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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #:	125559
Supplement #:	039
Drug Name:	Alirocumab
Indications:	As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C
Applicant:	Regeneron Pharmaceuticals, Inc.
Dates:	Stamp date: 5/10/2023 Primary review Due date: 2/9/2024 PDUFA date: 3/10/2024
Review Priority:	Standard
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Keywords: pediatric subjects, HeFH

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1 EXECUTIVE SUMMARY

Regeneron Pharmaceuticals, Inc. has developed alirocumab for the treatment of pediatric patients (8 to 17 years of age) with heterozygous familial hypercholesterolemia (HeFH). It is currently approved:

- To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.

- As adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C.

  and

- As an adjunct to other LDL-C lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

They are currently seeking the following approval, as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C.

The efficacy and safety for alirocumab for the proposed indication stated above was primarily supported by study EFC14643, hereafter referred to as study 14643. Study 14643 was a phase 3 randomized, 24-week double-blind treatment, placebo-controlled, parallel-group, multi-national, multi-center study followed by an open-label treatment period of 80 weeks to assess the efficacy and safety of alirocumab in children and adolescents with HeFH. It was conducted as part of the Pediatric Research Equity Act (PREA) Post marketing Requirement (PMR). This study consisted of two dosing regimens, every 2 weeks (Q2W) and every 4 weeks (Q4W). The starting doses of both cohorts were based on body weight (BW), 40 mg (for BW <50 kg) or 75 mg Q2W (for BW ≥50 kg) and 150 mg (for BW <50 kg) or 300 mg Q4W (for BW ≥50 kg).

The applicant's pre-specified analysis of the primary endpoint, percent change in LDL-C from baseline to week 24, was performed in each dosing regimen cohort. Both cohorts analyzed the primary endpoint using a mixed effect model with repeated measures (MMRM). No missing value imputations were conducted in the primary analysis. The primary endpoint for both cohorts was the percent change in LDL-C from baseline to week 24. Superiority was achieved for the primary endpoint in both cohorts in favor of alirocumab.

There were no major statistical issues identified. The percent of missing data was 5% in the Q2W cohort and 13% in the Q4W cohort. Sensitivity analyses using different methods for handling missing data produced similar results as the primary analysis.

The applicant initially did not include subgroup analyses for the primary endpoint for race and ethnicity. An information request (IR) was sent to request those analyses. It should be noted that

the two treatment dosing cohorts, Q2W and Q4W, should not be compared statistically due to subjects being randomized to the two groups at different times.

Overall, the study supports the proposed indication for an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Regeneron Pharmaceuticals, Inc. has developed alirocumab for the treatment of pediatric patients (8to 17 years of age) with HeFH. They are seeking a new pediatric indication as an adjunct to diet and other LDL-C lowering therapies in pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C.

2.1.2 Studies Reviewed

This review will focus on the results from study 14643.

2.2 Data Sources

The submission of BLA 125559 was received on May 10, 2023. The study reports, protocols, statistical analysis plan, 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\0359. Information necessary for this review was contained in Module 1, Module 2, and Module 5.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted data are acceptable in terms of quality. I was able to reproduce the primary and secondary endpoint analyses for the clinical study submitted.

3.2 Evaluation of Efficacy

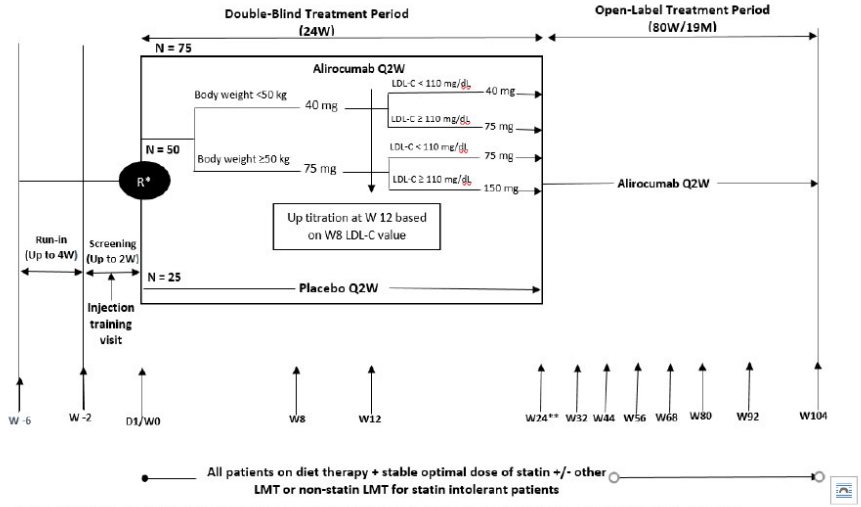
3.2.1 Study Design and Endpoints

Study 14643 was a phase 3, randomized, 24-week double-blind (DB) treatment, placebo-controlled, parallel-group, multi-national, multi-center study followed by an open-label treatment period of 80 weeks to assess the efficacy and safety of alirocumab in children and adolescents

with HeFH. This study consisted of two dosing regimen cohorts, every 2 weeks (Q2W) and every 4 weeks (Q4W). The starting doses of both cohorts were based on body weight (BW), 40 mg (for BW <50 kg) or 75 mg Q2W (for BW ≥50 kg) and 150 mg (for BW <50 kg) or 300 mg Q4W (for BW ≥50 kg), with a subsequent option of up-titration if specific LDL-C goals were not achieved at week 12, on top of stable lipid modifying therapy (LMT) background treatment(s). Subjects were randomized 2:1 to receive either alirocumab or placebo in each cohort. There was a total of 74 subjects in the Q2W cohort and 79 subjects in the Q4W cohort. Randomization were stratified according to previous participation (yes or no) in the phase 2 DFI14223 study and baseline body weight (<50 or ≥50 kg) in the Q2W cohort and baseline body weight (<50 or ≥50 kg) in the Q4W cohort.

