CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Indication(s):	LDL-C lowering
Applicant:	Sanofi
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1 EXECUTIVE SUMMARY

Sanofi submitted a supplemental biologic licensure application (sBLA) based on findings from the clinical trial ODYSSEY ESCAPE. (b) (4)

Brief overview of Clinical Studies

ODYSSEY ESCAPE was a randomized, double-blind, placebo-controlled, parallel-group study in 62 patients with heterozygous familial hypercholesterolemia (HeFH) undergoing lipid apheresis therapy. In the first 6 weeks of the double-blind treatment period, apheresis frequency was fixed according to a patient's established apheresis schedule (QW or Q2W). From week 7 to 18, LDL apheresis was administered only if the reduction in pre-apheresis LDL-C did not exceed 30%. The primary efficacy endpoint was the rate of apheresis treatment during the 12-week period from week 7 to week 18.

Statistical Issues

Two significant issues related to the device/data used to determine apheresis need between weeks 7 and 18 were identified (Section 3.2.2). Efficacy data collected during this period were found not to meet the regulatory definition of being adequate and well controlled, due the method of assessment of patients' response not being reliable (21 CFR 314.126(b)(6)). The issues resulted in apheresis being inappropriately withheld or performed, with the majority of patients having either the primary efficacy endpoint not being accurate (biased) or its accuracy could not be confirmed (Table 2). The primary efficacy endpoint and select key secondary endpoint were not reviewed due to the issues.

During the first 6 weeks of the double-blind treatment period where patients received study drug (alirocumab or placebo) in combination with apheresis, the device associated with the issues used to determine apheresis need was not used, resulting in data from this period being considered reliable to allow for the evaluation of the effect of alirocumab plus apheresis compared to apheresis alone. This review focuses on exploratory analyses using data from this period.

Conclusions and Recommendations

While significant issues limit what information can be extracted from ODYSSEY ESCAPE, I consider the supplement approvable as there is reliable statistical evidence that alirocumab plus apheresis lowers LDL-C more than apheresis alone. At week 6, the estimated average reduction from baseline in pre-apheresis LDL-C was 47% for alirocumab plus apheresis compared to an increase of 1% for apheresis alone (Table 8). The Division of Metabolism and Endocrinology Products (DMEP) could describe this finding in the package insert if additional LDL-C lowering for patients undergoing apheresis is important information to convey to a prescriber.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Praluent (alirocumab) is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor approved July 24, 2015 and indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

2.1.2 History of Drug Development

Praluent was developed under IND 105574. There were multiple interactions between Sanofi and DMEP regarding the trial (ODYSSEY ESCAPE) used to support the sBLA under review. Pertinent parts of the communications to the statistical review are summarized herein.

On 10/24/2014 FDA provided following comments on the clinical trial protocol:

- Disagreed with the threshold (30% LDL-C reduction) to withhold LDL apheresis and believed 40 or 50% is a more reasonable threshold to withhold apheresis therapy.
- The trial would not support any efficacy claim or support a justification that treatment [redacted] (b) (4)

On 7/24/2017 preliminary comments for a sBLA meeting were issued to the Applicant. A summary of select comments are below:

- The 'apheresis withholding' phase largely reflects achieving a pre-specified categorical decrease in LDL-C (above or below a 30% decrease), which has been well-characterized for patients with HeFH in other trials. Not obvious why the ability of alirocumab to lower LDL-C by at least 30% should be considered new information.
- The first 6 weeks of the trial evaluated the effect of alirocumab + apheresis vs. placebo + apheresis, which could 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, additional granularity beyond what is in the CSR is needed to characterize LDL-C in each treatment group. For example, for the placebo group it is misleading to represent the LDL-C profile using only pre-apheresis values, since mean LDL-C during the interval between procedures is substantially lower than this.
- The trial was not designed to determine whether alirocumab is superior to apheresis with respect to reducing LDL-C.

2.1.3 Studies Reviewed

This review will focus on the results from study R727-CL-1216 (ODYSSEY ESCAPE), hereafter referred to as ESCAPE.

2.2 Data Sources

The submission of sBLA 125559 was received October 24, 2017. The study report, including protocols, statistical analysis plans, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path location: \\CDSESUB1\evsprod\BLA125559\0172.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Significant issues related to the data used to determine apheresis need was uncovered, discussed in detail in Section 3.2.2.

The table below summarizes additional data issues uncovered during the review

Issue	Comment
The apheresis treatment log for patient (b) (6) had the patient receiving apheresis at week 8 but the PR SDTM dataset did not have any information on the procedure.	The Sponsor clarified that apheresis was not performed (IR sent 03/02/2018).
A dataset (poc_unblinded) generated from the IVRS and included raw POC LDL-C values was not submitted with the sBLA eDATA package.	The Sponsor provided the dataset and relevant documentation (IR sent 03/01/2018).

The datasets, and analysis and dataset documentation were generally found to be of high quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

ESCAPE was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab in patients with HeFH undergoing lipid apheresis therapy. A total of 62 patients in the US and Germany were randomized in a 1:2 ratio to placebo or 150 mg Q2W alirocumab, stratified by apheresis frequency (QW vs. Q2W) and baseline Lp(a) levels (< 30 mg/dL vs. ≥ 30 mg/dL).

ESCAPE consisted of a 2-week screening period, an 18-week double-blind treatment period, a 58-week open-label period (for patients where alirocumab is not commercially available [Germany]), and an 8-week follow-up period. In the first 6 weeks of the double-blind treatment period, apheresis frequency was fixed according to a patient's established apheresis schedule (weekly for patients with QW apheresis procedure, and at Baseline, Weeks 2, 4, and 6 for patients with Q2W apheresis procedure). From week 7 to 18, LDL apheresis was performed if the reduction from baseline in pre-apheresis LDL-C at the visit did not exceed 30%. The apheresis treatment decision was based on a post-baseline LDL-C value obtained from a point-of-care (POC) portable lipid device.

Significant limitations in the data that supported the decision to withhold apheresis were found (detailed in the next Section), resulting in:

- **Efficacy data from the apheresis sparing period of the study not meeting the regulatory definition of being adequate and well controlled, due the method of assessment of patients' response not being reliable (21 CFR 314.126(b)(6)); and**
- **It not being possible to derive reliable estimates of the effect of alirocumab on the primary efficacy endpoint and select key secondary efficacy endpoints.**

Reviewer Comment: Due to the implication and extent of the issue, this review focuses on exploratory analyses using data primarily from the period of the study where the portable lipid device was not used to determine apheresis need. Data from this period is considered reliable. The goal of these analyses is to investigate the effect of alirocumab given in combination apheresis compared to apheresis alone, which could be useful to prescribers and possibly warrant presentation in Section 14 of the package insert.

