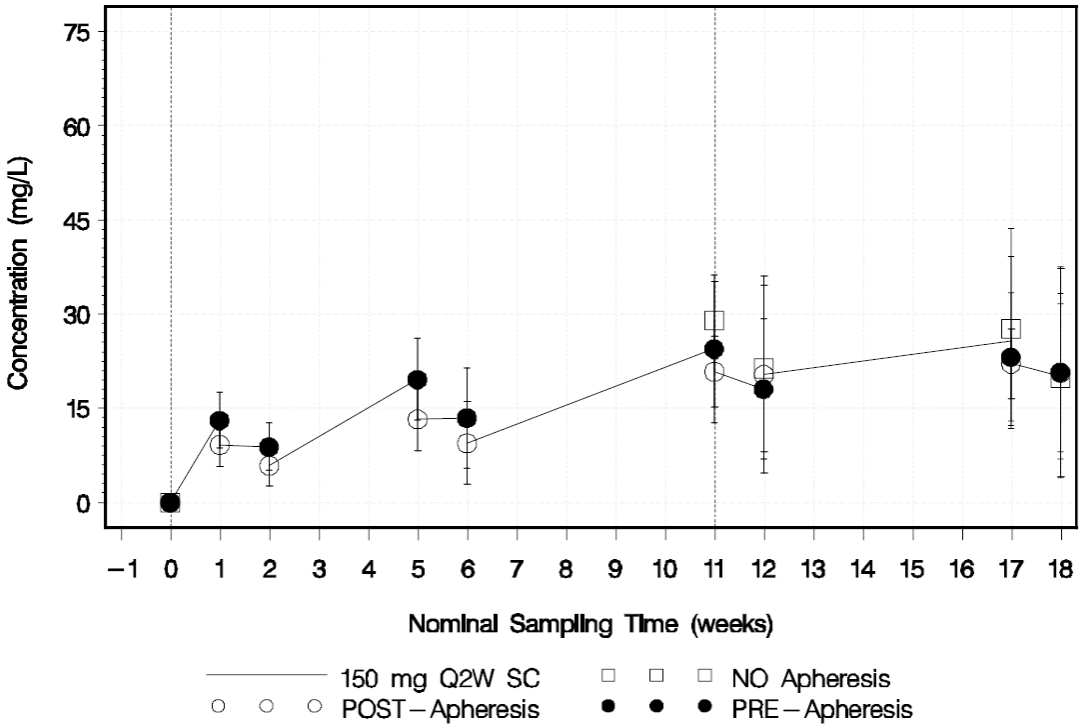
Source: Clinical Pharmacology Report, Figure 7

4.4.3 Pharmacokinetics

The pharmacokinetics (PK) of alirocumab was described in the original BLA review. This section will focus on PK information relevant to utilizing alirocumab with apheresis. PK results were presented as the concentrations of total alirocumab.

A numeric difference was observed post-apheresis compared to pre-apheresis in total alirocumab concentrations, but this difference was not considered clinically meaningful. The following figure illustrates the mean concentrations, with the concentrations in patients who received no apheresis over the tested period included for descriptive purposes.

Figure 2. Mean (±SD) Total Alirocumab Concentrations Obtained Pre- and Post-Apheresis or Without Apheresis vs. Nominal Time



Note: BLQs were set to 0. Week 11 (vertical dotted line) is the first sampling when apheresis schedules were no longer fixed and some patients did not receive apheresis.
Source: Summary of Clinical Pharmacology, Figure 1

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Not applicable. Only one trial was submitted in this submission: R727-CL-1216, hereafter referred to as ESCAPE.

5.2 Review Strategy

This efficacy supplement relies on the safety and efficacy of the single phase 3 trial, ESCAPE.

5.3 Discussion of Individual Studies/Clinical Trials

The ESCAPE trial was a randomized, double-blind, placebo-controlled phase 3 study to compare the effect of alirocumab 150 mg Q2W vs. placebo on the frequency of LDL apheresis treatments in patients with HeFH who were already undergoing LDL apheresis therapy every 1 to 2 weeks. The primary endpoint was the rate of apheresis

treatments during the 12-week period from week 7 to week 18, normalized by the number of planned apheresis treatments according to each patient's established schedule at screening. Secondary objectives were to evaluate the effect of alirocumab vs. placebo on LDL-C, ApoB, non-HDL-C, total cholesterol, and other lipid parameters, in addition to evaluating the effect on safety and tolerability, PK, ADAs, PCSK9 levels, and QOL.

The study consisted of a screening period, a double-blind treatment period, an open-label treatment period, and a follow-up period (see Figure 3 for a schematic of the double-blind portion of the trial). Entry into the open-label treatment period was available only to patients who were study participants in a country in which alirocumab was not commercially available (i.e., Germany).

Figure 3. Study Design for the Double-Blind Portion of the ESCAPE Trial

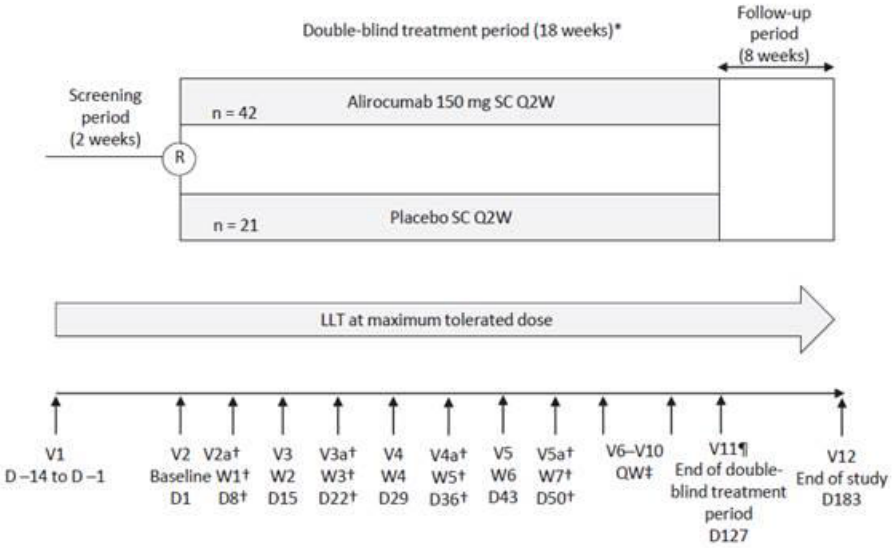


Figure 1 Study design. *Patients will receive alirocumab 150 mg subcutaneously or placebo Q2W at visits 2 through 10, starting at day 1. †Visits at these times are mandatory for patients undergoing lipoprotein apheresis QW but not for patients undergoing apheresis Q2W. ‡Visits 6 through 10 (as in visits 2 through 5) will each have an optional sub-visit, 6a through 10a, when study drug will not be administered but are mandatory for patients undergoing lipoprotein apheresis QW. ¶All patients will be seen at visit 11 and will complete all end of double-blind treatment period assessments; patients will then undergo dosing procedures for the first visit of the open-label treatment period. D, day; Q2W, every 2 weeks; QW, every week; V, visit; W, week.

Source: Clinical Overview, Figure 1

Patients who had been on a stable apheresis schedule (every 7 or 14 days) for at least 4 weeks prior to screening, and on stable background medical lipid-modifying therapy for at least 8 weeks prior to screening, entered a 2-week screening period, during which eligibility was confirmed. Patients were then randomized 2:1 to receive alirocumab or placebo. Randomization was stratified according to apheresis frequency (QW vs. Q2W) and baseline Lp(a) concentrations (normal [< 30 mg/dL] vs. elevated [≥ 30 mg/dL]).

In the first 6 weeks of the double-blind period, patients received study drug/placebo on days 1, 15, and 29 and apheresis frequency was fixed according to each patient's established schedule. During weeks 7 to 18 of the double-blind period, patients

received study drug/placebo on days 43, 57, 71, 85, 99, and 113 and apheresis frequency was adjusted based on each patient's response to treatment; i.e., apheresis was not administered when the point-of-care (POC)* LDL-C value at that visit was at least 30% lower than the pre-apheresis LDL-C value at baseline. The investigator was blinded to the LDL-C value and was only alerted as to whether LDL apheresis was needed.

Reviewer comment: FDA did not support this study design; in part, it was felt that it did not reflect a realistic clinical scenario, as decision-making would have to be made at every planned apheresis session. In order to evaluate whether alirocumab could substitute for apheresis long-term, one possible approach would be to randomize patients to alirocumab vs. apheresis (open-label), with LDL-C evaluated for either superiority or noninferiority between the two therapies. This concept was conveyed to the sponsor in pre-submission discussions; see Section 6.1.4. Other study designs might be reasonable, depending on the hypothesis.

* Technical issues with the calculation of LDL-C and LDL-C change include the following:

The POC calculated LDL-C used a different blood sample source (finger stick into portable device) than the sample used for the electronic data capture (EDC) calculated LDL-C (vial of blood collected for the central laboratory). POC calculated LDL-C blood samples were collected pre-apheresis and used to determine the necessity for apheresis (the POC calculated LDL-C percent change from baseline was derived using the EDC calculated LDL-C value at baseline). POC LDL-C was not collected prior to first administration of study drug. Blood samples for EDC calculated LDL-C were drawn immediately prior to and immediately following the apheresis procedure (where applicable).

Since LDL-C was only measured pre- and post-apheresis on a Q2W basis only, these results are not available in intervening weeks in patients on the QW apheresis schedule.

Reviewer comment: See Section 6.1.4, Analysis of the Primary Endpoint, for FDA communication to the sponsor regarding these issues during the filing period.

LDL-C was calculated using the Friedewald formula.[1] If TG values exceeded 400 mg/dL then the central lab would reflexively measure LDL-C using the beta quantification method.

1 Friedewald WT, et al. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.

Patients who chose not to participate in the open-label treatment period, or who were study participants in a country in which alirocumab was commercially available (i.e., U.S.), were seen at the week 26 double-blind treatment period end-of-study visit and were considered to have completed the study at this end-of-study visit.

Treatment with alirocumab 150 mg Q2W was administered to those patients who continued in the open-label period through week 76, or until alirocumab became commercially available in the patient's country, whichever came first.

Reviewer comment: The open-label portion of this trial was only evaluated for safety in this review.

Key inclusion criteria were as follows: adults with a diagnosis of HeFH by either genotypic or clinical criteria, and undergoing a stable schedule of LDL apheresis[2] therapy every week (QW) for at least 4 weeks or Q2W for at least 8 weeks prior to screening with the initiation of apheresis at least 5 months prior to that. Key exclusion criteria were as follows: HoFH, newly diagnosed or poorly controlled DM, use of systemic corticosteroids, SBP/DBP > 160/100, history of MI, hospitalized unstable angina, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, TIA, or carotid revascularization within 3 months, endovascular procedure or surgical intervention for PVD within 1 month, NYHA Class III or IV heart failure within 12 months, history of hemorrhagic stroke, cancer within 5 years, pregnancy, TG > 500 mg/dL, eGFR < 15 mL/min/1.73 m^2, or ALT/AST/CK > 3x ULN.

6 Review of Efficacy

Efficacy Summary

The ESCAPE trial was an 18-week double-blind, randomized controlled trial evaluating alirocumab 150 mg Q2W vs. placebo in patients with HeFH on regular (Q2W or QW) LDL apheresis. In the first 6 weeks of the double-blind period, patients received study drug/placebo Q2W and apheresis frequency was fixed according to each patient's established schedule. During weeks 7 to 18 of the double-blind period, patients received study drug/placebo Q2W and the individual patient's apheresis frequency was adjusted based on his or her LDL-C result. The primary endpoint was the rate of apheresis treatment from week 7 to week 18, normalized by the number of planned apheresis treatments according to each patient's established schedule.