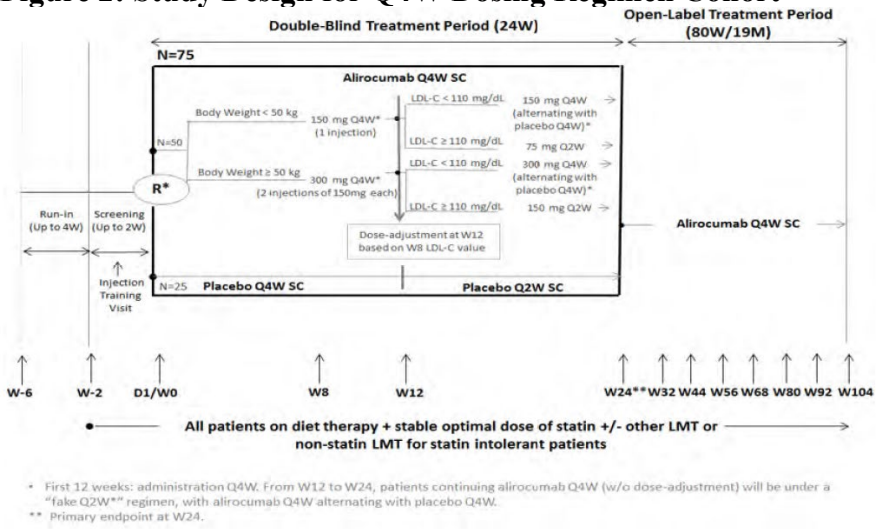
Subjects were in the screening period for up to 2 weeks. Eligible subjects were enrolled into the DB 24-week treatment period. Subjects were to maintain their starting doses until week 12. Dose up-titration or adjustment occurred in a blinded manner at week 12, based on their LDL-C level at week 8. Note that the start of the recruitment in the Q4W dosing regimen cohort depended on the status of the recruitment in the Q2W dosing regimen cohort and the status of the protocol amendment approval. There was a follow-up period of 80 weeks open label. Figure 1 and Figure 2 below shows the scheme of the study design for Q2W and Q4W cohorts, respectively.

Figure 1: Study Design for Q2W Dosing Regimen Cohort



Source: Clinical Study Report - Trial ID: SAR236553-EFC14643 Figure 1, page 25

Figure 2: Study Design for Q4W Dosing Regimen Cohort



* First 12 weeks: administration Q4W. From W12 to W24, patients continuing alirocumab Q4W (w/o dose-adjustment) will be under a "fake Q2W*" regimen, with alirocumab Q4W alternating with placebo Q4W.
** Primary endpoint at W24.

Source: Clinical Study Report - Trial ID: SAR236553-EFC14643 Figure 2, page 26

The primary objective was to evaluate the efficacy of alirocumab administered Q2W and Q4W versus placebo after 24 weeks of DB treatment on LDL-C levels in patients with HeFH 8 to 17 years of age on optimal stable daily dose of statin therapy ± other LMTs or a stable dose of non-statin LMTs in case of intolerance to statins.

The secondary objectives were to:

- To evaluate the efficacy of alirocumab versus placebo on LDL-C levels after 12 weeks of DB treatment.
- To evaluate the effects of alirocumab versus placebo on other lipid parameters (e.g., Apolipoprotein B (Apo B), non-high density lipoprotein cholesterol (non-HDL-C), Total cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), Lipoprotein (a) (Lp[a]), Triglycerides (TGs), Apolipoprotein A-1(Apo A-1) levels) after 12 and 24 weeks of treatment.

The efficacy analyses used the following analysis populations:

- The intent-to-treat (ITT) population: All randomized subjects analyzed according to the intervention group allocated by randomization.
- Modified intent-to-treat (mITT) population: all randomized subjects who took at least one dose or part of a dose of the double-blind IMP injection.
- Safety Population: All patients who received at least 1 dose of study drug or part of a dose (placebo or alirocumab). Analysis performed on the safety set will be based on patients according to treatment received.

The primary endpoint was the percent change in LDL-C from baseline to week 24 in the ITT population. The key secondary confirmatory endpoints were as follows:

- Percent change in LDL-C from baseline to Week 12
- Percent change in Apo B from baseline to Week 24
- Percent change in non-HDL-C from baseline to Week 24
- Percent change in Total-C from baseline to Week 24
- Percent change in Apo B from baseline to Week 12
- Percent change in non-HDL-C from baseline to Week 12
- Percent change in Total-C from baseline to Week 12
- Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week
- Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12
- Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week
- Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12
- Percent change in Lp (a) from baseline to Week 24
- Percent change in Lp (a) from baseline to Week 12
- Percent change in HDL-C from baseline to Week 24
- Percent change in fasting TG from baseline to Week 24
- Percent change in Apo A-1 from baseline to Week 24
- Percent change in HDL-C from baseline to Week 12
- Percent change in fasting TG from baseline to Week 12
- Percent change in Apo A-1 from baseline to Week 12

This review will focus on the following key secondary endpoints:

- Percent change in LDL-C from baseline to Week 12
- Percent change in Apo B from baseline to Week 24
- Percent change in non-HDL-C from baseline to Week 24
- Percent change in Total-C from baseline to Week 24

These are proposed endpoints for labeling. The applicant tested the primary and key secondary confirmatory endpoints in the pre-defined hierarchical order as seen above. The Bonferroni adjustment was applied to handle multiplicity for the comparison of each alirocumab dosing regimen group versus its corresponding placebo group (i.e., alirocumab Q2W versus placebo Q2W; alirocumab Q4W versus placebo Q4W) for the primary efficacy endpoint (two-sided 0.025 alpha level was applied for each comparison).

For the key secondary endpoints, the overall type-I error was controlled by the use of a sequential inferential approach applied independently within each dosing regimen cohort (Q2W and Q4W). Statistical significance of the primary parameter at the two-sided 0.025 alpha level was required before drawing inferential conclusions for that dosing regimen cohort about first key secondary parameter. Inferential conclusions about successive key secondary parameters for a given dosing regimen cohort require statistical significance of the prior one in that dosing

regimen cohort. The Bonferroni adjustment and this fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the two-sided 0.05 level.

3.2.2 Statistical Methodologies

All efficacy analyses were performed using the ITT population. Formal statistical hypothesis testing was performed on the primary and key secondary endpoints at 2-sided, 0.025 level of significance per comparison. The statistical analyses for the primary and secondary efficacy endpoints compared each alirocumab dosing regimen to its randomized placebo group within the same dosing regimen cohort:

- alirocumab Q2W versus placebo Q2W
- alirocumab Q4W versus placebo Q4W.

The applicant's pre-specified analysis of the primary endpoint, percent change in LDL-C from baseline to week 24, was performed in each dosing regimen cohort. Both cohorts analyzed the primary endpoint using a mixed effect model with repeated measures (MMRM). No missing imputations were conducted in the primary analysis, the applicant stated that missing data was accounted for by the MMRM model. The analysis assumes unequal residual variances between treatment groups since the randomization ratio was 2:1 in both cohorts.

