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 #:	125522
Supplement #:	29
Drug Name:	Repatha injection
Indications:	Treatment of pediatric patients aged 10 years and older with HeFH to reduce LDL-C
Applicant:	Amgen Inc.
Dates:	Stamp date: 11/24/2020 Primary review Due date: 07/30/2021 PDUFA date: 09/24/2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Satyajit Ghosh, Ph.D.
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Keywords: LDL-C reduction, pediatrics.

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1 EXECUTIVE SUMMARY

Amgen is seeking a new indication for Repatha (evolocumab) - as an add-on to diet and lipid-lowering therapy, in pediatric subjects 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH) to reduce Low density Lipoprotein-cholesterol (LDL-C). In this submission, the applicant submitted one phase 3 study, Study 20120123, to support this new indication. Overall, the study supports the proposed indication for LDL-C reduction in pediatric patients aged 10 years and older with HeFH.

Study 20120123 demonstrated superiority of evolocumab 420 mg over placebo for the primary endpoint. The difference (evolocumab - placebo) for the primary endpoint, percentage change in LDL-C from baseline to week 24, was -38.30, with 95% confidence interval (-45.54, -31.06). No major statistical issues were identified in this submission.

There was no severe treatment emergent adverse event in this study. Overall, the study provided evidence that evolocumab is efficacious for the proposed indication and the benefit-risk profile supports approval.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Evolocumab is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor. The safety and efficacy of evolocumab 420 mg subcutaneous (s.c.) once monthly (QM) in adults have been extensively studied in phase 2 and phase 3 clinical trials. It is approved

i. to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with cardiovascular (CV) disease,
ii. as an adjunct to diet for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C and
iii. as an adjunct to diet in patients with homozygous familial hypercholesterolemia **(**HoFH) who require additional lowering of LDL-C.

On November 24, 2020, Amgen submitted a supplementary BLA for approval of evolocumab injection for lowering of LDL-C in pediatric subjects 10 to 17 years of age with HeFH.

2.1.2 History of Drug Development

There were some interactions between Amgen and the Agency regarding study 20120123 under IND 105188. In addition to the Study 2012 0123, the applicant has also submitted an interim analysis from their 18-months open label extension, Study 20120124, to address the following Post Marketing Requirement (PMR),

“2946-1: Conduct an efficacy and safety study evaluating Repatha (evolocumab) in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. The

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study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study (Part A) followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid modifying therapy with LDL-C ≥ 130 mg/dL (Part B)."

The applicant is required to submit the final report for Study 20120124. This review will primarily focus on the results from Study 20120123 and provide a brief overview of Study 20120124.

2.2 Data Sources

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 file://cdsesub1/evsprod/BLA125522/0297/. 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 20120123 was a phase 3, randomized, double-blind, parallel-group, placebo-controlled, multinational study in pediatric subjects aged 10 years to less than 18 years with HeHF. Subjects were randomized in 2:1 to receive either evolocumab 420 mg or placebo once monthly s.c. injection.

Overall, 158 subjects (105 in evolocumab, 53 in placebo) were enrolled and randomized. Randomization was stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years). Details of the stratification is shown in Table 1.

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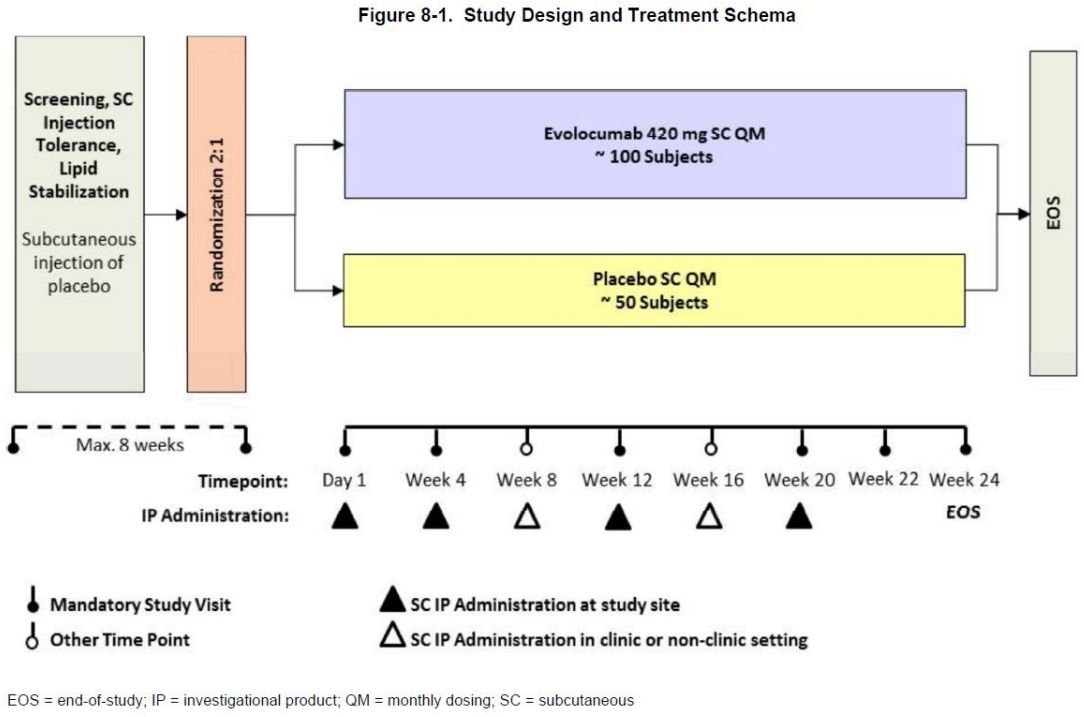
Table 1: Subject Stratification