The primary endpoint was the rate of apheresis treatment 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. Key secondary efficacy endpoints were:

- Percent change from baseline to week 6 in LDL-C (pre-apheresis)
- Rate of apheresis treatment from week 15 to week 18
- Percent change from baseline to week 6 in ApoB (pre-apheresis)
- Percent change from baseline to week 6 in non-HDL-C (pre-apheresis)
- Percent change from baseline to week 6 in total cholesterol (pre-apheresis)
- Percent change from baseline to week 6 in ApoA-1 (pre-apheresis)
- Proportion of patients with ≥ 30% reduction in LDL-C (pre-apheresis) at week 6
- Proportion of patients with ≥ 50% reduction in LDL-C (pre-apheresis) at week 6
- Percent change from baseline to week 18 in LDL-C (pre-apheresis)
- Percent change from baseline to week 18 in ApoB (pre-apheresis)
- Percent change from baseline to week 18 in non-HDL-C (pre-apheresis)
- Percent change from baseline to week 18 in total cholesterol (pre-apheresis)
- Percent change from baseline to week 18 in ApoA-1 (pre-apheresis)
- Proportion of patients with ≥ 30% reduction in LDL-C (pre-apheresis) at week 18
- Proportion of patients with ≥ 50% reduction in LDL-C (pre-apheresis) at week 18
- Change of W-BQ22 index score from baseline to week 18
- Percent change from baseline to week 6 in Lp(a) (pre-apheresis)
- Percent change from baseline to week 6 in HDL-C (pre-apheresis)
- Percent change from baseline to week 6 in TG (pre-apheresis)
- Percent change from baseline to week 18 in Lp(a) (pre-apheresis)
- Percent change from baseline to week 18 in HDL-C (pre-apheresis)
- Percent change from baseline to week 18 in TG (pre-apheresis)

3.2.2 Point-of-Care Device and Apheresis Withholding

This section describes and explores the impact of two significant issues around the use of the POC portable lipid device used for determining apheresis need during the apheresis sparing part of the trial. The two issues are:

1. The POC device reported an error code due to an inability to calculate LDL-C, which was then incorrectly used as actual values when determining apheresis need. These data should not have been used when determining apheresis.
2. Due to how percent change in LDL-C was derived when determining apheresis need, apheresis was withheld when the reduction exceeded a level that was on average less than the 30% defined per protocol.

Error Codes: The POC device reported an error code due to an inability to calculate LDL-C, which were then incorrectly used by the IVRS system as actual values when determining apheresis need. Error codes took the values of 1 to 8, resulting **in every instance an error code was encountered apheresis was withheld.** Error codes should not have been used when determining apheresis need.

In total, there were 103 visits where the POC device reported an error code, with the majority (95) occurring in the alirocumab group (Table 1). While the total number of patients that had apheresis inappropriately withheld is unknown due to LDL-C from the central laboratory not being collected at odd-numbered weeks per protocol, it is estimated:

- At least 14% of placebo treated patients had apheresis inappropriately withheld (i.e., apheresis was withheld but reduction in pre-apheresis LDL-C based on central laboratory did not exceed 30%), with the estimate being as high as 19% if the 1 patient that did not have an available central laboratory result is assumed to have apheresis inappropriately withheld. This assumption may be reasonable since in all 6 instances where an error code was observed and a central laboratory value was also available, the reduction in LDL-C based on the central laboratory result did not exceed 30%.
- At least 5% of alirocumab treated patients had apheresis inappropriately withheld. Although the percentage could be as high as 29% (status of 10 patients is unknown since central laboratory data were unavailable), it is presumably lower than this given that 2/15 patients with available central laboratory data had apheresis appropriately withheld.

Table 1. Error code and availability of LDL-C from the central laboratory

	Alirocumab		Placebo	
	Patients N=41	Instances	Patients N=21	Instances
Error code reported	25 (61%)	95	4 (19%)	8
Error code reported and LDL-C (central laboratory) available	15 (37%)	54	3 (14%)	6
LDL-C reduction (central laboratory) does not exceed 30%	2 (5%)	4	3 (14%)	6

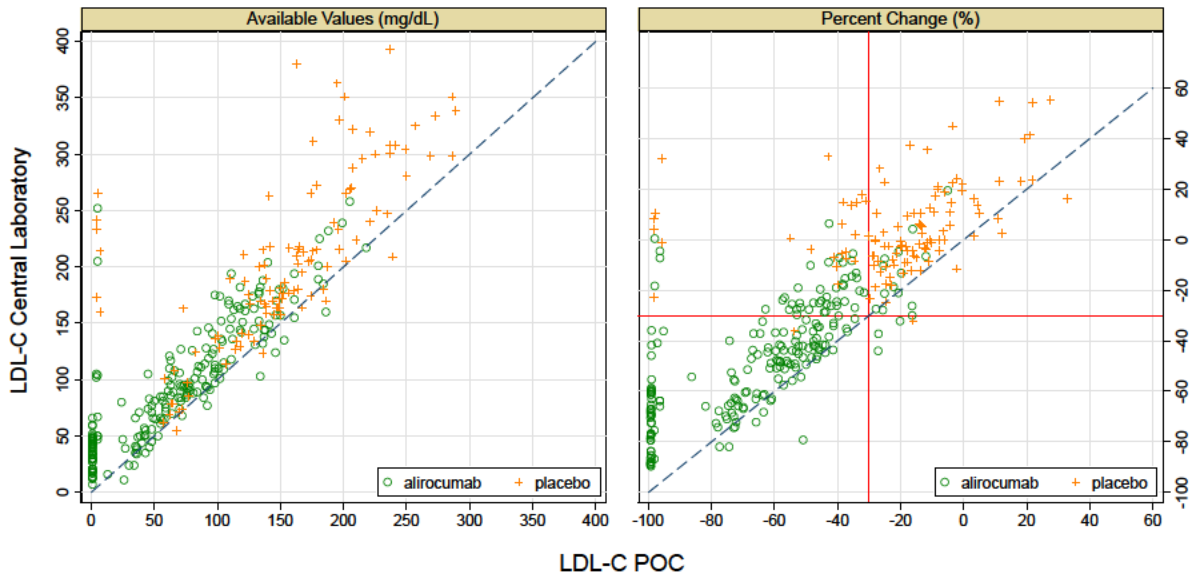
Source: Statistical Reviewer

In summary, the use of error codes values in determining apheresis need caused patients in both treatment groups to have apheresis to be inappropriately withheld, resulting in the primary efficacy endpoint (rate of apheresis during weeks 7 to 18) being overstated. The overall impact

of this issue is unknown since central laboratory data were not available in every instance an error code was encountered.