The model for the Q2W doing regimen cohort included treatment group, randomization strata (previous participation [yes or no] to DFI14223 phase 2 study, baseline body weight [<50 kg or ≥50 kg]), time point (week 8, week 12, week 24), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time interaction.

The model for the Q4W doing regimen cohort included treatment group, randomization strata (baseline body weight [<50 kg or ≥50 kg]), time point (week 8, week 12, week 24), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time interaction. The strata variable, previous participation (yes or no) to DFI14223 phase 2 study was not included in the Q4W dosing regimen cohort model due to very few subjects from this phase 2 study being enrolled in the Q4W regimen. The start of the recruitment in the Q4W dosing regimen cohort depended on the status of the recruitment in the Q2W dosing regimen cohort and the status of the amendment approval.

The null and alternative hypotheses for each cohort are defined as:

- Q2W dosing regimen cohort: H0: $\mu_0 = \mu_1$ versus H1: $\mu_0 \neq \mu 1$
- Q4W dosing regimen cohort: H0: $\mu_{0'} = \mu_{1'}$ versus H1: $\mu_{0'} \neq \mu_{1'}$

where μ_0, μ_1 are the population means of the percent change from baseline in calculated LDL-C at week 24 under placebo and alirocumab in the Q2W dosing regimen cohort, and respectively $\mu_{0'}$, $\mu_{1'}$ the corresponding population means in the Q4W dosing regimen cohort.

The continuous secondary endpoints were analyzed using the same MMRM model as the primary efficacy endpoint with the corresponding baseline values in the ITT population.

There were 4 (5%) (4 alirocumab subjects) with missing week 24 data in the Q2W dosing regimen cohort and 10 (13%) (4 placebo subjects and 6 alirocumab subjects) with missing week 24 data in the Q4W dosing regimen cohort. The applicant conducted a pattern mixture model approach as a sensitivity analysis to address missing data. For the Q2W dosing regimen cohort, the applicant stated that multiple imputations were used with different imputation strategies applied to LDL-C values missing during the on-treatment period (i.e., within the time period from the first double-blind IMP injection up to the day of last double-blind injection +21 days) versus LDL-C values missing after treatment discontinuation (i.e., after the day of last double-blind injection +21 days). Missing data during on treatment period were imputed using observed data within each treatment. Missing data after treatment discontinuation were imputed based on a multiple imputation with patients' own baseline value as the mean and a variance conditional on baseline observation. For patients who permanently discontinued the treatment due to the COVID-19 pandemic, missing post-treatment data were considered "Missing at Random" and imputed based on other on-treatment measurements in the same treatment group. The imputed dataset was analyzed using the analysis of covariance (ANCOVA) model with model terms including treatment, randomized strata, and corresponding baseline value, assuming unequal variances by treatment group. The same approach was conducted for the Q4W dosing regimen. This reviewer conducted a placebo washout multiple imputation to address missing data.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The summary of the subject disposition is given below in Table 1 and Table 2 by dosing regimen cohort. The Q2W cohort had 74 subjects randomized (49 to the alirocumab group and 25 to placebo). All subjects were treated and had a baseline value. Approximately 5% of the subjects prematurely discontinued the double-blind treatment.

The Q4W cohort had 79 subjects randomized (52 to the alirocumab group and 27 to placebo). All subjects were treated and had a baseline value. Approximately 5% of the subjects prematurely discontinued the double-blind treatment.

Table 1. Subject Disposition Overall for Q2W Cohort

	Alirocumab N=49 n(%)	**Placebo N=25** n(%)	**Total N=74** n(%)
ITT	49 (100.0)	25 (100.0)	74 (100.0)
Discontinued treatment	4 (8.2)	0	4 (5.4)
Adverse event	0	0	0
Death	0	0	0
Other	0	0	0
Related to COVID-19	0	0	0
Not Related to COVID-19	4 (8.2)	0	4 (5.4)

Subject Non-compliant	1 (2.0)	0	1 (1.4)
Life events made continuing on the protocol too difficult	1 (2.0)	0	1 (1.4)
Subject forgot to apply week20 and week22 IMP	1 (2.0)	0	1 (1.4)
Subject moved	1 (2.0)	0	1 (1.4)
Site terminated by sponsor	0	0	0
Subject missing week 24 observation	4 (8.2)	0	4 (5.4)

ITT: intent-to-treat: defined as randomized subjects; IMP: Investigational medicinal product
Source: Clinical Study Report- Trial ID: EFC14643 Table 5, page 45-47

Table 2. Subject Disposition Overall for Q4W Cohort

	Alirocumab N=52 n(%)	**Placebo N=27** n(%)	**Total N=79** n(%)
ITT	52 (100.0)	27 (100.0)	79 (100.0)
Discontinued treatment	3 (5.8)	1 (3.7)	4(5.1)
Adverse event	2 (3.8)	0	0
Related to COVID-19	0	0	0
Not Related to COVID-19	2 (3.8)	0	2 (2.5)
Other	1 (1.9)	1 (3.7)	2 (2.5)
Related to COVID-19	1 (1.9)	0	2 (2.5)
Related to IMP Administration	0	1 (3.7)	1 (1.3)
Site terminated by sponsor	0	0	0
Subject missing week 24 observation	6 (11.5)	4 (14.8)	10 (12.7)

ITT: intent-to-treat: defined as randomized subjects; IMP: Investigational medicinal product
Other: Related to COVID-19: COVID-19 SUBJECT NOT WILLING TO CONTINUE THE STUDY TREATMENT. AND AS WELL AS THE PATIENT'S DECISION NOT TO RECEIVE ANY MORE INJECTIONS
Source: Clinical Study Report- Trial ID: EFC14643 Table 6, page 46-47

Baseline demographics are shown in Table 3 for Q2W and Q4W. The subjects' mean age was approximately 13 years old in both cohorts. The majority of the subjects were white in both cohorts, with male (49%) and female (51%) in Q2W; male (38%) and female (62%) in Q4W. Note that this disease has high prevalence in Caucasian (white) population, which explains the high percentage of whites in both cohorts. About 12% of the subjects were from the United States in the Q2W cohort and 5% in the Q4W. Baseline characteristics were generally well-balanced across the treatment groups.