The efficacy review is substantially limited by: (1) the clinical meaningfulness of the primary endpoint; i.e., it is not clear if the benefits of apheresis withdrawal – primarily related to presumed improvement in QOL – outweigh the risks of potentially suboptimal LDL-C control, and (2) the systematic errors and biases introduced into the trial,

2 Acceptable apheresis techniques were: Double membrane filtration, Immunoadsorption, Heparin-induced LDL precipitation, Direct adsorption of lipids, Dextran sulfate adsorption (plasma), Dextran Sulfate adsorption (whole blood)

primarily related to the POC device for calculating LDL-C in the field as compared to the central laboratory LDL-C result. Specifically, LDL-C values obtained using the POC device were consistently lower than test results from the central laboratory, and in addition, no baseline LDL-C values were collected using the POC device (baseline from the central laboratory was used in the calculation of percent change in LDL-C). Because the POC tended to overestimate LDL-C lowering, the primary error leading to systematic bias was the inappropriate withholding of apheresis in some patients. Additionally, an error in the POC device was uncovered during the review [missing value codes in the POC device were coded as numeric values (1-8) and these values were then mistakenly interpreted by the automated IVRS system as actual LDL-C values]. Finally, an additional complication in interpretation was that pre- and post-apheresis LDL-C values were not collected for odd-numbered weeks in patients who had apheresis performed weekly.

Reviewer comment: For these reasons, although the primary endpoint is statistically positive, I believe the result is uninterpretable and therefore inappropriate for product labeling.

In the first 6 weeks of the trial, prior to adjustments being made in apheresis, the mean pre-apheresis LDL-C reductions from baseline in patients randomized to alirocumab + apheresis were greater than in those randomized to placebo + apheresis. The following table provides the results of some of the key lipid secondary endpoints, controlled for multiplicity. Because an analysis of the time-averaged LDL-C supports these findings, I believe that changes in LDL-C (if confirmed by the FDA statistical reviewer) are appropriate to include in the clinical studies section of the Praluent label:

Table 5. Pre-Apheresis Lipid Changes at Week 6 by Treatment

Key Secondary Endpoint	Alirocumab	Placebo	P-value
LS mean percent change from baseline in LDL-C	-53.7%	1.6%	<0.0001
LS mean percent change from baseline in ApoB	-42.8%	1.2%	<0.0001
LS mean percent change from baseline in non-HDL-C	-47.1%	2.8%	<0.0001
LS mean percent change from baseline in total cholesterol	-36.4%	3.1%	<0.0001

Source: Clinical Overview, Table 3

6.1 Indication

The sponsor is not seeking a new indication from this supplement, with the exception of [redacted] (b) (4) See section 2.2, Currently Available Treatment for Proposed Indications for the approved indication in U.S. labeling.

6.1.1 Methods

Only 1 trial was evaluated in this supplement, the ESCAPE trial. See Sections 5.3 and 6.1.4 for a description of the study design, primary endpoint, and major challenges.

6.1.2 Demographics

A total of 62 patients were randomized into the trial: 41 in the alirocumab 150 mg Q2W group and 21 in the placebo group. Patient demographics and baseline characteristics are summarized in the table below.

Table 6. Patient Demographics and Baseline Characteristics, Double-Blind Period

	Alirocumab N=41	**Placebo N=21**
Age (years)		
Mean (SD)	59.5 (9.2)	57.0 (10.5)
≥ 65, n (%)	16 (39.0%)	5 (23.8%)
Sex		
Female, n (%)	15 (36.6%)	11 (52.4%)
Race		
White, n (%)	39 (95.1%)	21 (100%)
Black, n (%)	2 (4.9%)	0
Ethnicity		
Hispanic or Latino	0	0
Weight (kg)		
Mean (SD)	90.0 (16.1)	86.9 (21.3)
≥ 50 to < 70	4 (9.8%)	7 (33.3%)
≥ 70 to < 100	25 (61.0%)	6 (28.6%)
≥ 100	12 (29.3%)	8 (38.1%)
BMI (kg/m^2)		
Mean (SD)	30.5 (5.0)	30.3 (6.2)
≥ 30	23 (56.1%)	8 (38.1%)
Country		
Germany	20 (48.8%)	10 (47.6%)
U.S.	21 (51.2%)	11 (52.4%)
Time from HeFH diagnosis (years)		
Mean (SD)	13.28 (12.89)	15.17 (14.00)
Confirmation of HeFH diagnosis		
Genotyping	8 (19.5%)	8 (38.1%)
WHO/Simon Broome, definite/certain	33 (80.5%)	12 (57.1%)
Frequency of apheresis		
QW	18 (43.9%)	9 (42.9%)
Q2W	23 (56.1%)	12 (57.1%)
Treatment technique currently used		

Dextran sulfate adsorption (plasma)	18 (43.9%)	15 (71.4%)
Dextran sulfate adsorption (whole blood)	2 (4.9%)	2 (9.5%)
Direct adsorption of lipids	4 (9.8%)	2 (9.5%)
Double membrane filtration	6 (14.6%)	2 (9.5%)
Heparin-induced LDL precipitation	11 (26.8%)	0
Time from first known apheresis treatment (years)		
Mean (SD)	7.22 (7.60)	8.32 (8.11)
Baseline Lp(a) status		
Elevated	16 (39.0%)	8 (38.1%)
Medical history		
Coronary heart disease	347 (90.2%)	18 (85.7%)
Hypertension	29 (70.7%)	14 (66.7%)
Type 1 diabetes	0	1 (4.8%)
Type 2 diabetes	5 (12.2%)	4 (19.0%)
Background lipid-modifying therapy (LMT)		
Any statin	19 (46.3%)	13 (61.9%)
High-intensity statin	13 (31.7%)	12 (57.1%)
Any other LMT (± statin)	24 (58.5%)	16 (76.2%)

Source: ESCAPE CSR, Tables 9, 10, 11, 12, 13, 17, 19

Reviewer comments:

Some imbalances in baseline characteristics between treatment groups were noted (e.g., proportion of patients over 65 years, sex, HeFH diagnosis, background LMT). This might be expected in a fairly small trial, and alirocumab was shown to be effective in LDL-lowering in the large phase 3 program across subgroups. These imbalances were unlikely to have substantially biased the observed effect of alirocumab on LDL-C.

The imbalances in type of apheresis were noted as well. Percent change in pre-apheresis LDL-C in the alirocumab group at week 6 across types of apheresis appeared within acceptable variability (Table 15).

Approximately 50% of patients in this trial were not on statins, which suggests that at least some of these patients may have been treated with apheresis because they were unwilling or unable to take statins.

The country of residence was associated with apheresis schedule:

Table 7. Apheresis Schedule According to Country of Residence

	U.S.	Germany	Total
QW	2	26	28
Q2W	30	4	34
Total	32	30	62

Source: Reviewer created from ESCAPE datasets

A summary of baseline pre-apheresis, post-apheresis, and estimated time-averaged LDL-C by treatment group and apheresis schedule is shown in the following table:

Table 8. Baseline LDL-C, by Treatment and Apheresis Schedule

	Overall		Q2W apheresis		QW apheresis	
	Alirocumab	**Placebo**	**Alirocumab**	**Placebo**	**Alirocumab**	**Placebo**
Pre-apheresis LDL-C						
N	41	21	23	11	18	10
Mean (SD)	175.1 (54.6)	191.6 (68.9)	204.3 (42.5)	206.2 (79.2)	137.7 (45.1)	175.6 (54.9)
Median	176.0	180.0	215.0	224.0	125.0	172.5
Q1, Q3	129.0, 219.0	140.0, 240.0	175.0, 238.0	138.0, 274.0	109.0, 167.0	140.0, 191.0
Min, Max	53, 275	81, 316	129, 275	81, 316	53, 231	82, 286
Post-apheresis LDL-C						
N	40	20	22	11	18	9
Mean (SD)	49.9 (24.6)	42.6 (25.9)	55.5 (24.3)	42.9 (31.8)	43.1 (23.9)	42.2 (18.2)
Median	46.5	40.5	52.0	42.0	36.5	39.0
Q1, Q3	33.5, 62.5	24.0, 62.0	44.0, 64.0	10.0, 70.0	27.0, 49.0	29.0, 56.0
Min, Max	14, 124	0, 93	14, 124	0, 93	14, 103	15, 68
Estimated time-averaged LDL-C*						
N	40	20	22	11	18	9
Mean (SD)	140.3 (44.5)	155.4 (53.2)	163.3 (35.5)	162.1 (64.3)	112.2 (38.2)	147.2 (37.6)
Median	139.3	148.5	168.5	184.3	98.4	104.7
Q1, Q3	103.0, 178.9	113.4, 192.5	139.0, 193.7	108.6, 218.9	86.6, 130.9	127.1, 155.1
Min, Max	43, 220	59, 244	106, 220	59, 244	43, 196	106, 224

* Estimated from LDL-C pre- and post-apheresis on Day 1, prior to receiving study treatment; see Section 6.1.6 for the formula used in estimating time-averaged LDL-C

Source: Sponsor response to questions from 13Mar18, Tables 1.1, 1.2, 1.3, 1.4, 1.5, 1.6

Reviewer comment: The mean baseline pre-apheresis and time-averaged LDL-C values are lower in the weekly apheresis group randomized to alirocumab vs. the group randomized to placebo. This does not appear to impact the interpretation of the results; see Section 6.1.7, Table 14.

6.1.3 Subject Disposition

A total of 62 patients were randomized (41 patients to alirocumab, 21 patients to placebo). Sixty of the 62 patients (40 out of 41 patients [97.6%] in the alirocumab group and 20 out of 21 patients [95.2%] in the placebo group) completed the first 6-week double-blind treatment period; 57 patients completed the entire 18-week double-blind

treatment period (37 out of 41 patients [90.2%] in the alirocumab group and 20 out of 21 patients [95.2%] in the placebo group).

The most common reason for treatment discontinuation during the double-blind treatment period was AEs (4.9% alirocumab, 4.8% placebo). Other reasons for treatment discontinuation were poor compliance to protocol and withdrawal of patient consent, in 1 patient each (2.4%) in the alirocumab group.

Twenty-nine out of the 30 enrolled patients from Germany continued in the open-label phase; 27 (93.1%) of these patients completed the open-label study. Reasons for discontinuation were patient withdrawal of consent and loss to follow-up (1 patient each).

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was evaluated by comparing alirocumab to placebo on the rate of LDL apheresis from week 7 to week 18, normalized by the number of planned apheresis treatments according to each patient's established apheresis schedule. The apheresis frequency was adjusted based on each patient's response to treatment as indicated by the LDL-C value. When a patient's LDL-C value at a given visit was at least 30% lower than the pre-apheresis LDL-C value at baseline, apheresis was not administered.

The analysis of the primary endpoint is hindered by 2 main limitations: (1) the clinical meaningfulness of the primary endpoint is unknown; i.e., it is not clear if the benefits of apheresis withdrawal – primarily related to presumed improvement in QOL – outweigh the risks of potentially suboptimal LDL-C control, and (2) there were significant systematic errors and biases introduced into the trial, primarily related to the POC device for calculating LDL-C on the field, that rendered the primary endpoint uninterpretable. These issues and the resulting communication with the sponsor are discussed further below.

(1) The Division had concerns about the clinical meaningfulness of the primary endpoint prior to submission and discussed this issue with the sponsor during the pre-sBLA meeting. The following is an excerpt from that meeting:

(b) (4)

We do note that the first 6 weeks of the trial evaluated the effect of alirocumab + apheresis vs. placebo + apheresis, so this portion of the trial might be used to assess the effect of alirocumab in patients on apheresis.

Given the acute lowering of LDL-C with the apheresis procedure followed by a rebound, it will be important to describe LDL-C in each treatment group with more granularity than what has been presented in the CSR. For example, it is misleading to represent the LDL-C profile for the placebo group using only pre-apheresis values, since mean LDL-C during the interval between treatments is substantially lower than this. Similarly, we would be interested in any patient-level data you have that describes the mean reduction in LDL-C achieved with alirocumab + withholding apheresis compared with the mean reduction in LDL-C that the patient had been achieving with apheresis prior to initiating alirocumab.