Stratification Factor Category	Placebo QM (N=53)	Evolocumab 420mg QM (N=104)	Total (N=157)
Age			
< 14 years	25 (47.2%)	48 (46.2%)	73 (46.5%)
≥ 14 years	28 (52.8%)	56 (53.8%)	84 (53.5%)
Screening LDL-C level			
< 160 mg/dL	16 (30.2%)	33 (31.7%)	49 (31.2%)
≥ 160 mg/dL	37 (69.8%)	71 (68.3%)	108 (68.8%)

N = Number of subjects randomized and dosed in full analysis set;
QM = monthly (subcutaneous); LDL-C = Low-density lipoprotein cholesterol
Source: Clinical Trial Report Trial ID: 20120123 Table 9-2, page 35

Figure 1: Study Design for Study 20120123



Source: Clinical Trial Report Trial ID: 20120123 Figure 9-1, page 34

An interactive voice response system and/or interactive web response system (IVRS/IWRS) allocated subjects to the investigational products. Subjects visited the study site for assessments at weeks 4, 12, 20, 22, and 24 (end-of-study [EOS]). Investigational product administration at

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week 8 and week 16 could be at the study site (optional visit) or at a non-clinic location (e.g. in the home). The study design and treatment schema are provided in Figure 1. This study was conducted at 47 centers in 23 countries in the regions of Asia Pacific (3.8%), Europe (65.8%), Latin America (16.5%), and North America (13.9%).

The primary objective was to evaluate the effect of 24 weeks of s.c. evolocumab compared with placebo, when added to standard of care (statins are currently the standard of care for primary hyperlipidemia), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with HeFH. The secondary objective was to assess the effects of s.c. evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH.

The applicant defined the primary endpoint to be the percentage change from baseline to week 24 in LDL-C. The secondary endpoints are
1) Mean percent change from baseline to weeks 22 and 24 in LDL-C
2) Change from baseline to week 24 in LDL-C
3) Percent change from baseline to week 24 in the
   A) non-HDL-C
   B) ApoB
   C) total cholesterol/HDL-C ratio
   D) ApoB/ApoA1 ratio.

In addition to the above, the following tertiary endpoints were analyzed.

1) Percent change from baseline to week 24 in the following:
   − total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides and Lp(a).
2) Mean percent change from baseline to weeks 22 and 24 in the following:
   − non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides and Lp(a)

3.2.2 Statistical Methodologies

All analyses were performed using the full analysis set (FAS) which was defined as all randomized subjects who had received at least one dose of the investigational product (IP). The applicant defined two observation periods, in-trial and on-treatment. The superiority of evolocumab to placebo was assessed for all efficacy endpoints. The estimand of primary interest was the difference in mean percent change from baseline in reflexive LDL-C at week 24 regardless of treatment adherence for subjects in the FAS. A repeated measures linear effects model was used to compare the efficacy of evolocumab with placebo. The repeated measures model included terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. To account for the repeated LDL-C measurements within a subject across the visits, the repeated measures linear effects model used an unstructured covariance. Missing values were not imputed when the repeated measures linear effects model was used.

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The statistical model and testing of the secondary efficacy endpoints were similar to the primary analysis of the primary endpoint.

In order to preserve the familywise error rate at 0.05, multiplicity adjustment for the multiple endpoints (primary efficacy endpoint: percent change from baseline to week 24 in LDL-C and secondary efficacy endpoints: mean percent change from baseline to weeks 22 and 24 in LDL-C, change from baseline to week 24 in LDL-C and percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio) was be performed using sequential gatekeeping and Hochberg procedures (Hochberg, 1988) as follows:

1) If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, statistical testing of the "mean percent change from baseline to weeks 22 and 24 in LDL-C and change from baseline to week 24 in LDL-C" will proceed using the sequential procedure with a significance level of 0.05 (i.e., "change from baseline to week 24 in LDL-C" will be tested only if "mean percent change from baseline to weeks 22 and 24 in LDL-C" is statistically significant at 0.05 significance level).
2) If the treatment effect from change from baseline to week 24 in LDL-C is significant at a significance level of 0.05, statistical testing of the "percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio**"** will follow the Hochberg procedure at a significance level of 0.05.