Table 3. Demographics and Baseline Characteristics – by Cohort ITT Population

	Q2W			Q4W		
	Alirocumab N = 49	**Placebo N = 25**	**Total N = 74**	**Alirocumab N = 52**	**Placebo N = 27**	**Total N = 79**
Age (years)						
Mean (SD)	12.5 (2.7)	13.2 (2.4)	12.8 (2.6)	13.1 (3.0)	12.8 (3.0)	13.0 (3.0)
Sex, n (%)						
Female	30 (61.2)	8 (32.0)	38 (51.4)	34 (65.4)	15 (55.6)	49 (62.0)
Male	19 (38.8)	17 (68.0)	36 (48.6)	18 (34.6)	12 (44.4)	30 (38.0)
Ethnicity, n (%)						
Hispanic or Latino	2 (4.1)	2 (8.0)	4 (5.4)	18 (34.6)	6 (22.2)	24 (30.4)
Not Hispanic or Latino	46 (93.9)	23 (92.0)	69 (93.2)	34 (65.4)	21 (77.8)	55 (69.6)
Not reported	1 (2.0)	0	1 (1.4)	0	0	0
Race, n (%)						
White	42 (85.7)	23 (92.0)	65 (87.8)	38 (73.1)	22 (81.5)	60 (75.9)
Black or African American	1 (2.0)	0	1 (1.4)	1 (1.9)	1 (3.7)	2 (2.5)
Black or African American/White	3 (6.1)	1 (4.0)	4 (5.4)	0	0	0
Asian	1 (2.0)	1 (4.0)	2 (2.7)	0	0	0
Native Hawaiian or other Pacific Islander	1 (2.0)	0	1 (1.4)	0	0	0
Native Hawaiian or other Pacific Islander/White	1 (2.0)	0	1 (1.4)	0	0	0
American Indian or Alaska Native	0	0	0	12 (23.1)	4 (14.8)	16 (20.3)
Not Reported	0	0	0	1 (1.9)	0	1 (1.3)
Country, n (%)						
USA	6 (12.2)	3 (12.0)	9 (12.2)	3 (5.8)	1 (3.7)	4 (5.1)
Outside of USA	43 (87.8)	22 (88.0)		49 (94.2)	26 (96.3)	75 (94.9)
Weight (kg)						
Mean (SD)	53.9 (22.2)	50.4 (15.1)	52.7 (20.1)	54.7 (20.2)	50.9 (14.0)	53.4 (18.3)
Previous participation to the DFI14223 study, n (%)						
Yes	19 (38.8)	10 (40.0)	29 (39.2)	2 (3.8)	1 (3.7)	3 (3.8)
No	30 (61.2)	15 (60.0)	45 (60.8)	50 (96.2)	26 (96.3)	76 (96.2)

n: Number of subjects
USA: United States of America

Source: Clinical Study Report- Trial ID: EFC14643 Table13, pages 58-60 and Table 14, pages 60-61

3.2.4 Results and Conclusions

The applicant's primary efficacy results were confirmed by the statistical review team. The primary analysis results for LDL-C are shown in Table 4. Missing data was not imputed in the primary analysis by the applicant. This analysis assumes unequal residual variances between treatment groups since the randomization ratio was 2:1 in both cohorts. Both cohorts showed a statistically significant difference in the percent change in LDL-C from baseline to week 24, in favor of alirocumab. It seems that the placebo group in the Q2W cohort did worse than the placebo group in the Q4W cohort. However, any statistical comparisons between the Q2W and Q4W cohorts need to be interpreted with caution as the subjects could have some systematic differences due to the enrollment of Q4W cohort was after Q2W cohort and Q2W cohort enrolled more subjects who participated a phase 2 study. If the subjects were randomized to Q2W and Q4W at the same time, we could make some interpretable statistical comparisons. With that being said, we should not compare the two cohorts statistically.

Table 4. Reviewer Analysis on Percent Change from Baseline in LDL-C at Week 24, ITT Population

	Q2W		Q4W	
	Alirocumab N=49	**Placebo** N=25	**Alirocumab** N=52	**Placebo** N=27
Baseline mean LDL-C	169.69	175.29	176.79	176.57
n	45	25	46	23
LS Means (SE)	-33.6 (3.4)	9.7 (4.3)	-38.1 (4.0)	-4.2 (3.7)
Treatment difference Alirocumab-Placebo at week 24	-43.3		-33.8	
97.5% CI	-55.9, -30.6		-46.4, -21.2	

n: subjects with observed data at week 24.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LS = least-squares; Q2W = every 2 weeks; Q4W = every 4 weeks; SE: standard error
Q2W: The model includes the fixed categorical effects of treatment group, randomization strata (BW, participation in DFI14223), time point, treatment-by-time point interaction, strata-by-time point interaction (BW, participation in DFI14223), as well as the continuous fixed covariates of baseline LDL-C value and baseline value by time-point interaction.
Q4W: The model includes the fixed categorical effects of treatment group, BW randomization strata, time point, treatment-by-time point interaction, BW strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value by time-point interaction.
Source: Statistical Reviewer's Analysis; adlbus.xpt

Table 5 shows the analysis results for the primary endpoint including the imputed data for missing LDL-C values using a placebo washout imputation assuming unequal variance. There was 5% missing data at week 24 in the Q2W cohort, all in the alirocumab group; there was 13% missing data in the Q4W cohort at week 24. The placebo washout imputation method multiply imputed missing data using placebo data and baseline data from the active drug arm. No intermediate data on active drug were used in imputation. The mean LDL-C difference between alirocumab and placebo and the 97.5% confidence intervals were -40.2 (-53.2, -27.3) in the Q2W dosing regimen cohort and -31.2 (-43.7, -18.8) in the Q4W dosing regimen cohort. Both cohorts are still in favor of alirocumab

Table 5. Reviewer Analysis on Percent Change from Baseline in LDL-C at Week 24, ITT Population - Placebo Washout Imputation

	Q2W		Q4W	
	Alirocumab N=49	**Placebo** N=25	**Alirocumab** N=52	**Placebo** N=27
Baseline mean LDL-C	169.69	175.29	176.79	176.57
LS Means (SE)	-30.4 (3.9)	9.7 (4.2)	-34.3 (4.2)	-3.1 (3.7)
Treatment difference Alirocumab-Placebo at week 24	-40.2		-31.2	
97.5% CI	-53.2, -27.3		-43.7, -18.8	

n: subjects with observed data at week 24.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LS = least-squares; Q2W = every 2 weeks; Q4W = every 4 weeks; SE: standard error
Q2W: The model includes the fixed categorical effects of treatment group, randomization strata (BW, participation in DFI14223), as well as the continuous fixed covariate of baseline LDL-C value.
Q4W: The model includes the fixed categorical effects of treatment group, BW randomization strata, as well as the continuous fixed covariate of baseline LDL-C value.
Multiple imputation: Washout imputation
Source: Statistical Reviewer's Analysis; adlbus.xpt

Since the primary endpoint achieved superiority according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the second endpoints. Table 6 shows the results for the four key secondary endpoints of interest assuming unequal variances:

- Percent change in LDL-C from baseline to Week 12
- Percent change in Apo B from baseline to Week 24
- Percent change in non-HDL-C from baseline to Week 24
- Percent change in Total-C from baseline to Week 24.