We are not convinced that withholding of apheresis (or 'apheresis-sparing') is clinically beneficial. The cardiovascular risk of withholding apheresis is unknown, and you did not design the trial to determine whether alirocumab is superior to apheresis with respect to reducing LDL-C. Furthermore, while we understand that apheresis may be highly burdensome for some patients, the study was not designed to answer quality-of-life questions (although the changes in the W-BQ22 index scores and the p-value of 0.1886 were noted).

(2) Regarding the identified concern with the POC device, the following is an excerpt from a teleconference the Division had with the sponsor at the time of application filing, noting likely significant review issues (see Dr. Brad McEvoy's review for details):

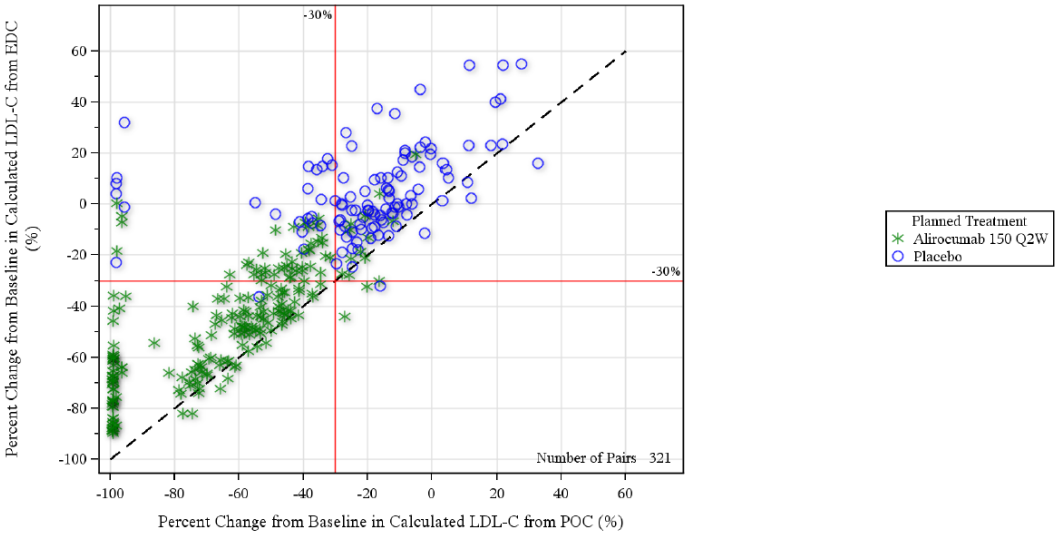
FDA communicated to the applicant that upon initial, high-level review of the data, significant issues were found. Specifically, LDL-C values were collected from two different sources: a point-of-care (POC) instrument and a central laboratory. Values obtained using the POC device were consistently lower than test results from the central laboratory. In addition, no baseline LDL-C values were collected using the POC device. Both of these issues contributed to systemic bias during the study.

Another major concern was that per protocol, apheresis was withheld starting at week 7 if LDL-C levels decreased by more than 30%. Because baseline from the POC device was not collected, baseline from the central laboratory was used in the calculation of percent change. Because this approach overestimated LDL-C lowering, apheresis may have been inappropriately withheld. FDA stated that trial results might be uninterpretable after week 7.

In addition, pre- and post-apheresis LDL-C values were not collected for odd numbered weeks when apheresis was performed weekly, which complicates efforts to estimate the time-averaged LDL-C over these intervals.

A graphical representation of the bias observed between percent change in LDL-C utilizing the POC vs. the central laboratory LDL-C was provided by the sponsor in response to FDA request and is shown in the figure below.

Figure 4. Scatter Plot of Percent Change from Baseline in Calculated LDL-C from POC Versus Central Laboratory Pre-Apheresis for the Double-Blind Period



This scatter plot contains POC and EDC calculated LDL-C pre-apheresis patient data collected on the same date.
Source: Sponsor response to FDA request dated 21Nov2017

The following table presents the proportions of patients with LDL-C less than 30% from baseline, at the patients' first opportunity to have apheresis withheld (week 7 for those on weekly apheresis, week 8 for those on Q2W apheresis). Note that as LDL-C was not calculated at week 7 using the central laboratory values, the comparison of POC to central laboratory is only available for week 8 in those on a Q2W schedule.

Table 9. Proportions of Patients with Less Than 30% Reduction in Calculated LDL-C Pre-Apheresis Over Time by Measurement Device

	POC		Central Laboratory	
	Aliro	Pbo	Aliro	Pbo
Week 7 – QW apheresis	1/17 (5.9%)	5/8 (62.5%)	NA	NA
Week 8 – Q2W apheresis	0/20	9/11 (81.8%)	3/20 (15.0%)	10/11 (90.9%)

Source: Sponsor response to FDA request dated 21Nov2017, Tables 2.1 and 2.2

Reviewer comment: As shown in the table above, for patients on the Q2W apheresis schedule, 3/20 (15%) patients on alirocumab and 1/11 (9%) patients on placebo had apheresis withheld inappropriately. As these errors in apheresis withholding would then necessarily propagate to subsequent weeks (by changing LDL-C profiles over subsequent intervals), evaluation of withholding apheresis beyond the first timepoint is uninterpretable.

Given that the sponsor had already been informed during the pre-BLA meeting that the Division had concerns with the primary endpoint (see discussion under (1), above), this

new information did not preclude filing the application, as it was considered a review issue whether any information from the ESCAPE trial would be appropriate for labeling.

As part of an inquiry into the above issue with POC and the central laboratory, in which a number of large discrepancies were identified between POC and central laboratory LDL-C results, the sponsor identified an additional systematic error: a missing value code that was reported by the POC device in the event the LDL-C value could not be calculated was misinterpreted as the LDL-C value. Specifically, the missing value codes in the POC device were coded as numeric values (1-8) and these values were then mistakenly interpreted by the automated IVRS system as actual LDL-C values (see Table 10).

Table 10. POC Device Error Code Descriptions

POC Device Error Code	Description
1	Total Cholesterol below the allowable range
2	Total Cholesterol above the allowable range
3	HDL Cholesterol below the allowable range
4	HDL Cholesterol above the allowable range
5	Triglycerides below the allowable range
6	Triglycerides above the allowable range
7	Triglycerides above 400 mg/dL
8	LDL being calculated to be less than 0 mg/dL

In total, 103 visits (from a study total of 499 visits) showed an erroneous LDL-C value of 1-8, with 95 (92%) of those visits corresponding to patients receiving alirocumab.

Error code 1 accounted for 76 visits (74%) of the missing LDL-C values, with all visits corresponding to patients receiving alirocumab study treatment (i.e., known alirocumab effect of lowering total cholesterol). The remaining error codes 2-8 accounted for 27 visits (26%), with 8 visits on placebo and 19 visits on alirocumab (similar proportions with a 2:1 randomization). Apheresis treatment was not administered during any of the 103 visits with an error code.

In summary, while the table below presents the sponsor's analysis of the primary endpoint, the above substantial limitations should be considered in its interpretation. See Dr. McEvoy's statistical review for additional details.

Table 11. Primary Endpoint: Standardized Rate of Apheresis Treatments from Week 7 to Week 18

	Alirocumab N=41	**Placebo N=21**
Standardized rate of apheresis treatments from week 7 to week 18		
Mean (SD)	0.128 (0.242)	0.806 (0.191)
Median	0.000	0.833
Q1 : Q3	0.000 : 0.167	0.667 : 1.000
Min: Max	0.00 : 1.00	0.42: 1.00
H-L estimate of median treatment difference (placebo – alirocumab) in apheresis rate reduction	0.750	
95% CI	(0.667, 0.833)	
p-value	<0.0001	
Note: Only legitimate apheresis treatment skipping per point-of-care LDL-C value is counted as "apheresis not occurred". Missing apheresis treatment information (any reason) from week 7 to week 18 is assigned an outcome of the apheresis treatment occurred at the visit (i.e. impute 1 apheresis treatment for that patient visit).		

Source: ESCAPE CSR, Table 21

The other subsections in Section 6 will be devoted to additional analyses, particularly regarding LDL-C changes during the first 6 weeks of the trial, prior to the reliance on a POC LDL-C value for treatment decisions.

Reviewer comment: For the reasons stated above, primarily that the POC LDL-C on which treatment decisions were made is biased, as well as identified errors with the POC device, the primary endpoint result is uninterpretable. Qualitatively, if treatment decisions regarding withholding apheresis on a particular week were going to be based on a 30% decrease in LDL-C from baseline, it is likely that patients with HeFH on alirocumab would receive fewer apheresis sessions than those not on a PCSK9 inhibitor.[3] As seen in the LDL-C analyses below, the clinical advantages of withholding apheresis are not well-defined, and it seems therefore that such decisions should be left to the practice of medicine. For

(b) (4)

6.1.5 Analysis of Secondary Endpoints

Secondary endpoints included changes in the pre-apheresis levels of various lipid parameters at different time points as well as a general well-being questionnaire[4],

3 See Praluent (alirocumab) prescribing information
4 The W-BQ22 questionnaire includes 4 subscales to measure depression, anxiety, energy and positive well-being. The general well-being score is calculated as the sum of the 22 questions (4 domains) collected from the W-BQ22 questionnaire. The assessments were done at baseline (week 0) and week 18/or end of double-blind early termination visit. The score for each question was worth a score from 0 (worst) to 3 (best), and was calculated for a given visit only when all questions were completed. https://www.healthpsychologyresearch.com/find-a-questionnaire/well-being-questionnaire-2

designed to measure "the impact of hypercholesterolemia and treatment on well-being" (as per the sponsor).

Statistically significant changes were observed up to the fifth key efficacy endpoint (percent change in total cholesterol from baseline to week 6 pre-apheresis) in the hierarchical testing order (i.e., percent change in pre-apheresis ApoA-I to week 6 was not statistically significant). Reviewer-selected efficacy endpoints after the sixth key endpoint and their p-values are provided in the following table for descriptive purposes only.

Table 12. Selected Key Secondary Endpoints

Key Secondary Endpoint	Alirocumab	Placebo	P-value
Percent change from baseline in LDL-C (pre-apheresis) to week 6	-53.7%	1.6%	<0.0001
Standardized rate of apheresis treatments during the 4-week period from week 15 to week 18 (median)	0.000	1.000	<0.0001
Percent change from baseline in ApoB (pre-apheresis) to week 6	-42.8%	1.2%	<0.0001
Percent change from baseline in non-HDL-C (pre-apheresis) to week 6	-47.1%	2.8%	<0.0001
Percent change from baseline in total cholesterol (pre-apheresis) to week 6	-36.4%	3.1%	<0.0001
Percent change from baseline in ApoA-I (pre-apheresis) to week 6	4.2%	0%	0.3012
Proportion of patients with ≥ 30% reduction in LDL-C (pre-apheresis) at week 6	95.1%	4.8%	<0.0001
Proportion of patients with ≥ 50% reduction in LDL-C (pre-apheresis) at week 6	63.4%	0%	<0.0001
Percent change from baseline in LDL-C (pre-apheresis) to week 18	-42.3%	4.0%	<0.0001
Change of W-BQ22 index score from baseline to week 18	0.91%	-1.43%	0.1886
Note: p-values beyond the 6th secondary endpoint provided for descriptive purposes only			

Source: ESCAPE CSR, Table 26

Reviewer comments:

The endpoint with the proportion of patients with ≥ 30% reduction in LDL-C pre-apheresis at week 6 essentially reflects an apheresis decision that would happen at the first timepoint, prior to apheresis rates changing over time (as discussed in other sections of this review, in practice, a clinician may make different determinations for apheresis necessity based on his/her patient's individual needs, taking into account, for example, cardiovascular risk, LDL-C concentrations, and patient preference).