In one sensitivity analysis of the primary endpoint, the completer analysis set (CAS) was used. The CAS included subjects in the FAS who adhered to the scheduled investigational product (IP) and have observed values for the primary endpoint. The applicant mentioned that to evaluate the robustness of the analysis results, sensitivity analyses will be performed with 1) the primary analysis repeated using the CAS and 2) non-parametric analysis (Quade test) using CAS. The applicant also mentioned that if there are at least 25 subjects who discontinue IP but have non-missing week 24 endpoint data, the primary analysis model will be repeated using FAS with missing values imputed for subjects who discontinued IP. Missing values will be imputed using non-missing data from subjects who discontinued IP within the same treatment group.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The summary of the subject disposition in study 20120123 is given below in Table 2. There were 105 subjects randomized to evolocumab and 53 subjects to placebo. One subject in the evolocumab group did not receive any investigational product. Overall, 153 (96.8%) subjects completed investigational product in the study. Four subjects (all in the evolocumab group) discontinued investigational product: 2 at the subject's request, 1 subject due to an adverse event, and 1 subject due to "other". Overall, 157 (99.4%) subjects completed the study with 1 subject in the evolocumab group discontinuing the study by withdrawing consent.

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Table 2: Subject Disposition

	Placebo QM (N=53)	Evolocumab 420mg QM (N=105)	Total (N=158)
Investigational product			
Subjects who never received IP	0 (0.0)	1 (1.0)	1 (0.6)
Subjects who received IP	53 (100.0)	104 (99.0)	157 (99.4)
Subjects who completed IP	53 (100.0)	100 (95.2)	153 (96.8)
Subjects who discontinued IP	0 (0.0)	4 (3.8)	4 (2.5)
Adverse event	0 (0.0)	1 (1.0)	1 (0.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subject request	0 (0.0)	2 (1.9)	2 (1.3)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.0)	1 (0.6)
Study completion			
Subjects who completed study	53 (100.0)	104 (99.0)	157 (99.4)
Subjects who discontinued study	0 (0.0)	1 (1.0)	1 (0.6)
Withdrawal of consent from study	0 (0.0)	1 (1.0)	1 (0.6)

N = Number of subjects randomized; QM = monthly (subcutaneous); IP= Investigational Product;
Percentages are shown within parentheses.
Source: Clinical Trial Report Trial ID: 20120123 Table 14-1.1.1, page 96

Baseline demographics for the FAS population are shown in Table 3. Overall, 56.1% of subjects were female, the majority (84.7%) were white, and 8.3% were of Hispanic/Latino ethnicity. The mean (SD) age at time of enrollment was 13.7 (2.4) years with the range of 10 to 17 years of age. Thirty-nine (24.7%) subjects were children 10 to 11 years of age and 119 (75.3%) subjects were adolescents between 12 and 17 years of age.

Table 3: Demographics and Baseline Characteristics – FAS

	Placebo QM (N=53)	Evolocumab 420mg QM (N=104)	Total (N=157)
Sex - n (%)			
Male	26 (49.1)	43 (41.3)	69 (43.9)
Female	27 (50.9)	61 (58.7)	88 (56.1)
Ethnicity - n (%)			
Hispanic/Latino	7 (13.2)	6 (5.8)	13 (8.3)

Not Hispanic/Latino	46 (86.8)	98 (94.2)	144 (91.7)
Race - n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	2 (1.9)	2 (1.3)
Black (or African American)	0 (0.0)	2 (1.9)	2 (1.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	44 (83.0)	89 (85.6)	133 (84.7)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (17.0)	11 (10.6)	20 (12.7)
Region - n (%)			
North America	10 (18.9)	12 (11.5)	22 (14.0)
Europe	35 (66.0)	68 (65.4)	103 (65.6)
Latin America	8 (15.1)	18 (17.3)	26 (16.6)
Asia Pacific	0 (0.0)	6 (5.8)	6 (3.8)
Age group - n (%)			
< 14 years	25 (47.2)	48 (46.2)	73 (46.5)
≥ 14 years	28 (52.8)	56 (53.8)	84 (53.5)

N = number of subjects randomized and dosed in the full analysis set;
QM = monthly (subcutaneous)

3.2.4 Results and Conclusions

There were overall 17 (10.8%) subjects in which 9 (16%) from the placebo group and 8 (7.6%) from the evolocumab had missing primary endpoint data at week 24. In Table 4, missing LDL-C values over study visits are listed.