Missing data were not imputed in these analyses. There were 5 (7%) (2 alirocumab subjects and 3 placebo subjects) with missing week 24 data in the Q2W dosing regimen cohort and 11 (14%) (7 alirocumab subjects and 4 placebo subjects) with missing week 24 data in the Q4W dosing regimen cohort for LDL-C at week 12. There were 4 (7%) (4 alirocumab subjects) with missing week 24 data in the Q2W dosing regimen cohort and 9 (11%) (5 alirocumab subjects and 4 placebo subjects) with missing week 24 data in the Q4W dosing regimen cohort for Apo-B at week 24. One subjects did not have baseline Apo-B data. There were 4 (7%) (4 alirocumab subjects) with missing week 24 data in the Q2W dosing regimen cohort and 10 (13%) (6 alirocumab subjects and 4 placebo subjects) with missing week 24 data in the Q4W dosing regimen cohort for Non-HDL-C at week 24. There were 4 (7%) (4 alirocumab subjects) with missing week 24 data in the Q2W dosing regimen cohort and 9 (11%) (5 alirocumab subjects and 4 placebo subjects) with missing week 24 data in the Q4W dosing regimen cohort for Non-HDL-C at week 24. Each of the endpoints show statistical significance in favor of alirocumab in each cohort.

Table 6. Key Secondary Analyses on Percent Change from Baseline, ITT Population

	Q2W		Q4W	
	Alirocumab N=49	**Placebo** N=25	**Alirocumab** N=52	**Placebo** N=27
LDL-C at Week 12				
Baseline mean LDL-C	169.69	175.29	176.79	176.57
n*	47	22	45	23
LS Means at week 12 (SE)	-34.8 (3.0)	10.6 (3.6)	-39.1 (3.3)	2.4 (3.6)
Treatment difference Alirocumab-Placebo at week 12	-45.4		-41.5	
97.5% CI	-56.3, -34.6		-52.7, -30.2	
Apo-B at Week 24				
n**	48	25	52	27
Baseline mean Apo-B	115.7	115.2	119.7	118.4
n*	44	25	47	23
LS Means at week 24 (SE)	-27.4 (3.1)	10.4 (2.8)	-34.3 (2.8)	-3.1 (3.9)
Treatment difference Alirocumab-Placebo at week 24	-37.9		-31.2	
97.5% CI	-47.5, -28.2		-42.3, -20.1	
Non-HDL-C at Week 24				
Baseline mean Non-HDL-C	186.8	191.6	197.2	195.4
n*	45	25	46	23
LS Means at week 24 (SE)	-31.0 (3.1)	9.6 (3.9)	-35.7 (2.9)	-3.4 (4.1)
Treatment difference Alirocumab-Placebo at week 24	-40.7		-32.3	
97.5% CI	-52.2, -29.1		-43.8, -20.8	
Total-C at Week 24				
Baseline mean Total-C	234.7	242.9	247.0	249.7
n*	45	25	47	23
LS Means at week 24 (SE)	-23.5 (2.4)	7.4 (3.2)	-27.6 (2.3)	-3.9 (3.3)
Treatment difference Alirocumab-Placebo at week 24	-30.8		-23.7	
97.5% CI	-39.9, -21.8		-32.9, -14.4	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LS = least-squares; Q2W = every 2 weeks; Q4W = every 4 weeks; SE: standard error
n*: Number of subjects at the corresponding timepoint
n**: Number of subjects at baseline
Q2W: The model includes the fixed categorical effects of treatment group, randomization strata (BW, participation in DFI14223), time point, treatment-by-time point interaction, strata-by-time point interaction (BW, participation in DFI14223), as well as the continuous fixed covariates of baseline corresponding variable value and baseline value by time-point interaction.
Q4W: The model includes the fixed categorical effects of treatment group, BW randomization strata, time point, treatment-by-time point interaction, BW strata-by-time point interaction, as well as the continuous fixed covariates of baseline corresponding variable value and baseline value by time-point interaction.
Source: Statistical Reviewer's Analysis; adlbus.xpt

Table 7 shows the result using the placebo washout imputation method for missing data. Each of the endpoints still show statistical significance in favor of alirocumab in each cohort.

Table 7. Key Secondary Analyses on Percent Change from Baseline, ITT Population–Placebo Washout Imputation

	Q2W		Q4W	
	Alirocumab N=49	**Placebo** N=25	**Alirocumab** N=52	**Placebo** N=27
LDL-C at Week 12				
Baseline mean LDL-C	169.69	175.29	176.79	176.57
LS Means at week 12 (SE)	-32.9 (3.2)	10.4 (3.4)	-34.5 (3.8)	2.6 (3.6)
Treatment difference Alirocumab-Placebo at week 12	-43.3		-37.2	
97.5% CI	-53.7, -32.8		-48.8, -25.5	
Apo-B at Week 24				
n**	48	25	52	27
Baseline mean Apo-B	115.69	115.24	119.65	118.41
LS Means at week 24 (SE)	-24.1 (3.5)	10.5 (2.8)	-31.2 (3.2)	-2.0 (3.7)
Treatment difference Alirocumab-Placebo at week 24	-34.6		-29.2	
97.5% CI	-44.5, -24.7		-40.2, -18.2	
Non-HDL-C at Week 24				
Baseline mean Non-HDL-C	186.75	191.61	197.16	195.37
LS Means at week 24 (SE)	-28.1 (3.7)	9.7 (3.8)	-31.7 (3.8)	-1.6 (3.8)
Treatment difference Alirocumab-Placebo at week 24	-37.9		-30.1	
97.5% CI	-49.7, -26.0		-42.0, -18.1	
Total-C at Week 24				
Baseline mean Total-C	234.69	242.88	246.98	249.74
LS Means at week 24 (SE)	-21.3 (2.9)	7.5 (2.9)	-25.3 (3.0)	-2.9 (3.3)
Treatment difference Alirocumab-Placebo at week 24	-28.8		-22.4	
97.5% CI	-38.0, -19.6		-32.5, -12.4	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LS = least-squares; Q2W = every 2 weeks; Q4W = every 4 weeks; SE: standard error
n**: Number of subjects at baseline
Q2W: The model includes the fixed categorical effects of treatment group, randomization strata (BW, participation in DFI14223), as well as the continuous fixed covariate of baseline corresponding variable value.
Q4W: The model includes the fixed categorical effects of treatment group, BW randomization strata, as well as the continuous fixed covariate of baseline corresponding variable value.
Multiple imputation: Washout imputation
Source: Statistical Reviewer's Analysis; adlbus.xpt