It is also noted that the difference in the well-being questionnaire, W-BQ22, was not nominally statistically significant between groups. The clinical significance of the observed average changes in the W-BQ22 scores is unknown.

6.1.6 Other Endpoints

This section primarily focuses on the pre-apheresis and time-averaged LDL-C over the first 6 weeks of treatment, in which randomized treatment was administered to patients receiving apheresis on their regular apheresis schedule (i.e., either Q2W or QW).

Pre-apheresis LDL-C change at the 6-week time point was tested for multiplicity using a testing hierarchy. Time averaged LDL-C was calculated using the Kroon formula: post-apheresis LDL-C + 0.73 (pre-apheresis LDL-C – post-apheresis LDL-C).[5]

Reviewer comments: Although the time-averaged LDL-C over the first 6 weeks of treatment was not a pre-specified secondary endpoint, it is useful as it more fully reflects the impact of apheresis on LDL-C as compared to the pre-apheresis LDL-C, particularly in the placebo group (see Figure 5). The limitations of the pre-apheresis LDL-C were discussed with the sponsor during the pre-sBLA meeting (see Section 6.1.4). Time-averaged LDL-C is therefore being evaluated in a descriptive fashion in this section to support the pre-apheresis LDL-C endpoint.

Since pre- and post-apheresis LDL-C values were not collected for odd numbered weeks when apheresis was performed weekly, the ability to estimate the time-averaged LDL-C over these intervals for patients on weekly apheresis was limited (see Section 6.1.4).

Table 13. LDL-C Over Time by Treatment

	Alirocumab N=41			Placebo N=21		
LDL-C, LS mean (SE)	Value	Change from BL	% change from BL	Value	Change from BL	% change from BL
Pre-apheresis						
Baseline	175.1 (8.5)	NA	NA	191.6 (15.0)	NA	NA
Week 2	96.8 (3.9)	-83.8 (3.9)	-50.2 (2.4)	183.6 (5.5)	2.9 (5.5)	0.6 (3.4)
Week 4	89.1 (3.8)	-91.6 (3.8)	-54.7 (2.4)	185.7 (5.3)	5.0 (5.3)	2.0 (3.3)
Week 6	89.6 (4.1)	-91.1 (4.1)	-53.7 (2.3)*	184.9 (5.6)	4.2 (5.6)	1.6 (3.1)
Time-averaged						
Baseline¥	140.3 (44.5)	NA	NA	155.4 (53.2)	NA	NA
Weeks 0-2§	80.0 (42.0)	-60.3 (18.8)	-45.8 (16.2)	156.4 (54.2)	1.1 (19.7)	1.0 (12.4)
Weeks 2-4§	69.0 (38.5)	-72.6 (22.7)	-54.2 (16.7)	157.4 (53.8)	2.0 (18.9)	2.0 (13.6)
Weeks 4-6§	69.1 (36.5)	-71.9 (20.1)	-53.6 (14.3)	154.0 (52.4)	1.7 (24.8)	2.1 (15.6)

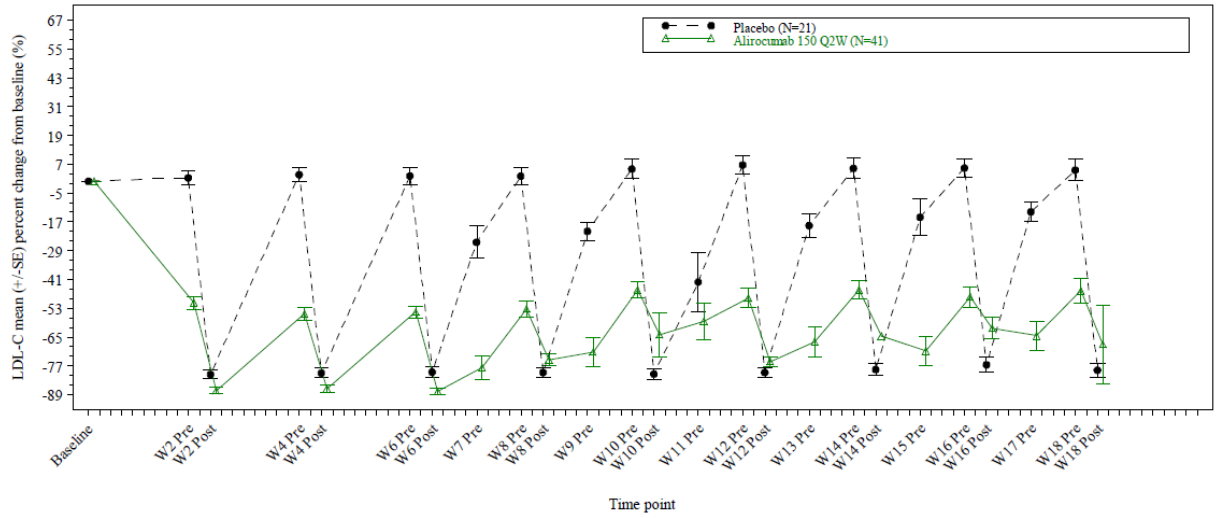
* p-value <0.0001 alirocumab vs. placebo in percent change from baseline to week 6 in pre-apheresis LDL-C; key secondary endpoint (hierarchical testing strategy applied)
¥ Time averaged calculated LDL-C for baseline apheresis treatment: Baseline post-apheresis LDL-C + {0.73*(baseline pre-apheresis LDL-C – baseline post-apheresis LDL-C)}
§ Time averaged calculated LDL-C for interval: Week beginning of interval pre-apheresis LDL-C + {0.73*(Week end of interval pre-apheresis LDL-C – Week beginning of interval pre-apheresis LDL-C)}

Source: ESCAPE CSR, Table 25; sponsor response to questions from 13Mar18, Table 1.4

Acknowledging that LDL-C beyond the 6-week timepoint has limitations outlined above, it is instructive to visualize LDL-C changes over the course of the trial, including both pre- and post-apheresis LDL-C values (Figure 5).

5 Kroon AA, et al. The rebound of lipoproteins after LDL-apheresis. Kinetics and estimation of mean lipoprotein levels. Atherosclerosis. 2000; 152(2): 519-26.

Figure 5. Percent Change from Baseline in Pre- and Post-Apheresis LDL-C



When an apheresis treatment was not performed, only one lipid blood sample was obtained, specifically at the pre-apheresis time point.
POC data is used only when the EDC LDL-C data is not available.
The visits with odd-number weeks (i.e. W7, W9, etc.) are based on the POC LDL-C collected for patients on QW apheresis schedule only (Placebo N=9, Alirocumab N=18).

Source: Clinical Overview Appendix, Figure 1.4

Reviewer comment: The mean LDL-C post-apheresis at weeks 2, 4, and 6 is similar or even slightly lower in the alirocumab group than the placebo group. The treatment effect is therefore fairly represented by the pre-apheresis LDL-C, as (b) (4) ***LDL-C values beyond week 6 are descriptive only, as some patients (particularly in the alirocumab group) had apheresis withheld.***

6.1.7 Subpopulations

The primary endpoint was evaluated in a variety of subgroups (baseline apheresis schedule, BMI, sex, age, baseline LDL-C, baseline HDL-C, baseline TG, baseline Lp(a), use of statins at randomization, use of lipid modifying therapy other than statins at randomization, diabetes, moderate chronic kidney disease, demographic characteristics, and other baseline characteristics) and according to the sponsor, a consistent decrease in the standardized rate of apheresis treatment was observed for all the subgroups listed. However, a formal review of these data was not conducted due to the limitations in the primary endpoint (see Section 6.1.4) as well as the fact that the study was too small to confidently assess this many subgroups.

Of some interest (for descriptive purposes) are the LDL-C changes over the first 6 weeks of the trial by baseline apheresis schedule (Q2W, QW), Table 14, and by apheresis type, Table 15.

Table 14. Time-Averaged LDL-C Over Time by Apheresis Schedule

	Alirocumab				Placebo			
LDL-C, LS mean (SE)	N	Value	Change from BL	% change from BL	N	Value	Change from BL	% change from BL
Q2W apheresis schedule								
Baseline¥	22	163.3 (35.5)	NA	NA	11	162.1 (64.3)	NA	NA
Weeks 0-2§	22	96.2 (40.0)	-67.1 (16.1)	-43.4 (15.7)	11	167.3 (66.5)	5.2 (20.9)	3.3 (13.6)
Weeks 2-4§	23	81.7 (35.9)	-81.8 (20.3)	-52.1 (16.4)	11	165.5 (61.4)	3.4 (18.9)	3.4 (15.3)
Weeks 4-6§	17	82.8 (34.1)	-80.2 (17.1)	-50.9 (13.6)	10	181.9 (53.2)	9.5 (22.3)	7.7 (14.4)
QW apheresis schedule								
Baseline¥	18	112.2 (38.2)	NA	NA	9	147.2 (37.6)	NA	NA
Weeks 0-2§	18	60.1 (36.3)	-52.1 (19.1)	-48.8 (16.7)	9	143.2 (33.1)	-4.0 (18.0)	-1.8 (10.8)
Weeks 2-4§	15	49.7 (35.1)	-59.1 (19.4)	-57.3 (17.2)	9	147.4 (44.2)	0.3 (19.9)	0.2 (11.8)
Weeks 4-6§	15	53.6 (33.7)	-62.4 (19.5)	-56.6 (14.9)	8	123.0 (30.9)	-8.0 (25.7)	-4.9 (14.9)

¥ Time averaged calculated LDL-C for baseline apheresis treatment: Baseline post-apheresis LDL-C + {0.73*(baseline pre-apheresis LDL-C – baseline post-apheresis LDL-C)}
§ Time averaged calculated LDL-C for interval: Week beginning of interval pre-apheresis LDL-C + {0.73*(Week end of interval pre-apheresis LDL-C – Week beginning of interval pre-apheresis LDL-C)}

Source: Sponsor response to questions from 13Mar18, Tables 1.5 and 1.6

Reviewer comment: The above table is descriptive. Given the small sample sizes, missing data, and differences in baseline LDL-C between apheresis schedule groups, The observed differences in LDL-C between apheresis schedule groups by treatment (if true, it is possible differences were due to chance) are unlikely to be clinically meaningful.