Bias in the data that supported the decision to withhold apheresis: Systematic bias was found in the data that supported the decision to withhold apheresis. The issue was that the calculation of percent change relied on LDL-C results from different sources (post-baseline LDL-C from the POC device, and baseline LDL-C from the central laboratory); results from the different sources are not interchangeable. LDL-C values from the POC device are consistently smaller than those from the central laboratory (Figure 1, left panel), resulting in the reduction in LDL-C used to evaluate apheresis need being overstated. If LDL-C values from the different sources were perfectly interchangeable, the values would fall along the y=x reference line in the scatter plot; however, the fact that the points in the plot are systematically above the reference line indicates that the LDL-C from the POC device were systematically smaller. This bias coupled with how LDL-C values from different sources were used in calculating LDL-C reduction, made it more likely that a patient appeared to meet the criterion for withholding apheresis when in fact they did not.

Figure 1. Relationship between pre-apheresis LDL-C values from different sources (Weeks 7 to 18)



Source: Statistical Reviewer; Program name: "aval LDL-C POC vs calc LDL-C explore.do".
Note 1: Percent change uses the central laboratory value for baseline. POC LDL-C was not collected at baseline.
Note 2: Paired data at odd-number weeks is not available as central laboratory values were not collected.
Note 3: POC error codes are plotted if the paired central laboratory result is available.
Note 4: Central laboratory not collected at odd-numbered weeks, so relationship at these visits cannot be evaluated

The right panel of the Figure is a scatter of percent change in LDL-C using central laboratory results on the y-axis and the POC (using central laboratory baseline) on the x-axis, with references lines at -30% on both axes (criteria for withholding apheresis) and one for y=x. There were 258/330 (78%) instances where the decision to withhold apheresis (bottom left quadrant) or perform apheresis (upper right quadrant) based on the POC device was supported by the central

laboratory value. There were 72 instances where the decision to withhold or perform apheresis based on the POC device was not supported by the magnitude of LDL-C reduction based on central laboratory data. In most of these instances (68) the reduction based on central laboratory data did not exceed a 30% reduction, meaning that the central laboratory result did not support the decision to withhold apheresis; these instances are represented in the top-left quadrant , which includes 10 instances where apheresis was inappropriately withheld due to the POC device reporting an error code. While the total number of patients that may have either had apheresis inappropriately performed or withheld is unknown (central laboratory data not available), it is estimated:

- At least 62% (13/21) and 41% (17/41) of the placebo and alirocumab treated patient respectively had at least one instance where the decision to withhold or perform apheresis was not supported the central laboratory data.

Furthermore, the lack of a 1:1 relationship between LDL-C values from the two sources in Figure 1 implies there is not a unique threshold for which apheresis was withheld. For the instances when the POC device did not produce an error code, the paired pre-apheresis central laboratory values are estimated to be on average 15.4% lower than POC results from the same day (average percent change for central laboratory values is -21.8% and -37.2% per POC). Based on this result, apheresis was effectively withheld if the reduction from baseline exceeded 15%, which is much lower than the 30% specified in the protocol, which the Agency communicated to the Sponsor was too low (Section 2.1.2).

In summary, this issue resulted in:

- Approximately half of the patients having at least one instance where the decision to perform or withhold apheresis was the incorrect apheresis treatment decision based on the central laboratory data, resulting in the estimate of primary efficacy endpoint being biased (overstated). The full extent of the bias is unknown due to the limited collection schedule of central laboratory data.
- Apheresis being withheld when the reduction in LDL-C was on average lower than the 30% specified in the protocol.

Extent of data issues due to the POC device: The two issues detailed above affect a large number of patients in both treatment groups (Table 2). For only 13 (32%) patients in the alirocumab group and 4 (19%) in placebo can we be confident that the primary efficacy endpoint is accurate. By accurate it is meant that the apheresis treatment decision (withhold or perform the procedure based on the POC data) over weeks 7 and 18 was supported by central laboratory data at every instance an apheresis treatment decision was made. For 41% and 62% of patients in the alirocumab and placebo group, respectively, the primary efficacy endpoint is not accurate. For an additional 27% of patients in the alirocumab group and 19% in placebo the accuracy cannot be determined based on available data, primarily due to central laboratory values not being available for patients undergoing weekly apheresis.

Given that for most patients the primary efficacy endpoint is either not accurate (biased) or the accuracy is unknown, it is not possible to derive reliable estimates of the primary efficacy endpoint with any degree of confidence.

Table 2. Summary of apheresis procedure during apheresis sparing period (weeks 7 to 18)

Apheresis procedure incorrectly performed or withheld	Alirocumab N=41	Placebo N=21
At least once	17 (41%)	13 (62%)
Unable to determine	11 (27%)	4 (19%)
Apheresis QW apheresis	10	3
Apheresis Q2W	1	1
No*	13 (32%)	4 (19%)

Source: Statistical Reviewer

** Includes 1 patient in each treatment group that discontinued before the apheresis sparing period of the study.*

Impact of erroneously withholding of apheresis: For the placebo group, there is evidence that a bias propagates from the inappropriate withholding of apheresis to lipid parameters evaluated at subsequent visits. This finding is based on comparing for the Q2W apheresis group the pre-apheresis lipid values at the visit in which apheresis was inappropriately withheld (based on central laboratory values) to their pre-apheresis value at their next visit (Table 3). A systematic shift in these data may suggest lipids parameters are different from what they may have been had apheresis been performed since a shift was not observed during the period of the study where apheresis was performed regardless of LDL-C reduction (See Table 4). For multiple lipid parameters (cholesterol, HDL-C, LDL-C, non-HDL-C), placebo had a notable shift in the average pre-apheresis levels at the visit following inappropriate withholding of apheresis that was not observed for alirocumab. For example, for LDL-C in the placebo group there was an average increase of 27.9 mg/dL in pre-apheresis LDL-C following inappropriate withholding of apheresis compared to 0.2 mg/dL for alirocumab. Between weeks 2 and 8 for placebo, there was essentially no change in average pre-apheresis LDL-C levels (0.3 mg/dL) between visits.