Table 4: Missing LDL-C values over study visit

Study Visit	Placebo N	Treatment N	Missing Placebo	Missing Treatment
Baseline	53	104		
Week 4	53	104	0(0%)	0(0%)
Week 12	53	101	0(0%)	3(3%)
Week 20	50	100	3(6%)	4(3.8%)
Week 22	49	97	4(7%)	7(7.5%)
Week 24	44	96	9(16%)	8(7.6%)

N = number of subjects randomized and dosed in the full analysis set.

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The primary analysis results for the primary endpoint, mean percentage change in LDL-C from baseline to week 24 are given in Table 5. These results do not include imputed data for missing values. There was a greater decrease in LDL-C in the treatment arm compared to placebo. The evolocumab group achieved a statistically significant difference in percentage change in LDL-C from baseline compared to placebo. The treatment difference was -38.30.

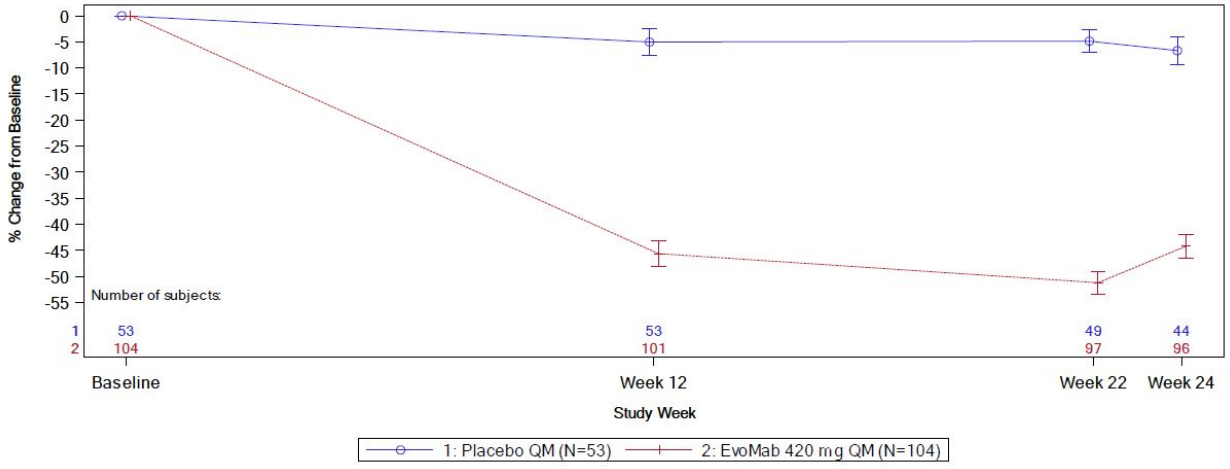
Table 5: Analysis of Primary Endpoint: Percent Change in LDL-C from Baseline to Week 24

	Placebo	Evolocumab 420mg QM
FAS	N =53	N =104
Change from baseline LS Means at week 24 (SE)	-6.23 (3.08)	-44.53 (2.17)
Treatment difference Evolocumab - Placebo	-38.30 (3.66)	
95% CI	(-45.54, -31.06)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error.
*nominal P-value. [Source: Reviewer Table]

In Figure 2, the percentage change from baseline in LDL-C values is plotted by scheduled visit and treatment groups. One can observe that the treatment effect on LDL-C reduction was slightly larger at week 22 (middle of the dosing interval) than at week 12 or week 24 (end of the dosing interval).

Figure 2: Mean Percent Change From Baseline in LDL-C by Scheduled Visit and Treatment Group (FAS)



N = number of subjects randomized and dosed in the full analysis set.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values. [Source: Clinical Trial Report Trial ID: 20120123 Figure 10-1, page 66]

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Sensitivity analyses of the primary endpoint were performed using the CAS. The results from the primary analysis repeated using the CAS are given in Table 6.

Table 6: Completer Analysis of Primary Endpoint: Percent Change in LDL-C from Baseline to Week 24

	Placebo	**Evolocumab** 420mg QM
FAS	N =44	N =92
Change from baseline LS Means at week 24 (SE)	-6.90 (3.27)	-44.83 (2.27)
Treatment difference Evolocumab - Placebo	-37.93 (3.87)	
95% CI	(-45.59, -30.28)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error.
*nominal P-value. [Source: Reviewer Table].

The reviewer also performed a separate analysis by imputing the missing primary endpoint values using baseline observation carried forward (BOCF) approach which yielded results (in Table 7) that were consistent with the primary efficacy analysis (Table 5).

Table 7: Additional Analysis (using BOCF) of Primary Endpoint: Percent Change in LDL-C from Baseline to Week 24

	Placebo	**Evolocumab 420mg QM**
FAS	N =53	N =104
Change from baseline LS Means at week 24 (SE)	-5.19 (2.25)	-35.06 (2.92)
Treatment difference Evolocumab - Placebo	-29.87 (3.96)	
95% CI	(-37.63, -22.11)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error.
Missing Week 24 LDL-C values were imputed using the baseline values.
*nominal P-value. [Source: Reviewer Table].