Table 15. Pre-Apheresis LDL-C Percent Change from Baseline at Week 6 by Apheresis Treatment Type

	Alirocumab N=41	Placebo N=21
Mean (SD)		
Dextran sulfate adsorption (plasma)	n=15	n=14
	-51.0 (9.3)	1.4 (16.9)
Dextran sulfate adsorption (whole blood)	n=2	n=2
	-54.7 (23.7)	-3.7 (12.1)
Direct adsorption of lipids	n=4	n=2
	-53.3 (11.7)	0.5 (18.2)
Double membrane filtration	n=5	n=2
	-63.3 (14.2)	15.1 (1.4)
Heparin-induced LDL precipitation	n=10	n=0
	-56.0 (22.0)	–

Source: ESCAPE CSR, Table 11.6.3.15A

Reviewer comment: Percent change in pre-apheresis LDL-C in the alirocumab group at week 6 across types of apheresis appeared within acceptable variability. The reason for the LDL-C outliers in the 2 placebo-treated patients receiving double membrane filtration is unclear.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

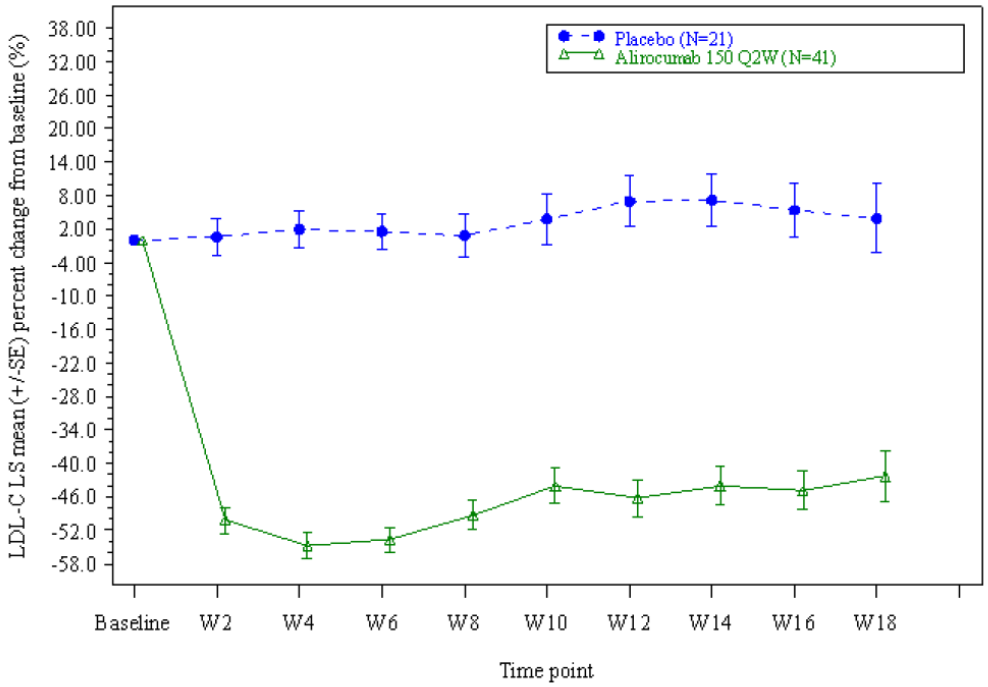
Not applicable, as only the 150 mg Q2W dose was studied in this trial.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The following figure presents mean pre-apheresis LDL-C percent change from baseline by treatment group over the 18-week double-blind trial. Despite some patients in the alirocumab group having some of their apheresis treatments inappropriately withheld from weeks 8-18, the pre-apheresis LDL-C (the nadir of LDL-C response over an interval) in the alirocumab group remains significantly reduced from baseline throughout the trial period.

Reviewer comment: In other words, this is a "worst-case" scenario for alirocumab, and is intended to demonstrate that despite the inappropriate withholding of apheresis in some patients in the alirocumab group, mean pre-apheresis LDL-C remained reduced over the duration of the trial.

Figure 6. Mean Pre-Apheresis LDL-C Percent Change from Baseline During the Double-Blind Period



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time point interaction. Time points in the model include bi-weekly timepoints from week 2 (pre-apheresis) to week 18 (pre-apheresis).

Source: ESCAPE CSR, Figure 6

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

In this relatively small trial in a population of patients with HeFH on regular LDL apheresis, the safety of alirocumab appeared generally consistent with the safety profile in other clinical trials of alirocumab.

Overall, more adverse events (AEs) of fatigue, myalgia, and diarrhea were reported in the alirocumab group versus the placebo group during the double-blind period. In the open-label period in a subgroup of patients, the only preferred term reported in more than 1 patient was anemia (2/29, 6.9%).

No deaths occurred during the ESCAPE trial. A total of 4 patients on alirocumab (9.8%) and 2 patients on placebo (9.5%) had at least 1 SAE during the double-blind treatment period, and 1 patient had 2 SAEs during the open-label portion of the trial. The relationship to alirocumab of an SAE of muscle rupture with compartment syndrome during the double-blind period could not be confirmed or dismissed by this reviewer. The other SAEs that occurred in alirocumab-treated patients seemed unlikely related to drug.

Two patients in the alirocumab group (4.9%) and 1 patient in the placebo group (4.8%) experienced AEs that led to study drug discontinuation during the double-blind period. No patients discontinued due to an AE during the open-label period.

Regarding AEs of special interest:

- Similar proportions of patients in the alirocumab and placebo treatment groups reported injection site reaction and potential allergy AEs.

- No increases of ALT meeting the prespecified criteria were observed either in the double-blind or the open-label periods of the trial.

- No AEs of hemolytic anemia were reported in the double-blind or open-label phases of the trial.

- A similar proportion of patients in both treatment groups had an event classified as a neurocognitive event; no other neurological events were reported in the trial. A similar proportion of patients in both treatment groups had an event in the ‘psychiatric disorders’ system organ class (SOC).

- No ophthalmologic disorders were reported in the double-blind or open-label periods of the trial.

- In the double-blind treatment period, cardiovascular AEs confirmed by adjudication were reported for 2 patients out of 41 (4.9%) in the alirocumab group and none out of 21 in the placebo group. There were no cardiovascular AEs confirmed by adjudication in the open-label treatment period.

- A greater proportion of patients in the alirocumab group experienced very low LDL-C (either less than 25 mg/dL or 15 mg/dL) in the trial as compared to placebo, despite undergoing fewer apheresis treatments. The majority of AEs in patients who experienced 2 consecutive very low LDL-C values were single events. No patient had 2 consecutive LDL-C values less than 25 mg/dL during the open-label treatment period.

- No patients in the trial had a hepatitis C seroconversion.

- Three patients treated with alirocumab and 1 patient treated with placebo developed treatment-emergent ADAs. All antibodies were considered transient, low-titer, and non-neutralizing. AEs in the 3 alirocumab-treated patients with positive ADAs during the double-blind period include memory impairment, radicular syndrome, gastroesophageal reflux disease, and joint injury. These AEs were only reported in 1 patient each.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The ESCAPE trial was evaluated for safety in this submission.

7.1.2 Categorization of Adverse Events

MedDRA version 18.1 was used to code adverse events. I assessed the categorization of events by comparing the verbatim terms used by investigators to the preferred terms. Based on this evaluation, I believe that AEs were generally categorized appropriately.

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

Not applicable; the safety assessment was based on the ESCAPE trial.

7.2 Adequacy of Safety Assessments

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

The sponsor chose the alirocumab 150 mg Q2W dose as the starting dose in this patient population with HeFH on apheresis. The 150 mg Q2W dose was used as a starting dose in the 'HIGH FH' trial in the original BLA, a relevant patient population with a relatively high baseline LDL-C.

Reviewer comment: This "high" dose is a reasonable choice for this patient population. Given the relatively high starting LDL-C, the risk for very low LDL-C is less of a concern than with other patient populations.

The duration of treatment exposure in the safety population was similar between treatment groups during the double-blind treatment period, with a mean exposure of 17.42 weeks in the alirocumab group and 17.48 weeks in the placebo group. A total of 38 out of 41 patients (92.7%) in the alirocumab group and 20 out of 21 patients (95.2%) in the placebo group were exposed to study drug for at least 16 weeks.

During the open-label treatment period, the duration of treatment was similar between patients originally randomized to alirocumab or placebo in the double-blind treatment period, with a mean exposure of 17.14 weeks in the alirocumab group and 17.11 weeks in the placebo group. Patients who received alirocumab during both the double-blind treatment period and the open-label treatment period had a mean exposure of 35.18 weeks.

7.2.2 Explorations for Dose Response

Not applicable; only one dose was studied.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing in ESCAPE was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events of special interest were assessed in ESCAPE based on current knowledge and experience with the two available PCSK9 inhibitors on the market: alirocumab and evolocumab; see Sections 7.3.4 and 7.3.5.

Reviewer comment: Selected AEs of special interest were appropriate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during this trial.

7.3.2 Nonfatal Serious Adverse Events

A total of 4 patients on alirocumab (9.8%) and 2 patients on placebo (9.5%) had at least 1 SAE during the double-blind treatment period. One of the SAEs in the alirocumab group was considered related to study drug: 'muscle rupture'. In addition, 1 patient had 2 SAEs during the open-label portion of the trial (the patient had been randomized to alirocumab in the double-blind portion). Narratives for SAEs in the 5 patients treated with alirocumab are briefly described below. SAEs for the 2 placebo-treated patients included shunt thrombosis in 1 patient and sinus bradycardia and angina pectoris in another patient.

- Patient (b) (6) is a 41-year-old black male with history of HeFH, obesity, degenerative joint disease, hypertension, and coronary revascularization procedure. On study day 22 he had non-serious AEs of allergic rhinitis and worsening asthma (treated with ipratropium bromide/albuterol), and on study day 37 he had a non-serious AE of rash. The patient recovered from these AEs. On study day 142, during the follow-up period, the patient had SAEs of muscle rupture (gastrocnemius muscle tear) and compartment syndrome of the right calf. He had presented to the emergency department on that day with sudden onset of severe pain with swelling to the right calf while playing kickball. The patient underwent urgent decompression/fasciectomy; on study day 145 he was re-operated for open fasciectomy wound irrigation and debridement. The event of compartment syndrome was considered recovered on day 151, and the event of muscle tear was considered resolved with sequelae (difficulty walking) on study day 299.

Reviewer comment: The investigator reported the following in his/her assessment of the event: "familiar [sic] hypercholesterolemia is associated with tendon deposits and Achilles tendonitis. Statins may increase tendon rupture, we think via affecting MMP9, but that's a hypothesis. So there may be a relationship between cholesterol, cholesterol drugs, and tendon issues so there is a definite

possible relationship." I agree (although it is noted that the patient's Achilles tendon was reportedly grossly intact; statins are also associated with muscle injury, including rhabdomyolysis). Any potential causal relationship specifically to alirocumab or other PCSK9 inhibitors is theoretical, but unknown. Tendon AEs are not currently reported in either the Praluent or Repatha labels, although myalgia, muscle spasms, and musculoskeletal pain were reported in slightly more alirocumab-treated patients than placebo in clinical trials.

- Patient (b) (6) is a 68-year-old white female with history of HeFH, acute myocardial infarction, chronic kidney disease, type 2 diabetes, ischemic stroke, hypertension, peripheral arterial disease, asthma, and allergies. On study day 43 she had non-serious AEs of pruritus (not at the injection site) and injection site reaction from which she recovered. On study day 67 she had SAEs of pneumonia and sepsis that required hospitalization. On study day 70 the patient had an SAE of congestive heart failure after infusion of fluids. She recovered from sepsis and CHF on study day 71, but had new SAEs of acute respiratory failure and acute myocardial infarction. She recovered from those events on study day 75 and pneumonia on study day 77. On study day 163 the patient had an SAE of aortic valve stenosis and underwent a transcatheter aortic valve replacement on the same day.

- Patient (b) (6) is a 68-year-old white female with history of HeFH, unstable angina, coronary revascularization procedures (3 stents), and peripheral arterial disease. On study day 74 she had a non-serious AE of allergic reaction to amoxicillin (treatment for sinusitis). On study day 113, approximately 5 hours after her most recent dose, the patient had an SAE of unstable angina. She was admitted to the ICU for observation and recovered and was discharged on study day 114.

- Patient (b) (6) is a 58-year-old white male with history of HeFH, coronary heart disease with revascularization, acute myocardial infarction, and hypertension who experienced resting chest pain and was admitted for an NSTEMI (SAE: acute myocardial infarction) on study day 6. Stenosis of the RCA in 2 locations was treated with PTCA and stents. No action was taken in regards to study drug.

- Patient (b) (6) is a 71-year old white male with a history of HeFH, acute myocardial infarction, coronary artery stent, congenital heart disease, hypertension, and peripheral artery disease with stent who underwent cardiac work-up on study day 162 (open-label period), which showed inferoseptal cardiac ischemia (SAE: myocardial ischemia), and elective cardiac catheterization on study day 168 showing 3-vessel coronary disease. Conservative medical management was recommended. Hospitalization was complicated by a 'possible' peripheral artery restenosis (SAE: peripheral artery restenosis). Hospitalization and work-up for this complication on study day 211 did not show any new findings and no interventions were performed.

Reviewer comment: Based on the known safety profile of alirocumab, there is no reason to suspect a causal relationship to the SAEs in the 4 patients listed above.