The implication of this finding is that the inappropriate withholding of apheresis at a visit affects subsequent visits, and thus the issue is not localized to only the visit where apheresis was inappropriately withheld. As it relates to the primary efficacy endpoint, a placebo treated patient would be more likely to have apheresis at a visit if, at the prior visit, apheresis was erroneously withheld compared to if apheresis was performed. In addition to impacting the accuracy the primary efficacy endpoint, this issue also impacts statistical inferences for key secondary efficacy endpoints. Specifically, the endpoints:

1. Evaluated at week 18 are presumably biased. The treatment effect estimates likely overstate the true effect since the change from baseline for placebo is likely understated. The degree to which the treatment effect is overstated is unknown; and
2. Evaluated at week 6 based on the Sponsor's prespecified analysis, which is before the period in the study where apheresis could be withheld, is also presumed to be biased since they are based on either a statistical or imputation model that depends on data from the apheresis sparing period of the study. Note: excluding data from the apheresis period in the analysis would resolve this bias concern.

Note: it was not possible to evaluate how the erroneous withholding of apheresis impacted specialty labs (i.e., ApoB, ApoA-1, Lp(a)) due to the limited frequency in which they were ascertained. The specialty lipid panel was collected only at baseline, and weeks 4, 6, 14 and 18.

Table 3. Change in pre-apheresis lipid parameters (central laboratory) between adjacent visits (weeks 8 and 16) when apheresis was inappropriately withheld – Q2W apheresis group

Parameter (unit)	Statistic	Alirocumab	Placebo
Cholesterol (mg/dL)	N	22	8
	mean (SD)	2.6 (21.5)	28.1 (25.5)
	min, max	-42 ,43	-13 ,60
HDL Cholesterol (mg/dL)	N	22	8
	mean (SD)	-2.1 (7.8)	-5.8 (8.5)
	min, max	-17 ,21	-20 ,5
LDL Cholesterol (mg/dL)	N	20	8
	mean (SD)	0.2 (22.7)	27.9 (21.4)
	min, max	-46 ,47	0 ,62
Non-HDL Cholesterol (mg/dL)	N	22	8
	mean (SD)	4.7 (21.7)	33.9 (26.5)
	min, max	-31 ,47	2 ,80
Triglycerides (mg/dL)	N	22	8
	mean (SD)	30.2 (76.6)	28.5 (32.7)
	min, max	-66 ,260	-5 ,92

N = number of adjacent visits compared (not number of patients)
Source: Statistical Reviewer

Table 4. Change in pre-apheresis lipid parameters (central laboratory) between adjacent visits (weeks 2 and 8) – Q2W apheresis group

Parameter (unit)	Statistic	Alirocumab	Placebo
Cholesterol (mg/dL)	N	63	33
	mean (SD)	-1.8 (18.1)	0.1 (24.2)
	min, max	-43 ,41	-46 ,65
HDL Cholesterol (mg/dL)	N	63	33
	mean (SD)	1.6 (5.5)	1.2 (6.2)
	min, max	-24 ,15	-12 ,20
LDL Cholesterol (mg/dL)	N	61	33
	mean (SD)	-2.6 (16.1)	0.3 (24.6)
	min, max	-34 ,41	-50 ,65
Non-HDL Cholesterol (mg/dL)	N	63	33
	mean (SD)	-3.4 (17.5)	-1.1 (25.3)
	min, max	-40 ,36	-45 ,67
Triglycerides (mg/dL)	N	63	33
	mean (SD)	-3.6 (45.8)	-7.2 (67.7)
	min, max	-152 ,115	-159 ,153

N = number of adjacent visits compared (not number of patients)
Source: Statistical Reviewer

Study Investigators and the Applicant: Study investigators unlikely knew about these issues since they were blinded to lipid values during the study, including LDL-C values from the POC device (POC LDL-C values were coded to a random number and upon entry of that number into the designated website, the investigator site was instructed from the IVRS to either perform or not perform the apheresis procedure [Response to 12/19/2017 IR]).

The Applicant's study team reportedly became aware that error codes were being treated as real LDL-C values during the supplement review (Response to 3/1/2018 IR). For the systematic difference in LDL-C values from the central laboratory and POC device, it is unknown when the Applicant first became aware of the issue that was raised during the review (11/21/2017 IR). Because the Applicant could have addressed/corrected/identified these issues prior to study initiation, it is of concern the Applicant did not perform appropriate due diligence either testing the IVRS or evaluate the suitability of the POC device with achieving study objectives prior to study initiation. However, while these issues resulted in the planned and actual study conduct diverging during the apheresis sparing period of the study, leading to obvious challenges interpreting data from this period, I am unaware of evidence that the planned/actual study conduct diverged during the period of the study where study drug was given with apheresis since the POC device was not used.

Summary: Two issues related to the device used to determine apheresis need do not make it possible to reliably evaluate the primary and secondary efficacy endpoints with a high degree confidence. Moreover, the threshold for which apheresis was withheld was found not to be empirically well defined and notably lower the 30% reduction stated in the protocol.

3.2.3 Statistical Methodologies

The section does not detail prespecified statistical methodology used by the Applicant due to issue detailed in Section 3.2.2. The reader is referred to the statistical analysis plan for details.

Exploratory analyses presented in this review are based on the intention-to-treat principle, meaning that efficacy data collected after a patient discontinued treatment is used. All FDA analyses used central laboratory results, unless noted otherwise. Details of statistical methods used are found in text or tables footnotes in Section 3.2.5.2.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition in the ESCAPE study is summarized in Table 5 below. Approximately 8% of the patients did not complete the double-blind treatment period, with more alirocumab treated patients not completing the period (10% vs 5%). The most common reason for not completing the double-blind treatment period was attributed to an adverse event. There were no deaths during the double-blind treatment period.