The results for the secondary endpoint, mean percentage change in LDL-C from baseline to weeks 22 and 24 are shown in Table 8. These results do not include imputed data for missing values. There was a greater decrease in LDL-C in the treatment arm compared to placebo. The mean percentage change in LDL-C from baseline to week 22 and week 24 was in favor of evolocumab compared to placebo. The treatment difference was -42.08.

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Table 8: Analysis of Secondary Endpoint for Mean Percent Change from Baseline in LDL-C to Weeks 22 and 24

	Placebo	Evolocumab 420mg QM
FAS	N =53	N = 104
Percentage change from baseline LS Means at week 22 and 24 (SE)	-5.87 (2.67)	-47.96 (1.92)
Treatment difference Evolocumab - Placebo	-42.08 (3.18)	
95% CI	(-48.34, -35.82)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error. *nominal P-value. [Source: Reviewer Table]

The change in LDL-C (in mg/dL) from baseline to week 24 are shown in Table 9. These results do not include imputed data for missing values. There was a greater decrease in LDL-C in the treatment arm compared to placebo. The evolocumab group achieved a statistically significant difference in change in LDL-C from baseline compared to placebo. The difference was -68.60 mg/dL.

Table 9: Analysis of Secondary Endpoint for Change from Baseline to Week 24 in LDL-C

	Placebo	Evolocumab 420mg QM
FAS	N = 53	N = 104
Change from baseline LS Means at week 24 (SE)	-9.0 (6.2)	-77.6 (4.4)
Treatment difference Evolocumab - Placebo	-68.6 (7.3)	
95% CI	(-83.3, -54.2)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error. *nominal P-value. [Source: Reviewer Table]

Table 10 shows the results for percentage change from baseline to week 24 in non-HDL-C. The evolocumab group achieved a statistically significant difference in change in non-HDL-C from baseline compared to placebo. The treatment difference was -35.04.

Table 10: Analysis of Secondary Endpoint for Percent Change from Baseline to Week 24 in non-HDL-C

	Placebo	Evolocumab 420mg QM
FAS	N = 53	N = 104
Percentage Change from baseline LS Means at week 24 (SE)	-6.14 (2.87)	-41.19 (2.01)
Treatment difference Evolocumab - Placebo	-35.04(3.41)	

95% CI	(-41.79, -28.30)
P-value*	<0.0001

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error. *nominal P-value. [Source: Reviewer Table]

The results for percentage change in ApoB from baseline to week 24 are shown in Table 11. The evolocumab group achieved a statistically significant difference in change in ApoB from baseline compare to placebo. The treatment difference was -32.45.

Table 11: Analysis of Secondary Endpoint for Percent Change from Baseline to Week 24 in ApoB

	Placebo	Evolocumab 420mg QM
FAS	N = 53	N = 104
Percentage Change from baseline LS Means at week 24 (SE)	-2.37 (2.70)	--34.57 (3.21)
Treatment difference Evolocumab - Placebo	-32.45 (3.22)	
95% CI	(-38.82, -26.13)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error *nominal P-value. [Source: Reviewer Table]

The percentage change in total cholesterol/HDL-C ratio from baseline to week 24 are shown in Table 12. There was a greater decrease in LDL-C in the treatment arm compared to placebo. The evolocumab group achieved a statistically significant difference in change in LDL-C from baseline compared to placebo. The difference was -30.33.

Table 12: Analysis of Secondary Endpoint for Percent Change from Baseline to Week 24 in Total Cholesterol/HDL-C ratio

	Placebo	Evolocumab 420mg QM
FAS	N = 53	N = 104
Change from baseline LS Means at week 24 (SE)	-4.66 (2.60)	-34.96 (1.82)
Treatment difference Evolocumab - Placebo	-30.33 (3.09)	
95% CI	(-36.40, -24.21.2)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error. *nominal P-value. [Source: Reviewer Table]

The last supportive secondary endpoint discussed in this review was, percentage change from baseline to week 24 in ApoB/ApoA1 ratio. A greater decrease was seen in evolocumab group at week 24 compared to placebo. The difference in percentage change in the ratio was -36.38.