3.3 Evaluation of Safety

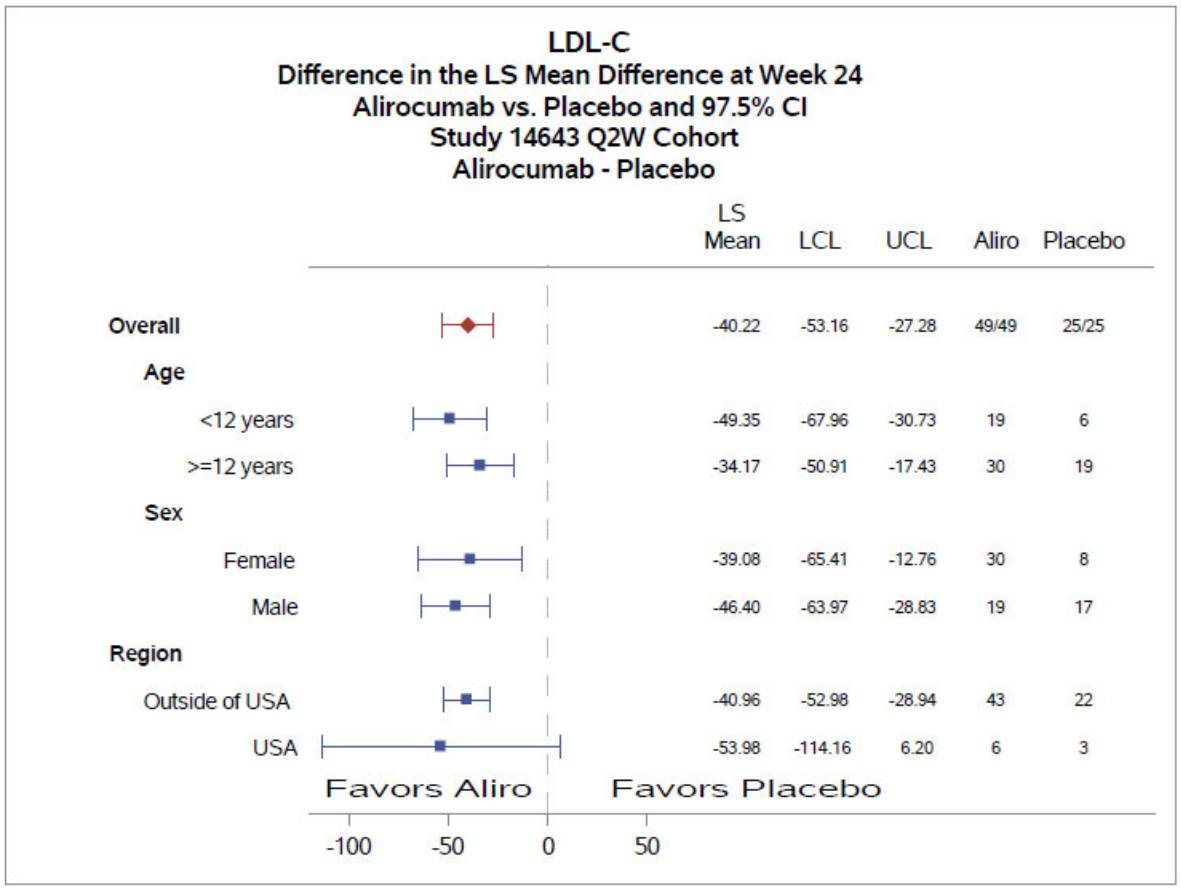
Analyses on safety events were reviewed by the Medical Reviewers, Craig Hales, M.D and Eileen Craig, M.D.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were performed on the primary endpoint, LDL-C for each cohort. The Q2W cohort was by age group (<12 years, ≥12 years), sex (Male, Female), and region (Outside of USA, USA). Race was not included due to 87.8% of subjects were white and the rest of the categories were very small. The Q4W cohort was by age group (<12 years, ≥12 years), sex

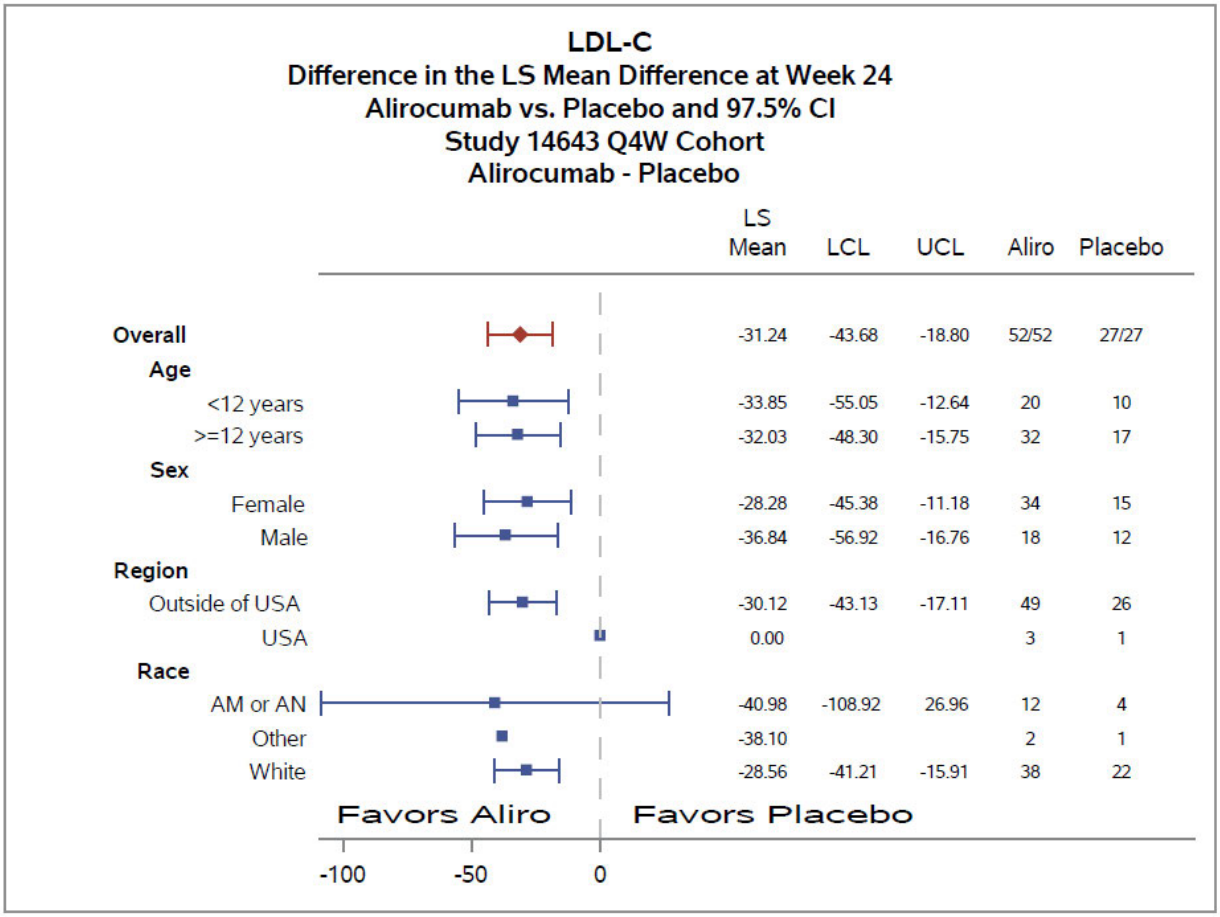
(Male, Female), region (Outside of USA, USA) and race (American Indian or Alaska Native, White, Other). Note the USA subgroup and the "Other" category in race was too small to analyze. The subgroup analyses were performed using the ITT population. The forest plot combining all results are presented in Figure 3 and Figure 4 for each cohort for the primary endpoint. Overall, the treatment effects within the subgroups favored alirocumab. This reviewer's subgroup analyses included all the covariates in the primary analysis using the washout imputation.