Table 5. Subject disposition

	Placebo N=21	Alirocumab 150 mg Q2W N=41
Randomized	21 (100.0%)	41 (100.0%)
Randomized and Treated	21 (100.0%)	41 (100.0%)
Did not complete first 6 weeks of double-blind treatment period	1 (4.8%)	1 (2.4%)
Completed double-blind treatment period	20 (95.2%)	37 (90.2%)
Reason for not completing double-blind treatment period		
Adverse event	1 (4.8%)	2 (4.9%)

Withdrew consent	0 (0.0%)	1 (2.4%)
Poor compliance to protocol	0 (0.0%)	1 (2.4%)

Source: Statistical Reviewer

Demographic and baseline characteristic for all randomized patients in the study is summarized in Table 6. The mean age was 59, the majority of patients were white, 58% of patients were male, and the average LDL-C was 181 mg/dL.

Table 6. Demographic and baseline characteristics – All randomized patients

Characteristic	Placebo N=21	Alirocumab 150 mg Q2W N=41	Total N=62
Age (years)			
mean (sd)	57 (11)	60 (9)	59 (10)
median (Q1, Q3)	59 (51, 62)	61 (52, 67)	60 (52, 66)
Sex			
F	11 (52%)	15 (37%)	26 (42%)
M	10 (48%)	26 (63%)	36 (58%)
Race			
BLACK OR AFRICAN AMERICAN	0 (0%)	2 (5%)	2 (3%)
WHITE	21 (100%)	39 (95%)	60 (97%)
Country			
Gernamy	10 (48%)	20 (49%)	30 (48%)
USA	11 (52%)	21 (51%)	32 (52%)
Baseline BMI (kg/m2)			
mean (sd)	30 (6)	31 (5)	30 (5)
median (Q1, Q3)	28 (26, 35)	31 (27, 33)	30 (26, 34)
Baseline BMI			
< 30	13 (62%)	18 (44%)	31 (50%)
>= 30	8 (38%)	23 (56%)	31 (50%)
Apheresis Frequency			
Apheresis Schedule Q2W	11 (52%)	23 (56%)	34 (55%)
Apheresis Schedule QW	10 (48%)	18 (44%)	28 (45%)
Baseline Lipoprotein-a Level			
Elevated Baseline Lp(a) Level	8 (38%)	16 (39%)	24 (39%)
Normal Baseline Lp(a) Level	13 (62%)	25 (61%)	38 (61%)
Baseline LDL-C (mg/dL)			
mean (sd)	192 (69)	175 (55)	181 (60)
median (Q1, Q3)	180 (140, 240)	176 (129, 219)	180 (133, 227)
Baseline LDL-C (mg/dL)			
<130 mg/dL / <3.37 mmol/L	3 (14%)	11 (27%)	14 (23%)
>=130 to <190 mg/dL / >=3.37 to <4.91 mmol/L	8 (38%)	14 (34%)	22 (35%)
>=190 mg/dL / >=4.91 mmol/L	10 (48%)	16 (39%)	26 (42%)
Statin use at randomization			
Not on statin therapy at randomization	8 (38%)	22 (54%)	30 (48%)
On statin therapy at randomization	13 (62%)	19 (46%)	32 (52%)
Lipid modifying therapy (LMT) at randomization			
Not on LMT at randomization	5 (24%)	17 (41%)	22 (35%)
On LMT at randomization	16 (76%)	24 (59%)	40 (65%)

Source: Statistical Reviewer

3.2.5 Results and Conclusions

3.2.5.1 Prespecified analysis of the primary and key secondary efficacy endpoints

Due to the issues described in Section 3.2.2, results for the primary efficacy endpoint and select key secondary efficacy are not reviewed.

3.2.5.2 Exploratory analyses

The number of patients that met the criteria for withholding apheresis based on central laboratory results was investigated for the first instance in the Q2W apheresis group where apheresis could have been withheld (Table 7). Note: the propagation of bias/error from the erroneous withholding of apheresis does not support the evaluation of whether patients met the criteria for withholding apheresis at subsequent visits. At week 8 there were statistically significantly more patients in the alirocumab group that had a 30% reduction in LDL-C. This was statistically significant compared to placebo (70% vs. 9%) at the nominal 5% level (difference = 60%; 95% CI = 22%, 99%). This analysis could not be done for the QW apheresis group since central laboratory results were not available per protocol at Week 7, the first instance where a decision to withhold apheresis could have been made for this group.

Table 7. Number and percentage of patients in the Q2W apheresis group that had LDL-C (central laboratory) reductions exceed 30% at Week 8

Pre-apheresis LDL-C (central laboratory)	Alirocumab N=23	Placebo N=11
Reduction exceeds 30%	16 (70%)	1 (9%)
Reduction does not exceed 30%	3 (13%)	10 (91%)
Missing	4 (17%)	-
Early termination	1	
Missing (only POC LDL-C available)	1	
Missed visit	2	

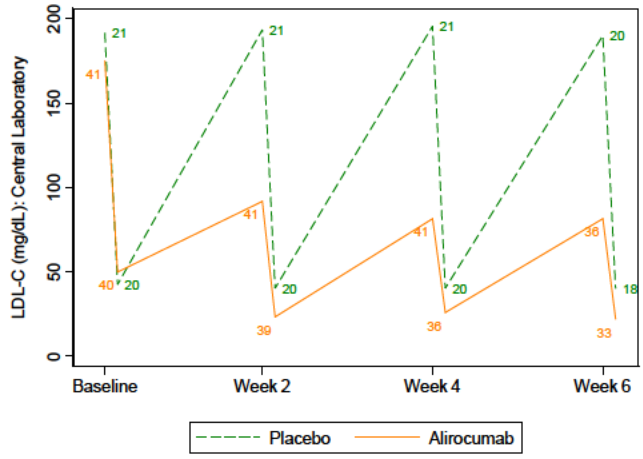
Source: Statistical Reviewer

Whether apheresis was appropriately administered at Week 8 for the Q2W apheresis group was explored by contrasting procedure status with the central laboratory results. For the 11 placebo treated patients, 9 (82%) correctly received apheresis, **1 (9%) patient did not receive apheresis but should have**, and 1 (9%) correctly did not receive apheresis. For the 23 alirocumab treated patients, 16 (70%) correctly did not receive apheresis, **3 did not receive apheresis but should have, 1 did not have apheresis but it is unknown whether they should have (missing central laboratory value)**, and 3 patients did not have the procedure (1 early terminated, and 2 missed the visit).

Error! Reference source not found. shows unadjusted mean LDL-C levels at pre- and post-apheresis in the ITT (randomized and treated) population during first 6 weeks of the double-blind treatment period. Over this period, adding alirocumab to apheresis resulted in lower pre- and post- apheresis average LDL-C levels over this period than apheresis alone. Within a treatment group the mean LDL-C levels pre- and post- apheresis were consistently higher in the Q2W apheresis group compared to the QW apheresis group (Figure 3).