A favorable cardiovascular outcomes trial (CVOT) with alirocumab in patients post-acute coronary syndrome (ACS) has recently been reported.[6]

7.3.3 Dropouts and/or Discontinuations

Two patients in the alirocumab group (4.9%) and 1 patient in the placebo group (4.8%) experienced AEs that led to study drug discontinuation during the double-blind period. No patients discontinued due to an AE during the open-label period. Narratives for AEs leading to discontinuation in the 2 patients treated with alirocumab are briefly described below. The patient treated with placebo discontinued due to an AE of neutrophil count decreased.

- Patient (b) (6) is a 62-year-old white female with a history of HeFH, anxiety, depression, gastroesophageal reflux, fibromyalgia, blood coagulation disorder, hypertension, and peripheral artery disease. On study day 99 after receiving an injection, the patient had AEs of tightness in the chest, chest congestion, and cough. On study day 100, the patient had a new AE of stiffness of her finger and toe joints. On study day 105 she had an AE of nasal congestion. The study drug was permanently withdrawn due to all of these events, and she recovered on study day 120. All events were considered possibly related to the study drug by the investigator.

- Patient (b) (6) is a 61-year-old white male with a history of HeFH, migraine, hard of hearing, hypertension, and degenerative joint disease of the lumbar spine. On study day 17 the patient had severe fatigue, muscle cramps (PT: 'muscle spasms' ***[reviewer comment: CK remained within normal limits during the trial]***), migraine, and moderate pruritus (not at injection site). The last dose of drug taken was on study day 14. The patient recovered from migraine on day 20, pruritus on day 34, and fatigue and muscle spasms on day 55. All events were considered possibly related to the study drug by the investigator.

7.3.4 Significant Adverse Events

Significant adverse events (i.e., events of special interest) are addressed in Section 7.3.5. This section will discuss severe AEs, local injection site reactions, and other allergic reactions.

Severe AEs

Five patients in the alirocumab group (12.2%) and 2 patients in the placebo group (9.5%) experienced at least 1 severe AE. Four of the 5 alirocumab patients' events were described in Section 7.3.2 (Serious Adverse Events), as summarized below:

6 http://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes

- (b) (6): pneumonia, sepsis, acute myocardial infarction, acute respiratory failure, cardiac failure congestive, and aortic valve stenosis
- (b) (6): unstable angina
- (b) (6): fatigue, muscle cramps, and migraine
- (b) (6): muscle tear and compartment syndrome

The additional alirocumab patient (b) (6) with severe (non-serious) AEs was a 67-year-old white female with severe nausea on day 55 that lasted 1 day, and severe diverticulitis on day 96 that lasted 10 days. No action was taken with the study drug and the events resolved.

In the placebo group, 1 patient had a severe SAE of shunt thrombosis (listed above in Section 7.3.2) and 1 patient had a severe (non-serious) hypotensive episode on day 71.

No AEs were reported as severe in the open-label period.

Injection Site Reactions

During the double-blind period, 4 patients in the alirocumab group (9.8%) and 2 patients in the placebo group (9.5%) had at least 1 local injection site reaction (ISR). ISRs are characterized further by group in the following table:

Table 16. Injection Site Reactions, Double-Blind Period

	Alirocumab N=41	**Placebo N=21**
At least 1 ISR	4 (9.8%)	2 (9.5%)
>1 ISR per patient	2 (4.9%)	0
Highest intensity		
Mild	3 (7.3%)	2 (9.5%)
Moderate	1 (2.4%)	0
Severe	0	0
Mean duration (days)	12.6	4.9
Mean time from first injection (days)	27.0	93.0

Source: ESCAPE CSR, Table 36

No patient had an ISR during the open-label treatment period.

Allergy Events

During the double-blind period, 6 patients in the alirocumab group (14.6%) and 3 patients in the placebo group (14.3%) had at least 1 general allergy AE (using a sponsor customized medical query [CMQ] based on the hypersensitivity SMQ excluding certain infusion- and ISR-related terms). No patient had any SAEs or AEs leading to discontinuation that were allergy-related.

Table 17. Allergic Reactions CMQ, Double-Blind Period

	Alirocumab N=41	**Placebo N=21**
At least 1 general allergic AE	6 (14.6%)	3 (14.3%)
Pruritus	2 (4.9%)	1 (4.8%)
Acute respiratory failure	1 (2.4%)	0
Asthma	1 (2.4%)	1 (4.8%)
Dermatitis	1 (2.4%)	0
Drug hypersensitivity	1 (2.4%)	0
Neurodermatitis	1 (2.4%)	0
Rash	1 (2.4%)	0
Rhinitis allergic	1 (2.4%)	0
Sneezing	1 (2.4%)	0
Bronchial hyperreactivity	0	1 (4.8%)
Throat tightness	0	1 (4.8%)

Source: ESCAPE CSR, Table 35

Reviewer comment: The event of 'acute respiratory failure' in the alirocumab patient is described under Section 7.3.2 (Serious Adverse Events). The event occurred in the setting of an acute myocardial infarction, so despite having been captured in the allergic reactions CMQ seems unlikely related to hypersensitivity.

One patient who received placebo during the double-blind period had a general allergic AE during the open-label period with alirocumab:

- Patient (b) (6) is a 67-year-old white male with history of HeFH, nodular goiter, seasonal allergy, and hypertension. On study day 141 during the open-label period the patient had a moderate allergic reaction while undergoing apheresis. Corrective treatment included dimethindene maleate (antihistamine) and prednisolone. The patient recovered on day 143. No action was taken to the study drug due to the event; his last dose was on day 309.

Reviewer comment: As the patient remained on study drug after this allergic event, the relationship to the drug is unlikely.

7.3.5 Submission Specific Primary Safety Concerns

Aside from ISRs and allergic reactions described above, certain AEs and other safety findings were considered AEs of special interest:

- Increased ALT
- Hemolytic anemia
- Neurologic (including neurocognitive) events
- Ophthalmologic events
- Adjudicated cardiovascular events
- Overdose

- Pregnancy
- 2 consecutive LDL-C < 25 mg/dL
- ADA titer ≥ 240
- Hepatitis C seroconversion

With the exception of overdose (section 7.6.4), pregnancy (section 7.6.2), and immunogenicity (section 7.4.6), the above items will be addressed in this section, not necessarily in the above order.

Reviewer comments:
It is noted that new-onset diabetes mellitus was not flagged as an AE of special interest, despite ongoing discussion of this potential safety concern pre- and post-marketing. In my review, I did not identify any AEs with PTs containing 'diabetes' in this trial. No meaningful difference was noted between the alirocumab and the placebo groups in change in hemoglobin A1c levels from baseline to week 6 or baseline to week 18.

As indicated in Section 2.4, a new TSI was opened for 'psychiatric events' as of May 1, 2018 for both marketed PCSK9 inhibitors based on post-marketing reports of a variety of psychiatric symptoms (subsequently closed, August 6, 2018). I reviewed the ESCAPE database to determine if there were any unusual psychiatric events reported in this trial. Two patients on alirocumab (4.9%) and 1 patient on placebo (4.8%) reported psychiatric events during the double-blind period. One event in the alirocumab group – confusional state – is discussed under the neurocognitive section, below. The other alirocumab-treated patient experienced mild events of insomnia and stress.

Additionally, as indicated in Section 2.4, a new TSI was opened for 'influenza-like illness' as of July 19, 2018 for both marketed PCSK9 inhibitors based on alirocumab post-marketing reports of terms including 'influenza' and 'influenza-like illness' (sponsor-initiated). I reviewed the ESCAPE database for these terms, and only 1 event of 'influenza' was reported in a patient randomized to placebo, occurring during the double-blind period.

Pre-specified Increases in ALT/Hepatic Disorders

No increases of ALT meeting the prespecified criteria (elevations of ALT ≥ 3 × ULN if baseline ALT was less than ULN or ALT ≥ 2 × baseline if baseline ALT was ULN or greater) were observed in the trial either in the double-blind or the open-label periods. In addition, no patients had increases of AST > 3x ULN in the double-blind period.

There were no AEs in the 'Hepatobiliary disorders' SOC in this trial. There were no AEs in the 'Investigations' SOC related to ALT or AST elevations.

One AE of 'gamma-glutamyltransferase increased' was reported in a 53-year-old male alirocumab-treated patient, who had a high GGT at screening (87 U/L, ref: 52) that gradually increased over the trial to a maximum value of 129 U/L post-treatment. Other liver parameters for this patient remained within the normal range except for ALT at the post-treatment follow-up visit (48 U/L, ref: 41). Overall, 34.1% vs. 28.6% of alirocumab- vs. placebo-treated patients had a GGT > ULN during the double-blind period. Of patients with normal GGT at baseline, 4/30 (13.3%) in the alirocumab group vs. 1/15 (6.7%) in the placebo group had a GGT > ULN during the double-blind period.

One patient in the alirocumab group (2.4%) vs. no patients in the placebo group had an increase of alkaline phosphatase > 1.5x ULN in the double-blind period.

One patient in the placebo group (4.8%) vs. no patients in the alirocumab group had an increase of bilirubin > 1.5x ULN in the double-blind period.

Table 21 in Section 7.4.2, Laboratory Findings, summarizes potentially clinically significant abnormalities in liver parameters during the double-blind period.

Hemolytic Anemia

No AEs of hemolytic anemia were reported in the double-blind or open-label phases of the trial.

During the double-blind phase of the trial, 1 patient treated with alirocumab and 1 patient treated with placebo reported AEs of anemia and iron deficiency anemia, respectively. One patient treated with alirocumab during the double-blind phase reported an AE of anemia during the follow-up period. Two patients treated with alirocumab during the double-blind phase reported anemia during the open-label phase.

Neurological and Neurocognitive AEs

No neurological events were reported in either the double blind or open-label periods; however, 2 patients in the alirocumab group (4.9%) and 1 patient in the placebo group (4.8%) had an event classified as a neurocognitive event in the "Neurocognitive Disorders" CMQ:

- Patient (b) (6) (alirocumab): A 66-year-old white male with a relevant medical history of cerebral palsy (1948), hypothyroidism (2010), and sporadic mental confusion (2014) experienced mild 'confusional state' on day 112. No action was taken with study treatment and the event resolved after 10 days without treatment. The event was considered related to study drug by the investigator.

- Patient (b) (6) (alirocumab): A 52-year-old white male with a relevant medical history of depression (2010) experienced mild 'memory impairment' four months after initiating study treatment (study day of onset not provided). No action was

taken with study treatment and the event did not resolve. The event was considered related to study drug by the investigator.

- Patient (b) (6) (placebo): A 60-year-old white female with no relevant medical history experienced mild 'disturbance in attention' on study day 187 that lasted for 2 days; the patient had received the last dose of study drug on day 127. The event was not considered related to study drug by the investigator.

Reviewer comment: All 3 patients (alirocumab- and placebo-treated) experienced 2 consecutive LDL-C values less than 25 mg/dL (but not 15 mg/dL) post-apheresis; none had 2 consecutive LDL-C values less than 25 mg/dL pre-apheresis. There were too few events to draw any conclusions.

Ophthalmologic Disorders

No ophthalmologic disorders were reported in the double-blind or open-label periods.