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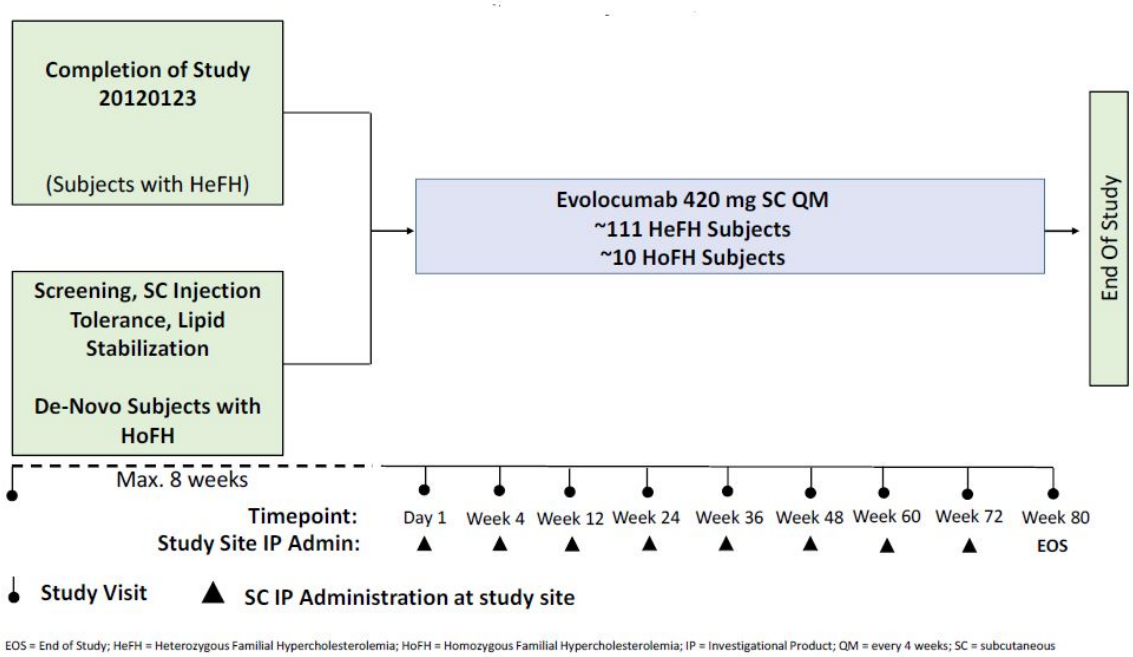
Table 13: Analysis of Secondary Endpoint for Percent Change from Baseline to Week 24 in ApoB/ApoA1 ratio

	Placebo	Evolocumab 420mg QM
FAS	N = 53	N = 104
Change from baseline LS Means at week 24 (SE)	-0.63 (2.80)	-37.02 (1.95)
Treatment difference Evolocumab - Placebo	-36.38 (3.34)	
95% CI	(-42.97, -29.80)	
P-value*	<0.0001	

N = number of subjects randomized and dosed in the full analysis set; CI =Confidence Interval; SE=Standard Error. *nominal P-value. [Source: Reviewer Table]

Interim Analysis of Open-label Treatment Period (OLTP, Study 20120124): This is an open-label, single-arm, multicenter study. Subjects were eligible for screening if they had completed Study 20120123 (and did not experience a treatment-related serious adverse event) or if they were 10 to 17 years of age at time of enrollment and had a diagnosis of homozygous familial hypercholesterolemia (HoFH). The end-of-study visit occurred at week 80. The first subject was enrolled on 10 September 2016. The data cutoff for this interim analysis was June 8, 2020 and the last subject visit on or prior to data cutoff was May 28, 2020. Overall, 162 subjects received at least 1 dose of evolocumab and were included in the FAS. One (0.6%) subject was excluded from the FAS as this subject did not receive any dose of evolocumab. A total of 150 HeFH subjects rolled over from the parent Study 20120123; 101 subjects received evolocumab in the parent study and 49 subjects received placebo in the parent study.

Figure 3: Study Design for Study 20120124



Source: Clinical Trial Report Trial ID: 20120124 Figure 8-1, page 27

As of data cutoff, 105 (70.0%) subjects have completed the study, 42 (28.0%) subjects are still on study, and 3 (2.0%) have discontinued the study by withdrawing consent. For efficacy analyses, the baseline value was defined as follows,

- For subjects that participated in parent study 20120123: the baseline was defined as the baseline of that parent study,
- For subjects not enrolling from the parent study: the baseline was defined as the baseline in this open label study.

The primary endpoint for this open label extension is treatment emergent adverse events at week 80. An overall summary of treatment-emergent adverse events is provided in Table 12. Overall, 100 (66.7%) HeFH subjects experienced at least 1 treatment-emergent adverse event. Subject incidence of treatment-emergent adverse events was similar between HeFH subjects receiving evolocumab (66.3%) or placebo (67.3%) in the parent study. The majority of treatment emergent adverse events were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 in severity. One (0.7%) HeFH subject experienced a CTCAE grade 4 serious event of anorexia nervosa. The event was considered not related to evolocumab. Overall, 7 (58.3%) HoFH subjects experienced at least 1 treatment-emergent adverse event. The majority of treatment-emergent adverse events were CTCAE grade 1 or 2 in severity. No HoFH subjects experienced a grade 4 treatment-emergent adverse event.