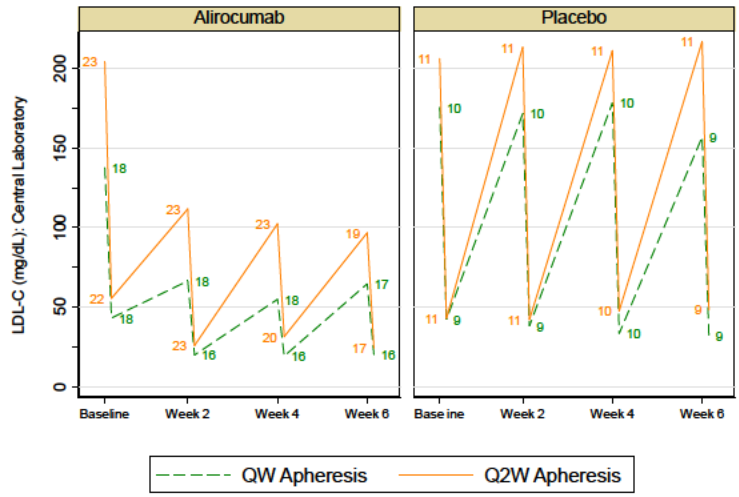
Missing week 6 pre-apheresis LDL-C was not notably high (6/62=10%), but the amount was greater in the alirocumab group (5/41 =12% vs. 1/21 = 5%).

Figure 2. Mean pre- and post- apheresis LDL-C during the first 6 weeks of the double-blind treatment period -- ITT population



Source: Statistical Reviewer; Program name: "LDL-C calc at week 6 explore.do".

Figure 3. Mean pre- and post- apheresis LDL-C during the first 6 weeks of the double-blind treatment period by apheresis schedule -- ITT population



Source: Statistical Reviewer; Program name: "LDL-C calc at week 6 explore.do".

Table 8 summarizes change from pre-apheresis baseline to pre-apheresis at Week 6 in the ITT population. LDL-C, ApoB, non-HDL-C, total cholesterol, Lp(a) and triglycerides were statistically significantly lower at the nominal 5% level when alirocumab was given with apheresis compared to apheresis based on the pre-apheresis levels, as evidence by the lower limit of the 95% CI excluding the null value of 0. There was no difference between treatment groups for ApoA-1 and HDL-C as the CI for difference included the null value. Treatment effect estimates should be interpreted with some caution since LDL-C for a patient undergoing

apheresis is not characterized by their pre-apheresis value, as commented in the pre-sBLA meeting (Section 2.1.2).

Table 8. Percent change in pre-apheresis lipid parameters (central laboratory) at week 6 – ITT population

Endpoint	Alirocumab LS mean	Placebo LS mean	Difference (95% CI) (Alirocumab - Placebo)
LDL-C	-47%	1%	-49% (-60, -37)
ApoB	-39%	1%	-40% (-49, -30)
non-HDL-C	-43%	3%	-45% (-56, -35)
total cholesterol	-33%	3%	-36% (-45, -28)
ApoA-1	3%	-1%	3% (-5, 11)
Lp(a)	-16%	3%	-19% (-34, -4)
HDL-C	8%	5%	3% (-5, 11)
Triglycerides	-9%	11%	-20% (-37, -4)

Note: Missing pre-apheresis week 6 value for both treatment groups were imputed using multiple imputation with a washout imputation approach that truncated imputed values at the minimum pre-apheresis value in the study. The imputation model had baseline LDL-C as a covariate and was estimated from patients in the placebo group with a week 6 value. Lp(a) and triglycerides were imputed on the log-scale and then tranformed. A total of 100 complete datasets were created. Patients missing baseline were excluded from the analysis. LS means and between group differences were estimated from an ANCOVA model with treatment, stratification factors and baseline value. Source: Statistical Reviewer; Program name: "Lipids at week 6 – washout imputation.do".

Time-averaged LDL-C is explored since the LDL-C profile between procedures (i.e., acute lowering followed by rebound) is not characterized by either the pre- or post- apheresis values. However, because intermediate LDL-C values between procedures were not collected per protocol, untestable assumptions must be made to calculate time-averaged LDL-C. Time-averaged LDL-C between procedures is expressed as a weighted average of the post-apheresis value at the start of the period value and the pre-apheresis value the end of a period. Note: a weight of 0.5 assumes a linear rebound, while weights > 0.5 are weighted more to the pre-apheresis value at the end of the period, with larger values reflecting a more immediate rebound. The weight 0.73 is noteworthy as it is the weight used by the Sponsor, which they label as being derived using Kroon's formula (Kroon et al. Atherosclerosis. 2000; 152(2):519-26). Because LDL-C was not ascertained at odd-numbered weeks, the investigation considers the Q2W apheresis group only.

Table 9 shows time-averaged LDL-C under different weights for the Q2W apheresis group between weeks 4 and week 6. For the weights considered, the confidence interval for the average difference between treatment groups exclude the null value of 0, allowing us to conclude that the time-averaged LDL-C is lower when alirocumab is administered in combination with apheresis compared to apheresis alone. However, the estimate that best characterizes the treatment effect is not known due to uncertainty about the appropriate weight to derive time-averaged LDL-C.

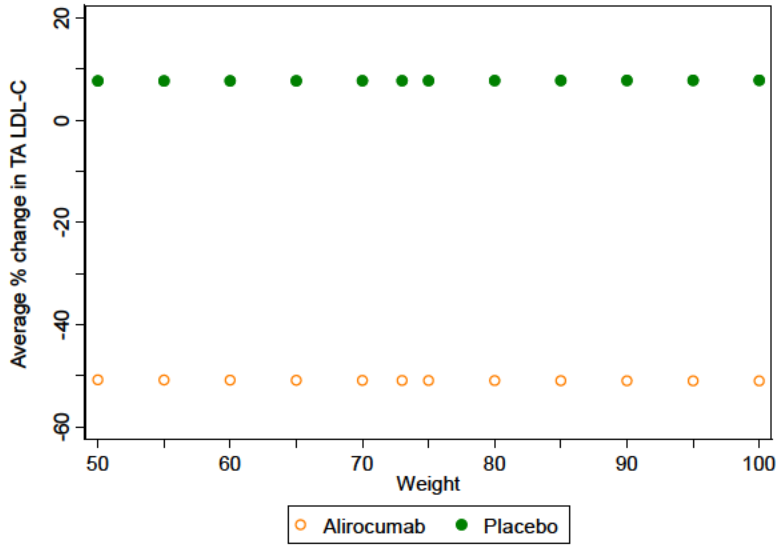
Table 9. Time-averaged LDL-C (interval: Week 4 to 6) using different weights – Q2W apheresis group