Adjudicated Cardiovascular Events

In the double-blind treatment period, cardiovascular AEs confirmed by adjudication were reported for 2 patients out of 41 (4.9%) in the alirocumab group and none in the placebo group. There were no cardiovascular AEs confirmed by adjudication in the open-label treatment period. Brief narratives follow:

- Patient (b) (6) was a 58-year-old white male in the alirocumab group (weekly apheresis) who experienced an acute myocardial infarction on day 6 that required hospitalization. The patient underwent a percutaneous coronary intervention (PCI) on the same day. He remained on the study after this event and received the last dose of study drug on day 113. The CEC classified the acute myocardial infarction and the PCI as an ischemia-driven coronary revascularization procedure. ***Reviewer comment: The patient received 1 dose of alirocumab (+ apheresis) at the time of the event. Baseline LDL-C was 114 mg/dL and time-averaged LDL-C off apheresis during weeks 7-18 ranged from 40-52 mg/dL.***

- Patient (b) (6) was a 67-year-old white female in the alirocumab group (biweekly apheresis) who experienced an acute myocardial infarction on day 71 that required hospitalization and that was positively adjudicated by the CEC as an event. The patient remained on study and received that last dose of study drug on day 110. ***Reviewer comment: Patient's baseline LDL-C was 126 mg/dL and time-averaged LDL-C (off apheresis) during weeks 8-18 ranged from 17-29 mg/dL.***

Reviewer comment (general): The cardiovascular benefits and risks of alirocumab will be reviewed upon submission of the recently reported CVOT. The numbers are too small to assess the incidence of CV events in this trial. It is

difficult to know what CV risk patients might face in the event of regular apheresis being withheld.

Very Low LDL Cholesterol

Three patients out of 41 (7.3%) in the alirocumab group and no patients of 21 in the placebo group had 2 consecutive pre-apheresis calculated LDL-C values less than 25 mg/dL during the double-blind treatment period. One patient out of 41 (2.4%) in the alirocumab group and no patients of 21 in the placebo group had 2 consecutive pre-apheresis calculated LDL-C values less than 15 mg/dL.

Twenty-three patients out of 41 (56.1%) in the alirocumab group and 4 patients (19.0%) of 21 in the placebo group had 2 consecutive post-apheresis calculated LDL-C values less than 25 mg/dL during the double-blind treatment period. Fourteen patients out of 41 (34.1%) in the alirocumab group and 1 patient out of 21 (4.8%) in the placebo group had 2 consecutive post-apheresis LDL-C values less than 15 mg/dL.

The following tables describe adverse events that occurred in patients with 2 consecutive LDL-C values less than 25 mg/dL pre- (Table 18) or post- (Table 19) apheresis. Preferred terms that are starred ('*') occurred in patients with 2 consecutive LDL-C values less than 15 mg/dL pre- and post-apheresis, respectively.

Table 18. AEs in Patients with Two Consecutive Pre-Apheresis LDL-C Values Less Than 25 mg/dL During the Double-Blind Period

	Alirocumab N=41	**Placebo N=21**
At least 2 consecutive pre-apheresis LDL-C < 25	3 (7.3%)	0
Patients with any AE	2 (66.7%)	0
Patients with any SAE	1 (33.3%)	0
Patients with any AE leading to permanent treatment discontinuation	0	0
Acute myocardial infarction	1 (33.3%)	0
Acute respiratory failure	1 (33.3%)	0
Anemia	1 (33.3%)	0
Aortic valve stenosis	1 (33.3%)	0
Cardiac failure congestive	1 (33.3%)	0
Injection site reaction	1 (33.3%)	0
Pain in extremity*	1 (33.3%)	0
Pneumonia	1 (33.3%)	0
Protein urine present*	1 (33.3%)	0
Pruritus	1 (33.3%)	0
Sepsis	1 (33.3%)	0
Skin abrasion	1 (33.3%)	0
Transfusion reaction*	1 (33.3%)	0
Urinary casts present*	1 (33.3%)	0

Note: Two consecutive pre-apheresis values in the double-blind period are considered if the consecutive pre-apheresis LDL-C values are spaced out by at least 10 days.
Note: Only TEAEs that occurred, worsened or became serious the day or after the first of the two calculated consecutive pre-apheresis LDL-C<25mg/dL are considered.
Note: The denominator of the percentage of AEs is the number of patients with two consecutive pre-apheresis calculated LDL-C <25 mg/dL in each treatment group.
Note: '*' indicates preferred terms that occurred in patients with 2 consecutive pre-apheresis LDL-C values <15 mg/dL

Source: ESCAPE CSR, Tables 11.8.14.1A, 11.8.14.3A, and 11.8.14.7A

Table 19. AEs in Patients with Two Consecutive Post-Apheresis LDL-C Values Less Than 25 mg/dL During the Double-Blind Period

	Alirocumab N=41	**Placebo N=21**
At least 2 consecutive post-apheresis LDL-C < 25	23 (56.1%)	4 (19.0%)
Patients with any AE	16 (69.6%)	2 (50.0%)
Patients with any SAE	0	0
Patients with any AE leading to permanent treatment discontinuation	1 (4.3%)	0
Arthralgia*¥	2 (8.7%)	0
Gastroesophageal reflux disease*¥	2 (8.7%)	0
Nausea*¥	2 (8.7%)	0
Procedural pain*¥	2 (8.7%)	0
Headache*¥	2 (8.7%)	1 (25.0%)
Upper respiratory tract infection*§	2 (8.7%)	1 (25.0%)
Back pain*	1 (4.3%)	0
Bacterial test positive*	1 (4.3%)	0
Blood creatinine phosphokinase increased*	1 (4.3%)	0
Blood protein urine increased	1 (4.3%)	0
Catheter site hemorrhage*	1 (4.3%)	0
Chest discomfort*	1 (4.3%)	0
Confusional state	1 (4.3%)	0
Contusion*	1 (4.3%)	0
Cough*	1 (4.3%)	0
Dermatitis*	1 (4.3%)	0
Device occlusion*	1 (4.3%)	0
Dislocation of vertebra	1 (4.3%)	0
Diverticulitis	1 (4.3%)	0
Dry mouth	1 (4.3%)	0
Dyspnea exertional*	1 (4.3%)	0
Edema peripheral*	1 (4.3%)	0
Fall	1 (4.3%)	0
Gastroenteritis	1 (4.3%)	0
Hematoma	1 (4.3%)	0
Joint injury	1 (4.3%)	0
Joint stiffness*	1 (4.3%)	0
Ligament sprain	1 (4.3%)	0
Musculoskeletal discomfort	1 (4.3%)	0
Musculoskeletal pain	1 (4.3%)	0
Myalgia*	1 (4.3%)	0
Nasal congestion*	1 (4.3%)	0
Nasophayngitis	1 (4.3%)	0
Neurodermatitis*	1 (4.3%)	0
Pain in extremity*	1 (4.3%)	0
Protein urine present*	1 (4.3%)	0
Pyrexia*	1 (4.3%)	0
Radicular syndrome*	1 (4.3%)	0
Red blood cells urine positive*	1 (4.3%)	0
Respiratory tract congestion*	1 (4.3%)	0

Tinnitus	1 (4.3%)	0
Urinary casts present*	1 (4.3%)	0
Urinary tract infection	1 (4.3%)	0
Urine leukocyte esterase positive*	1 (4.3%)	0
White blood cells urine positive*	1 (4.3%)	0
Wrist fracture*	1 (4.3%)	0
Blood pressure increased*¥	1 (4.3%)	1 (25.0%)
Arteriovenous fistula maturation failure	0	1 (25.0%)
Disturbance in attention	0	1 (25.0%)
Muscle twitching	0	1 (25.0%)

Note: Two consecutive post-apheresis values in the double-blind period are considered if the consecutive post-apheresis LDL-C values are spaced out by at least 10 days.
Note: Only TEAEs that occurred, worsened or became serious the day or after the first of the two calculated consecutive post-apheresis LDL-C<25mg/dL are considered.
Note: The denominator of the percentage of AEs is the number of patients with two consecutive post-apheresis calculated LDL-C <25 mg/dL in each treatment group.
Note: '*' indicates preferred terms that occurred in patients with 2 consecutive pre-apheresis LDL-C values <15 mg/dL
§ 'Upper respiratory tract infection' occurred in 1 patient treated with placebo with 2 consecutive post-apheresis LDL-C values <15 mg/dL
¥ "Arthralgia', 'Blood pressure increased', 'Headache', 'Gastroesophageal reflux disease', 'Nausea', and 'Procedural pain' each occurred in 1 patient treated with alirocumab with 2 consecutive post-apheresis LDL-C values <15 mg/dL

Source: ESCAPE CSR, Tables 11.8.14.4A, 11.8.14.6A, and 11.8.14.8A

Reviewer comment: The majority of these AEs were single events occurring in an at-risk patient population. It is very difficult to ascribe any particular event or constellation of events to very low LDL-C in this trial.

No patient had 2 consecutive LDL-C values less than 25 mg/dL during the open-label treatment period.

Hepatitis C Seroconversion

Hepatitis C testing was scheduled at screening and the end of the double-blind treatment period visit (week 18). One patient in the alirocumab group was positive at baseline and the same patient remained positive at the end of study. No patients in the trial had a hepatitis C seroconversion.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

More fatigue, myalgia, and diarrhea were observed in the alirocumab group vs. the placebo group during the double-blind period.

Table 20. Adverse Events Reported During Double-Blind Period, Two or More in Alirocumab Group

	Alirocumab N=41 n (%)	**Placebo N=21 n (%)**
Total AEs, Double-Blind Period	34 (82.9)	16 (76.2)
Fatigue	6 (14.6)	2 (9.5)
Myalgia	5 (12.2)	1 (4.8)
Diarrhea	4 (9.8)	0
Nasopharyngitis	4 (9.8)	2 (9.5)
Arthralgia	3 (7.3)	2 (9.5)
Headache	3 (7.3)	2 (9.5)
Upper respiratory tract infection	3 (7.3)	4 (19.0)
Acute myocardial infarction	2 (4.9)	0
Blood creatine phosphokinase increased	2 (4.9)	0
Cough	2 (4.9)	0
Gastroesophageal reflux disease	2 (4.9)	0
Non-cardiac chest pain	2 (4.9)	0
Pain in extremity	2 (4.9)	0
Pneumonia	2 (4.9)	0
Procedural pain	2 (4.9)	0
Sinus congestion	2 (4.9)	0
Sinusitis	2 (4.9)	0
Urine leukocyte esterase positive	2 (4.9)	0
Pruritus	2 (4.9)	1 (4.8)
Back pain	2 (4.9)	2 (9.5)
Nausea	2 (4.9)	3 (14.3)

Source: Reviewer created from ADAE dataset

In the open-label period, the only preferred term reported in more than 1 patient was anemia (2/29, 6.9%).