Figure 3. Subgroup Analysis: LDL-C at Week 24, Q2W Cohort



Abbreviations: Aliro: alirocumab; LCL: lower confidence interval; LS: least means; UCL: upper confidence interval
Race subgroups not listed: Asian=2, Multiple=5, Black or African American=1, Native Hawaiian or Other Pacific Islander=1, and White=65
Source: Statistical Reviewer's Analysis, adsl.xpt and adlbus.xpt

Figure 4. Subgroup Analysis: LDL-C at Week 24, Q4W Cohort



Abbreviations: Aliro: alirocumab; AM or AN: America Indian or Alaska Native; LCL: lower confidence interval; LS: least means; UCL: upper confidence interval
"Other" subgroup consists of: Black or African American=2 and Not Reported=1;
Source: Statistical Reviewer's Analysis, adsl.xpt and adlbus.xpt

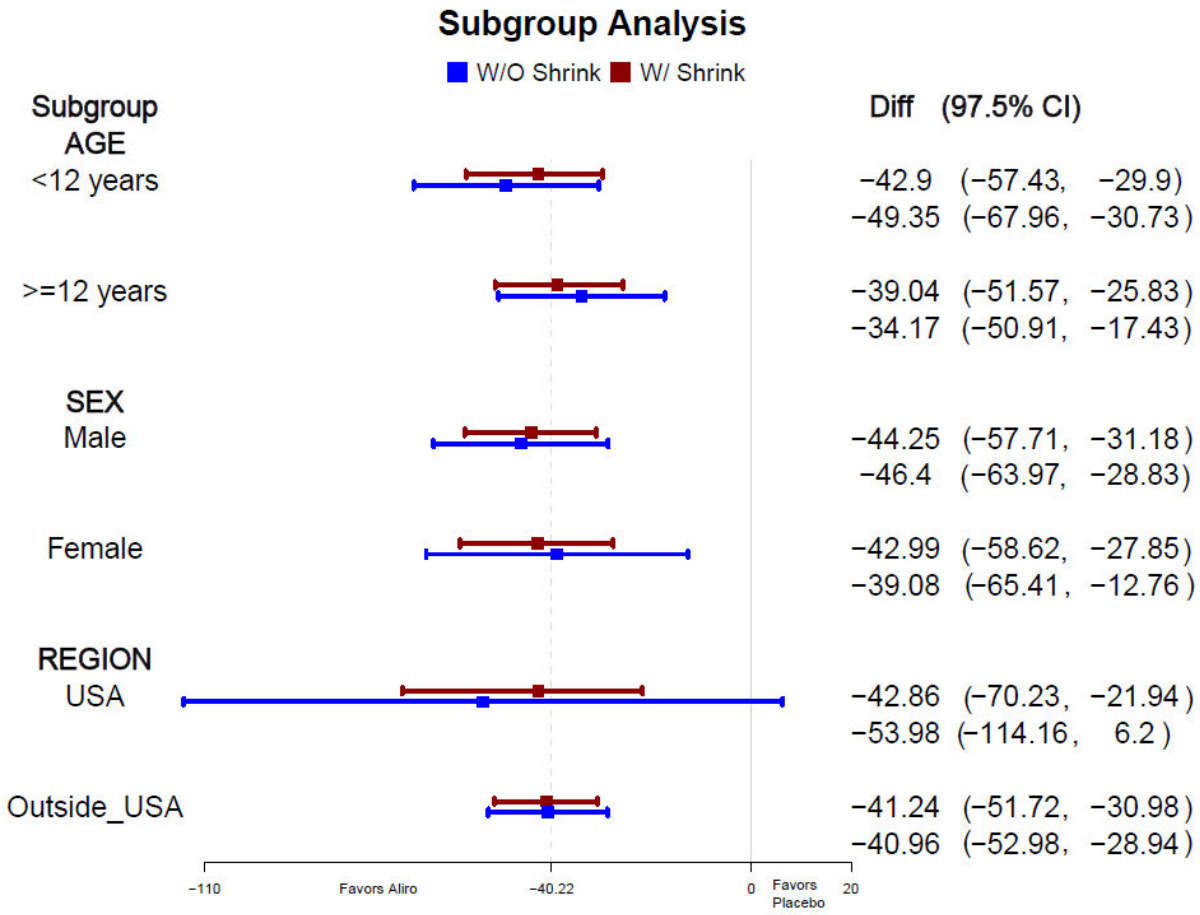
There were likely some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior to derive shrinkage estimates for all subgroups (age, sex, region, and race). The Bayesian hierarchical model assumptions for LDL-C at week 24 are:

For $i = 1, 2\ldots$ Yi represents the observed sample estimate of treatment effect in a subgroup level i, assume $Yi \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 100^2)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