	Time averaged LDL-C (mg/dL)		
Weight	Alirocumab LS mean	Placebo LS mean	Difference (95% CI) (Alirocumab - Placebo)
0.5	74	131	-57 (-89, -24)
0.55	79	139	-61 (-96, -26)
0.6	83	148	-65 (-102, -28)
0.65	87	157	-70 (-109, -31)
0.7	91	165	-74 (-115, -33)
0.73	94	170	-77 (-119, -34)
0.75	96	174	-78 (-122, -35)
0.8	100	183	-83 (-128, -37)
0.85	104	191	-87 (-135, -40)
0.9	108	200	-92 (-141, -42)
0.95	112	208	-96 (-148, -44)
1	117	217	-100 (-155, -46)

Note: Missing post-apheresis week 4 (pre-apheresis week 6) value was imputed for both treatment groups using multiple imputation with a washout imputation approach that truncated imputed values at 7. The separate imputation models had baseline LDL-C as a covariate and was estimated from patients in the placebo group with a post-apheresis week 4 (pre-apheresis week 6) value. A total of 100 complete datasets were created. Patients missing either value LDL pre- or post- apheresis at baseline were excluded from the analysis. LS means were estimated from an ANCOVA model with treatment as a covariate.
Source: Statistical Reviewer; Program name: "LDL-C calc at week 6 explore.do".

Figure 4 shows the unadjusted mean for percent change from baseline in time-averaged LDL-C between weeks 4 and 6 for different weights, revealing that the magnitude of change does not depend on weight (alirocumab: -51%; placebo: 8%).

Figure 4. Average percent change (unadjusted) in time-average LDL-C (interval: Week 4 to 6) using different weights – Q2W apheresis group



Note 1: time-average baseline is approximated using LDL-C values pre- and post- apheresis from Study Day 1.
Note 2: Missing data not imputed. Therefore, the analysis is based on complete cases.
Source: Statistical Reviewer

Table 10 shows the percent change from baseline in time-averaged LDL-C between weeks 4 and 6 for the Q2W apheresis group. The degree of LDL-C lowering was estimated to be 52% lower for the alirocumab group compared to placebo with nominal 95% CI = (-68, -36) that did not include 0. Thus, alirocumab given in combination with apheresis was associated with a reduction in time-averaged LDL-C that was not achieved with apheresis alone. Different weights were considered and yielded similar treatment effect estimates as the ones presented below (results not given); this finding is not however surprising given the relationship shown in Figure 4. It is also worth noting that the magnitude of percent change based on time-averaged LDL-C was similar to the estimate derived from pre-apheresis values (-52% vs. -49%).

In summary, I consider the finding that adding alirocumab to apheresis additionally lowers LDL-C real and not spurious, based on the consistency of findings across different ways of looking at LDL-C (i.e., time-averaged and pre-apheresis levels), the magnitude of the treatment effect from the different investigations, and that alirocumab has been previously shown to be efficacious in patients with HeFH not undergoing apheresis. This finding, nonetheless, must be interpreted in the context of a significantly flawed study, where the analyses were exploratory and done to see if possibly useful information to prescribers could be extracted. For this reason, I do not support presenting p-values in the package insert if these findings are to be summarized therein.

Table 10. Change in time-averaged LDL-C between Weeks 4 and 6 for the Q2W apheresis group – ITT population with baseline assessment available

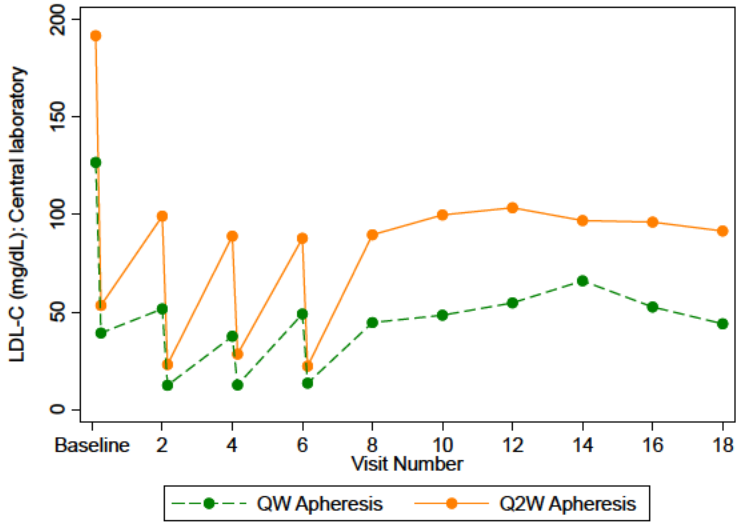
		Alirocumab	Placebo	Difference (95% CI) (Alirocumab - Placebo)
TA Baseline (mg/dL)	N	22	11	
	Mean (SD)	163 (35)	162 (64)	
Change from TA Baseline in TA LDL-C over between weeks 4 and 6 (%)	N	17	10	
	Mean (SD)	-51% (14)	8% (14)	
	LS Mean	-45%	7%	-52% (-68, -36)

TA – time averaged;
Note 1: Analyses assume a weight of 0.73
Note 2: time-average baseline is approximated using LDL-C values pre- and post- apheresis from Study Day 1.
Note 3: Missing post-apheresis week 4 (pre-apheresis week 6) value was imputed for both treatment groups using multiple imputation with a washout imputation approach that truncated imputed values at 7. The separate imputation models had baseline LDL-C as a covariate and was estimated from patients in the placebo group with a post-apheresis week 4 (pre-apheresis week 6) value. A total of 100 complete datasets were created. Patients missing either value LDL pre- or post- apheresis at baseline were excluded from the analysis. The within and between group difference was estimated from an ANCOVA model with treatment as a covariate.
Source: Statistical Reviewer; Program names: "LDL-C calc at week 6 explore.do" and "TA LDL-C calc at week 6 explore.do".