Table 14: Summary of Subject Incidence of Treatment-emergent Adverse Events Study 20120124

	HeFH			HoFH	Total
	Placebo in Parent Study (N=49)	**Evolocumab 420 mg QM In Parent Study (N = 101)**	**Overall (N=150)**	**Evolocumab 420 mg QM (N = 12)**	**Evolocumab 420 mg QM (N = 162)**
All treatment-emergent adverse	33 (67.3)	67 (66.3)	100 (66.7)	7 (58.3)	107 (66.0)
Grade ≥ 2	23 (46.9)	56 (55.4)	79 (52.7)	5 (41.7)	84 (51.9)
Grade ≥ 3	4 (8.2)	2 (2.0)	6 (4.0)	2 (16.7)	8 (4.9)
Grade ≥ 4	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Serious adverse events	2 (4.1)	2 (2.0)	4 (2.7)	2 (16.7)	6 (3.7)
Leading to discontinuation of IP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nonserious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Device-related treatment emergent adverse events	6 (12.2)	5 (5.0)	11 (7.3)	1 (8.3)	12 (7.4)
Grade ≥ 2	2 (4.1)	1 (1.0)	3 (2.0)	0 (0.0)	3 (1.9)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of subjects with HeFH enrolled and dosed from parent study 20120123 and number of subjects with HoFH enrolled and dosed in this study;
Interim analysis data cutoff date: June 8, 2020; Coded using MedDRA version 23.0

In addition, Table 15 shows descriptive statistical summaries for efficacy endpoints. Numerical reduction of each clinical parameter was observed for all endpoints.

Table 15: Summary of Secondary Efficacy Results for HeFH Subjects at Week 80 - Study 20120124 Full Analysis Set (Interim Analysis)

		Placebo (N=49) in Parent Study	Evolocumab 420 mg QM (N = 101) In Parent Study	Overall (N=150)
Calculated LDL-C % change from baseline to week 80	Mean	-38.90	-35.01	-36.23
	SE	4.58	3.04	2.53
Reflexive LDL-C %change from baseline to week 80	Mean	-38.90	-35.08	-36.27
	SE	4.58	3.03	2.52
Calculated LDL-C – change from baseline (mg/dL) to week 80	Mean	-74.0	-63.7	-66.9
	SE	9.2	5.4	4.7
Reflexive LDL-C – change from baseline (mg/dL) to week 80	Mean	-74.0	-63.8	-66.9
	SE	9.2	5.4	4.7
Non-HDL-C - % change from baseline to	Mean	-35.05	-32.06	-33.00
	SE	4.22	2.87	2.36

ApoB - % change from baseline to week	Mean	-29.40	-24.35	-25.98
	SE	3.30	2.94	2.26
TC/HDL-C ratio - %change from baseline	Mean	-31.03	-27.91	-28.88
	SE	4.13	2.71	2.26
ApoB/ApoA1 ratio - % change from	Mean	-32.94	-29.40	-30.55
	SE	4.15	3.13	2.50

N= number of subjects with HeFH enrolled and dosed from parent Study 20120123; QM = monthly (subcutaneous); TC= total cholesterol.
Interim analysis data cutoff date: June 8, 2020. [Source: Reviewer's Table]

The applicant mentioned that to evaluate the safety, tolerability and effect of 80 weeks of s.c. evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH, the primary analysis will be conducted when all the enrolled subjects in the study have either completed all the scheduled visits up to and including week 80 or have early terminated from the study.

3.3 Evaluation of Safety

This section summarizes the safety findings in Study 20120123. All safety analyses were conducted on the safety analysis set, which was defined to be same as full analyses set, that is, all randomized subjects that were treated with at least one dose of the study treatment. The percentage of subjects with any treatment-emergent adverse event (TEAE) was numerically similar in both the placebo (64.2%) and the evolocumab group (61.5%). The majority of treatment-emergent adverse events were CTCAE (Common Terminology Criteria for Adverse Events) grade 1 or grade 2 in severity. Four (3.8%) evolocumab subjects and no placebo subjects experienced a treatment-emergent adverse event that was CTCAE grade 3. No subject either experienced a grade 4 adverse event or died during the study. One (1.0%) subject in the evolocumab group experienced a serious adverse event of cholelithiasis; the event was not considered related to investigational product by the investigator. One (1.0%) subject in the evolocumab group experienced a nonserious adverse event of arthropathy leading to discontinuation of investigational product that was considered related to investigational product by the investigator.