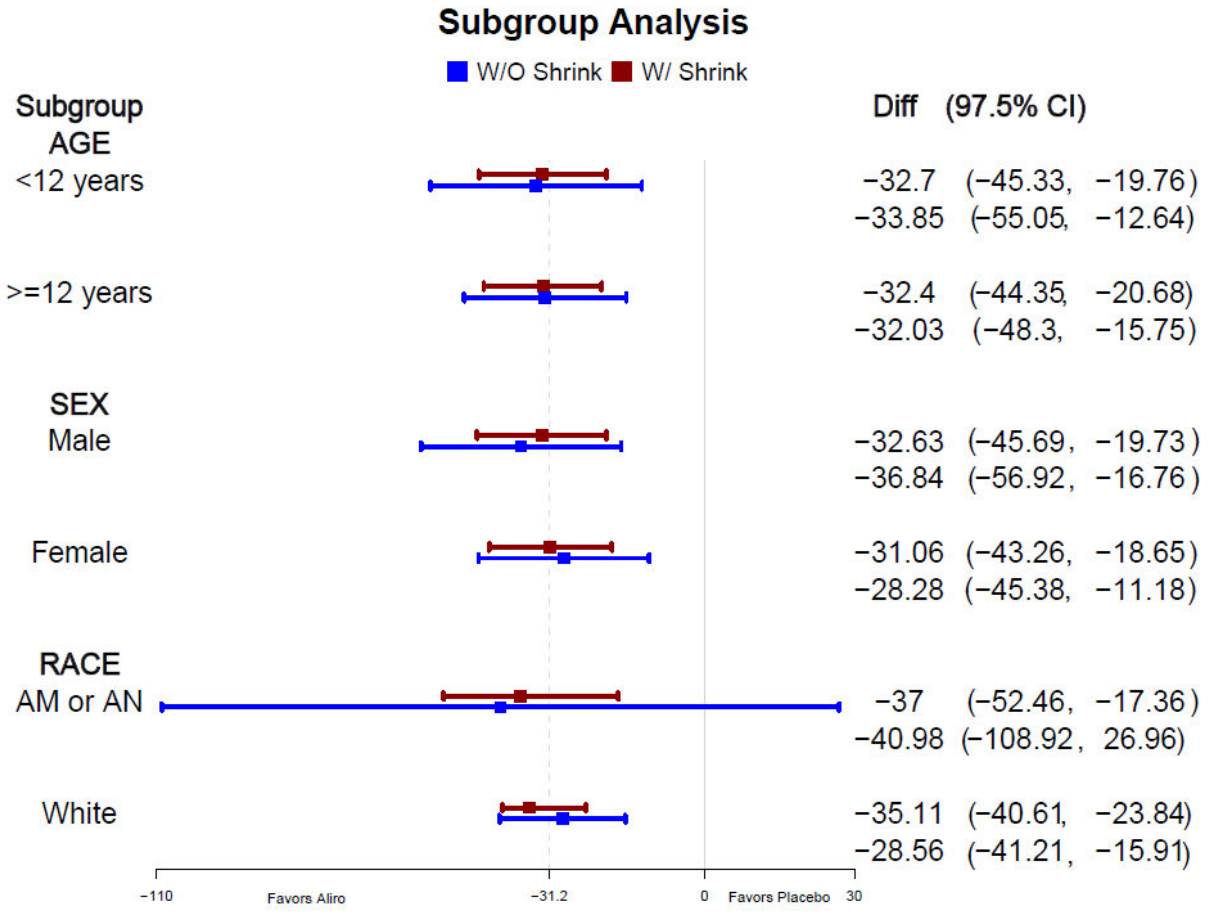
The variance should be selected relative to the residual standard deviation from the primary analysis model. In general, it should be four to ten times of the residual standard deviation. A flat prior with mean 0 and standard deviation of 100 was chosen. This standard deviation is 4 times the residual standard deviation and so this assumption would not be influential. Figure 5 compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of LDL-C at week 24 in the Q2W cohort. The overall treatment effect was -40.2 (97.5% CI: -53.2, -27.3). Figure 6 compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of LDL-C at week 24 in the Q4W cohort. The overall treatment effect was -31.2 (97.5% CI: -43.7, -18.8). Subgroup analysis using Bayesian shrinkage estimate exhibits narrower credible interval, and the shrinkage subgroup estimate is closer to the overall mean on both cohorts.

Figure 5. Subgroup Shrinkage Analysis: LDL-C at Week 24 – Q2W Cohort



Abbreviations: Aliro: alirocumab; W/O: without; W: with
97.5% CI refers to confidence intervals for the difference without shrinkage and credible intervals for difference with shrinkage
Race subgroups not listed: Asian=2; Multiple=5; Black or African American=0; Native Hawaiian or Other Pacific Islander=1; White=62
Source: Statistical Reviewer's Analysis, adsl.xpt and adlbus.xpt

Figure 6. Subgroup Shrinkage Analysis: LDL-C at Week 24 – Q4W Cohort



Abbreviations: Aliro: alirocumab; AM or AN: America Indian or Alaska Native; W/O: without; W: with
97.5% CI refers to confidence intervals for the difference without shrinkage and credible intervals for difference with shrinkage
"Other" subgroup not listed consists of: Black or African American=2 and Not Reported=1; USA subgroup only has 4 subjects, not shown in figure
Source: Statistical Reviewer's Analysis, adsl.xpt and adlbus.xpt

5 SUMMARY AND CONCLUSION

5.1 Statistical Issues

There were no major statistical issues identified for the applicant's pre-specified analyses. The applicant did not initially submit subgroup analysis for the primary endpoint for race and ethnicity. An information request (IR) was sent to request that analysis. The two treatment dosing cohorts, Q2W and Q4W, should not be compared statistically due to subjects being randomized to the two cohorts at different times.

Missing data was low in the Q2W cohort, 5% and moderate in the Q4W cohort, 13%. Sensitivity analyses using different methods for handling missing data produced similar results as the primary analysis.

5.2 Conclusions and Recommendations

Overall, the study has demonstrated efficacy of alirocumab in the proposed indication. Alirocumab was associated with a greater decrease in LDL-C values compared to placebo in both dosing cohort regimens. This NDA is approvable from statistical point of view.

Labeling

The applicant only presented the results for the Q4W cohort. We are requesting that they present the Q2W cohort as well in the label.

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/

KIYA HAMILTON
02/09/2024 11:14:16 AM

FENG LI
02/09/2024 11:16:07 AM