Figure 5 shows mean LDL-C throughout the double-blind treatment period in the subset of alirocumab treated patients that did not have apheresis during the apheresis sparing part of the double-blind treatment period (QW apheresis: 11/18; Q2W: 15/23). In this subset, mean LDL-C when alirocumab was given without apheresis was at or slightly above pre-apheresis levels when alirocumab was given with apheresis, suggesting that the time-averaged LDL-C likely achieves

lower levels when alirocumab is given with apheresis compared to alirocumab alone or alirocumab with intermittent apheresis.

Figure 5. Mean LDL-C (central laboratory) for alirocumab treated patients that did not have apheresis during the apheresis sparing period of the double-blind treatment period – ITT Population

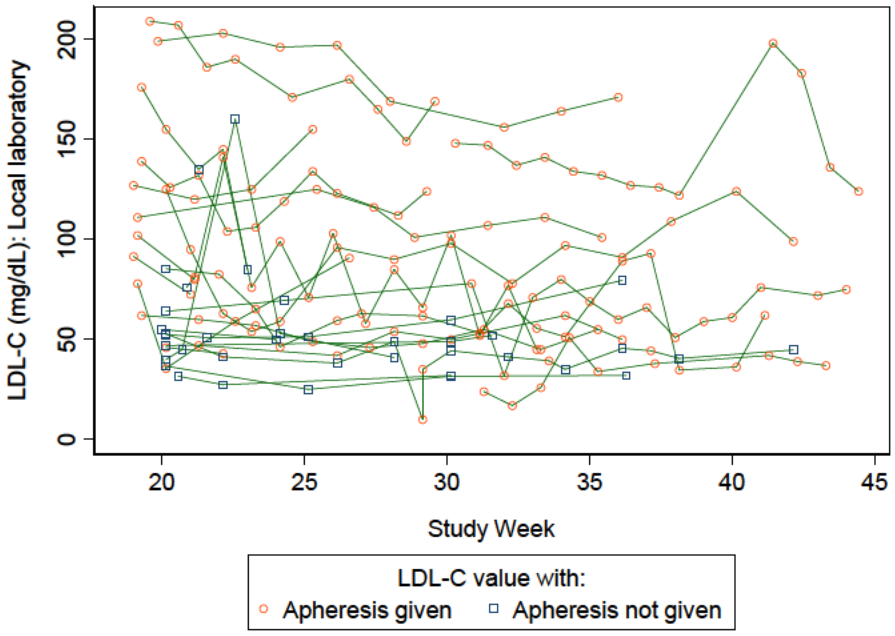


Source: Statistical Reviewer

In the open-label extension apheresis was not required but could be given based on the investigator's discretion and local laboratory values. As there were concerns conveyed by DMEP during the review of the study protocol (See Section 2.1.2) that the 30% threshold for withholding apheresis during the double-blind treatment period was not appropriate, LDL-C and apheresis data collected during the OLE period was reviewed. Local laboratory LDL-C data was found to be collected sparsely, adding uncertainty into how LDL-C may have been used to inform apheresis sparing "in practice." Specifically, if LDL-C was measured each time apheresis could have been given during the OLE based on the patient's apheresis schedule, we would expect that there would be a total of 486 LDL-C values but only observed 188 values. Thus, approximately 60% of the time there was no LDL-C value to inform the decision to withhold apheresis.

A spaghetti plot of LDL-C data from the local laboratory is shown in Figure 6, with different symbols for whether apheresis was given (open circle) or not (open square). The plot suggest that apheresis was likely to be withheld when LDL-C is low, however there is not a clear threshold for which apheresis was withheld. The mean LDL-C when apheresis was not given was 54 mg/dL (min: 25; Q1: 40; median: 48; Q3: 55; max: 160) and lower than the 94 mg/dL when it was given (min: 10; Q1: 55; median: 85; Q3: 126; max: 209).

Figure 6. LDL-C values (local laboratory) during the open label extension and apheresis status



Source: Statistical Reviewer

3.3 Evaluation of Safety

Safety data were not investigated as part of this statistical review. The reader is referred to the clinical review by Dr. Julie Golden for the safety evaluation of ESCAPE.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were not performed for the primary or secondary efficacy endpoints due to the issues described in Section 3.2.2.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Two significant issues were identified related to the POC portable lipid device that was used to determine apheresis need between weeks 7 and 18 of the double-blind treatment period. The two issues are:

- The POC device reported an error code (1-8) when LDL-C could not be calculated, which was then inappropriately treated as a real LDL-C value when determining apheresis need.
- A systematic bias in the data used to determine apheresis need, with the estimated LDL-C reduction being overstated.

Both issues resulted in apheresis being inappropriately withheld or performed. Consequently, efficacy data collected during the period in which the POC device was used are presumed to be biased and does not meet the regulatory definition of being adequate and well controlled, due the method of assessment of patients' response not being reliable (21 CFR 314.126(b)(6)). Primary and secondary efficacy endpoints from this period were not formally reviewed.

Data from the first 6 weeks of the double-blind treatment period where patients received study drug (alirocumab or placebo) in combination apheresis procedure is considered reliable since the POC device was not used to determine apheresis need. The review primarily focused on exploratory analyses from this period of the study.

5.2 Collective Evidence

Alirocumab plus apheresis lowered LDL-C more than apheresis alone, with the average reduction being approximately 50% greater for alirocumab. This finding was consistent across analyses investigating change in time-average LDL-C and change in pre-apheresis LDL-C. The magnitude of reduction is also consistent with the magnitude of reduction presented in the package insert for patients with HeFH not under apheresis.

5.3 Conclusions and Recommendations

There is reliable statistical evidence that alirocumab plus apheresis lowers LDL-C more than apheresis alone. DMEP should describe this finding in the package insert if additional LDL-C lowering for patients undergoing apheresis is important information to convey to a prescriber.

5.4 Labeling Recommendations

Due to the issues related the POC device, there should be limited information in the package insert derived from this study. I recommend that there is no suggestion that patients check LDL-C levels to determine apheresis need. Section 14 should only summarize LDL-C reduction derived from the first 6 weeks of the study and not describe the study design element related to apheresis sparing. Results should not be based on the Sponsor's prespecified analysis of change in pre-apheresis LDL-C at week 6. Instead, I support presenting only the average within arm change from baseline to Week 6 in pre-apheresis LDL-C level from Table 8, or from another analysis where missing data are handled in similar fashion as in Table 8; p-values should not accompany these estimates.

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/s/

BRADLEY W MCEVOY
07/11/2018

JENNIFER J CLARK
07/11/2018