Table 16: Summary of Subject Incidence of Treatment-emergent Adverse Events (TEAE) Study 20120123

	Placebo	**Evolocumab 420mg**
FAS	N = 53	N = 104
All treatment-emergent adverse events	34 (64.2)	64 (61.5)

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Grade ≥ 2	22 (41.5)	46 (44.2)
Grade ≥ 3	0 (0.0)	4 (3.8)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	1 (1.0)
Leading to discontinuation of IP	0 (0.0)	1 (1.0)
Serious	0 (0.0)	0 (0.0)
Non-serious	0 (0.0)	1 (1.0)
Fatal adverse events	0 (0.0)	0 (0.0)

Grading categories were determined using modified CTCAE version 4.03
IP = Investigational Product. [Source: excerpted from page 79 of 20120123 Study Report]

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were performed on the primary endpoint, by five major subgroup - Screening LDL-C (< 160 mg/dL [4.1 mmol/L], ≥ 160 mg/dL), Age (< 14 years, ≥14 years), Gender (Male/Female), Race (black, white, and other), Region (North America, Europe, other).
The subgroup analyses were performed using the FAS population. Overall, the treatment effects of the subgroups were consistent with that of the overall population. Note that the treatment effect for the Race 'Other' subgroup is not significant.

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 estimates 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).

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

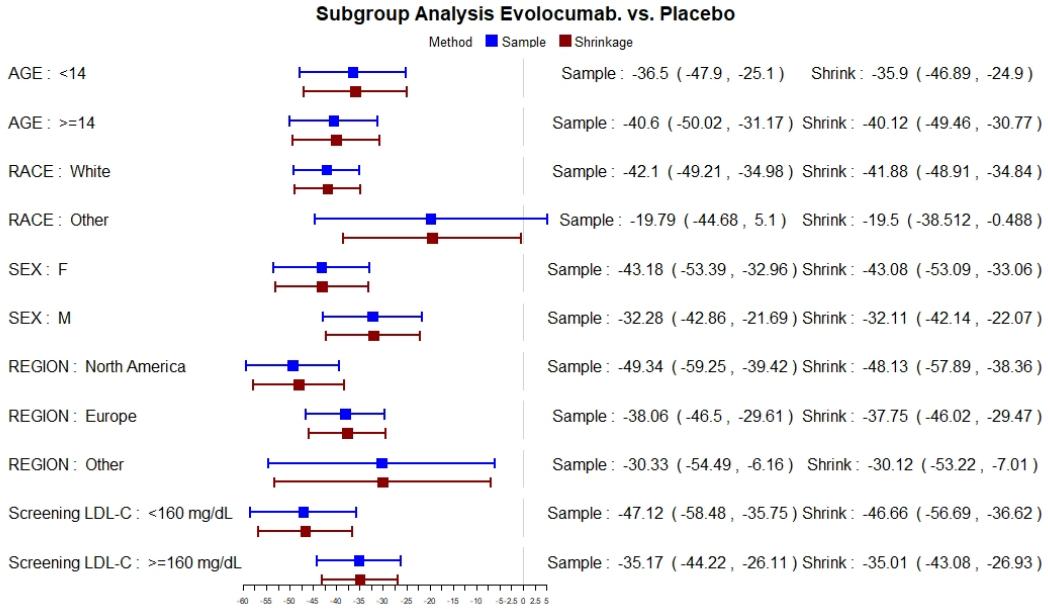
- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 100^2)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001).

All subgroups reported the upper limit of the 95% CI less than zero, in favor of evolocumab,

Reference ID: 4854488

except for 'Other' Race. However, with a shrinkage estimate, the upper limit of the 95% credible interval was also less than zero for 'Other' race, in favor of evolocumab. Note that in some subgroups, the number of patients was too small to obtain reliable estimates. For example, 'Glucose tolerance status: Metabolic Syndrome' only has 3 in the placebo arm and 1 subject in the evolocumab arm and we did not perform any shrinkage analyses on that subgroup.

Figure 4: Subgroup results by Age, Race, Sex, Region and Screening LDL-C



Source: Statistical Reviewer's Analysis.

For all subgroups, the Bayesian shrinkage estimate of mean differences were less than zero, indicating greater numerical reduction in the evolocumab group than in the placebo group.

5 SUMMARY AND CONCLUSION

5.1 Statistical Issues

There were no major statistical issues identified during the course of this review. There were 17 (10.8%) subjects who had missing primary endpoint data at week 24. The sensitivity analyses yielded results that were consistent with the primary efficacy analysis.

5.2 Collective Evidence

The primary analysis showed statistically significant treatment effect in reduction of LDL-C at Week 24. Secondary endpoints are consistently in favor of evolocumab.

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Results from subgroup efficacy analyses were consistent with findings from the overall population.

5.3 Conclusions and Recommendations

The collective evidence from the submitted data demonstrated efficacy of evolocumab in the study population. There was no major concern in the safety profile. We recommend approval for the proposed indication based on findings from the submitted results.

5.4 Labeling and Recommendations

Labeling review is still ongoing while this review is finalized. As (b) (4) is not a pre-specified endpoint, the following sentence is proposed to be removed from the label in section 14 under Study 6 (HAUSER-RCT, NCT02392559), (b) (4)

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