7.4.2 Laboratory Findings

Table 21. Number of Patients with Potentially Clinically Significant Abnormalities (PCSA) in Laboratory Values During the Double-Blind Period

	Alirocumab N=41 n (%)	**Placebo N=21 n (%)**
Hemoglobin		
≤ 11.5 g/L (male), ≤ 9.5 g/dL (female)	3 (7.3)	4 (19.0)
≥ 18.5 g/dL (male), ≥ 16.5 g/dL (female)	0	0
Decrease from baseline ≥ 1.5 g/dL	2 (4.9)	3 (14.3)
Decrease from baseline ≥ 2.0 g/dL	1 (2.4)	1 (4.8)
Hematocrit		
≤ 37% (male), ≤ 32% (female)	8 (19.5)	5 (23.8)
≥ 55% (male), ≥ 50% (female)	0	0

	Alirocumab N=41 n (%)	Placebo N=21 n (%)
Platelet count		
< 100,000/µL	0	0
≥ 700,000/µL	1 (2.4)	0
Leukocytes		
< 3000/µL (non-black), < 2000/µL (black)	1 (2.4)	1 (4.8)
≥ 16000/µL	0	0
Neutrophils		
<1500/µL (non-black), <1000/µL (non-black)	1 (2.4)	1 (4.8)
Glucose		
≤ 70 mg/dL and < LLN	0	1 (4.8)
≥ 200 mg/dL (unfasted), ≥ 126 mg/dL (fasted)	14 (34.1)	6 (28.6)
Creatine Kinase		
> 3x ULN	3 (7.3)	0
> 10x ULN	0	0
Sodium		
≤ 129 mmol/L	0	0
≥ 160 mmol/L	0	0
Potassium		
< 3 mmol/L	1 (2.4)	0
≥ 5.5 mmol/L	1 (2.4)	2 (9.5)
Chloride		
< 80 mmol/L	0	0
> 115 mmol/L	1 (2.4)	0
Bicarbonate	6 (14.6)	4 (19.0)
< LLN	0	0
> ULN		
Calcium		
< LLN	4 (9.8)	3 (14.3)
> ULN	0	0
Phosphate		
< LLN	3 (7.3)	0
> ULN	0	1 (4.8)

	Alirocumab N=41 n (%)	Placebo N=21 n (%)
Creatinine		
≥ 1.70 mg/dL (adults)	1 (2.4)	0
≥ 30% and < 100% from baseline	3 (7.3)	0
≥ 100% change from baseline	0	0
Blood Urea Nitrogen		
≥ 47.6 mg/dL	0	0
Urate		
< 2.02 mg/dL	0	0
> 6.86 mg/dL	17 (41.5)	6 (28.6)
Alanine Aminotransferase		
≥ 3x ULN (if baseline ALT < 2x ULN) or ≥ 2x baseline (if baseline ALT ≥ ULN)	0	0
> 3x ULN	0	0
Aspartate Aminotransferase		
> 3x ULN	0	0
Alkaline phosphatase		
> 1.5x ULN	1 (2.4)	0
Bilirubin		
> 1.5x ULN	0	1 (4.8)
> 2x ULN	0	0
ALT + total bilirubin		
ALT > 3x ULN + bili > 2x ULN	0	0
Lactate Dehydrogenase		
< LLN	0	0
> ULN	16 (39.0)	9 (42.9)
Gamma Glutamyl Transferase		
< LLN	0	1 (4.8)
> ULN	14 (34.1)	6 (28.6)

PCSA classification is performed on the worst value
The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period
Only the worsening of the worst case for each patient is presented by baseline status

Source: ESCAPE CSR post-text tables and figures, Tables 11.9.1.1.3A, 11.9.1.2.3A, 11.9.2.1.8A, 11.9.2.2.3A, 11.9.2.3.4A, 11.9.2.4.3A, 11.9.2.4.5A

Reviewer comment: Some imbalances between groups were noted. It is difficult to know in a study of this size whether any of the differences can be attributed to drug, LDL apheresis, withholding of apheresis, or chance.

7.4.3 Vital Signs

The majority of changes in vital signs were similar between groups with the exception of 4 patients (9.8%) on alirocumab vs. no patients on placebo experiencing an increase of systolic blood pressure ≥ 160 mmHg and increase from baseline ≥ 20 mmHg (Table 22).

Reviewer comment: I am unaware of any evidence that alirocumab is associated with increases in blood pressure. It is unknown if this observed imbalance could be due to the withholding of LDL apheresis in certain patients. Results of the recently completed CVOT should clarify the effects of alirocumab on blood pressure and other cardiovascular findings.

Table 22. Number of Patients with Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs During the Double-Blind Period

	Alirocumab N=41 n (%)	**Placebo N=21 n (%)**
Systolic Blood Pressure		
≤ 95 mmHg and decrease from baseline ≥ 20 mmHg	1 (2.4)	1 (4.8)
≥ 160 mmHg and increase from baseline ≥ 20 mmHg	4 (9.8)	0
Diastolic Blood Pressure		
≤ 45 mmHg and decrease from baseline ≥ 10 mmHg	2 (4.9)	0
≥ 110 mmHg and increase from baseline ≥ 10 mmHg	0	0
Pulse		
≤ 50 bpm and decrease from baseline ≥ 20 bpm	0	2 (9.5)
≥ 120 bpm and increase from baseline ≥ 20 bpm	0	0
Weight		
≥ 5% decrease from baseline	6 (14.6)	2 (9.5)
≥ 5% increase from baseline	2 (4.9)	0

Source: ESCAPE CSR post-text tables and figures, Table 11.10.1.7A

7.4.4 Electrocardiograms (ECGs)

Patients with potentially clinically significant abnormalities in ECGs are shown in the table below. Aside from some small numerical differences, there was no clear trend observed for ECG findings with alirocumab.

Table 23. Number of Patients with Potentially Clinically Significant Abnormalities (PCSA) in ECGs During the Double-Blind Period

	Alirocumab N=39 n (%)	**Placebo N=21 n (%)**
Ventricular Rate		
≤ 50 bpm and decrease from baseline ≥ 20 bpm	0	0
≥ 120 bpm and increase from baseline ≥ 20 bpm	0	0
PR Interval		
≥ 220 ms and increase from baseline ≥ 20 ms	1 (2.6)	0
QRS Interval		
≥ 120 ms	4 (10.3)	1 (4.8)
Corrected QTF Interval		
≥ 431 ms (male), ≥ 451 (female)	0	0
Increase from baseline ≥ 30 ms	0	0

Source: ESCAPE CSR post-text tables and figures, Table 11.10.2.1A

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

In the ESCAPE trial, 3 patients treated with alirocumab and 1 patient treated with placebo developed treatment-emergent ADAs. All antibodies were considered transient (that is, neither persistent nor indeterminate[7]), low-titer, and non-neutralizing.

7 Persistent ADA: at least 2 consecutive post-baseline samples with positive ADA separated by at least a 12-week period; indeterminate ADA: ADA positive response present only at the last sampling time point

Table 24. Anti-Alirocumab Antibodies, Double-Blind Period

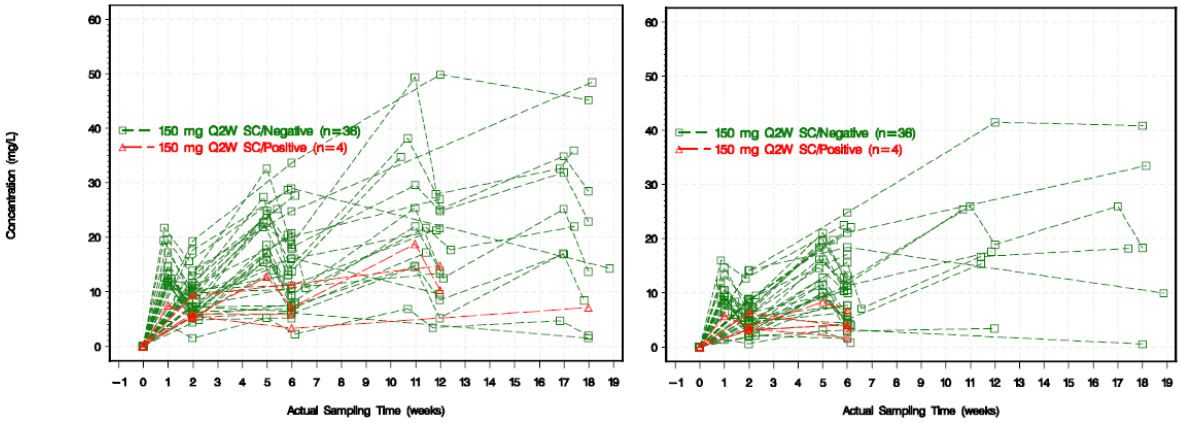
	Alirocumab N=40 n (%)	**Placebo N=20 n (%)**
Baseline		
Positive ADA status	1 (2.5)	1 (5.0)
Titer	30.0	30.0
Positive neutralizing status	0/1	0/1
Week 12		
Positive ADA status	3/38 (7.9)	2/18 (11.1)
Mean titer (SD)	40.0 (17.3)	30.0 (0.0)
Positive neutralizing status	0/3	0/2
Week 18		
Positive ADA status	2/38 (5.3)	1/19 (5.3)
Mean titer (SD)	45.0 (21.2)	30.0
Positive neutralizing status	0/2	0/1
Follow-up		
Positive ADA status	1/18 (5.6)	1/9 (11.1)
Titer	30.0	30.0
Positive neutralizing status	0/1	0/1

Source: ESCAPE CSR post-text tables and figures, Table 11.10.6.1A

Adverse events in the 3 alirocumab-treated patients with positive ADAs during the double-blind period include memory impairment, radicular syndrome, gastroesophageal reflux disease, and joint injury. These AEs were only reported in 1 patient each.

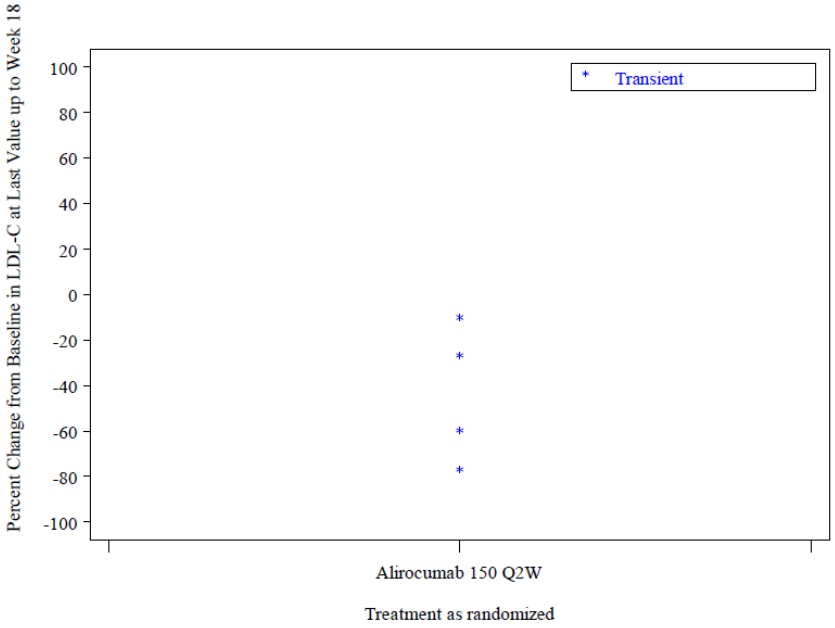
Although alirocumab concentrations and LDL-C responses in patients with a positive ADA response at any time were within the distribution of concentrations observed for patients with a negative response in the ADA assay, on average, drug concentrations and LDL-C response seems to be somewhat less than the group of patients with negative ADAs.

Figure 7. Total Alirocumab Concentrations Obtained Pre-Apheresis and Post-Apheresis vs. Actual Time by ADA Status at Any Time



Source: Summary of Clinical Pharmacology, Figure 6

Figure 8. Percent Change from Baseline in LDL-C at Last Value Up to Week 18 in Alirocumab-Treated Patients with Positive ADAs During the Double-Blind Period



Source: ESCAPE CSR post-text tables and figures, Figure 11.10.6.5A

7.5 Other Safety Explorations

Other safety explorations were not done in this small trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No neoplasm adverse events were reported in the ESCAPE trial.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in the ESCAPE trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No patient reported an overdose in the trial.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Postmarketing information was not included in this supplement. See discussion of the new TSIs, 'psychiatric events' and 'influenza-like illness', in Sections 2.4 and 7.3.5. The psychiatric events TSI is now closed.

9 Appendices

9.1 Literature Review/References

The ESCAPE trial was published in 2016 in the European Heart Journal.[8]

8 Moriarty PM, et al. Alirocumab in patients with heterozygous familial hypercholesterolemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. Eur Heart J. 2016; 37(48): 3588-95.

9.2 Labeling Recommendations

- Remove [redacted] (b) (4) as instructions for dosing alirocumab in patients with HeFH undergoing apheresis is sufficient to clarify that the drug can be used in these patients.
- Remove [redacted] (b) (4) from Section 2 as these are implied claims.
- Remove [redacted] (b) (4) since it does not include new safety information.
- Remove [redacted] (b) (4)
- Add PK and PD information of alirocumab in association with apheresis to Section 12.
- Remove [redacted] (b) (4) Include changes from baseline at the 6 weeks timepoint for LDL-C in alirocumab and placebo. Remove [redacted] (b) (4)

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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