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

NDA/BLA #:	NDA 22363
Supplement #:	S-015
Drug Name:	Pitavastatin calcium (LIVALO)
Indication(s):	(b) (4) in pediatric patients 8 to 16 years of age
Applicant:	Kowa Research Europe
Date(s):	Stamp: 11/16/18
Review Priority:	Priority Review Due Date: 4/1/19
Biometrics Division:	II
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Keywords: Missing data, multiple imputation, shrinkage analyses

Table of Contents

List of Tables

1 EXECUTIVE SUMMARY

On November 16, 2018, Kowa Research submitted a supplemental NDA 022363 S-015 to fulfill the clinical study requirements of a Written Request issued by FDA on November 2, 2016 for LIVALO to qualify for Pediatric Exclusivity in the United States. To fulfill the clinical study requirements of the Written Request, the sponsor relied on two previous clinical studies conducted in the European Union. The studies will be relied upon to update the product label for usage in pediatric patients from ages 8 to 16.

1.1 Brief Overview of Clinical Studies

The submission included the results from the analysis generated from a 12-week, randomized, multi-center, double-blind, placebo-controlled trial utilizing a subset of the original study population. The primary endpoint was percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to week 12.

1.2 Statistical Issues

- The amount of missing data in the sponsors analysis was large. The reason for this was due to most of the data being collected outside the prespecified window period of +/- 3 days. However, since this window is rather small and because most of the data was collected after the upper window date, the reviewer included data within +/- 9 days in the analysis. Table 1 below summarizes the number of patients who had missing week 12 efficacy data in each treatment arm from the sponsor's and reviewer's analysis. We see that the sponsor's window period of +/- 3 days results in 26.8% missing data. However, by expanding the window period to +/-9 days, missing data are only 2.4%.

Table 1: Missing Data at Week 12

		Sponsor		Reviewer's	
	Randomized and took at least one dose	**Missing Week 12 data**	**% Missing Week 12 data**	**Missing Week 12 data[a]**	**% Missing Week 12 data[a]**
Pitavastatin 1 mg	20	8	40	1	5
Pitavastatin 2 mg	24	9	37.5	1	4.2
Pitavastatin 4 mg	19	3	15.8	0	0
Placebo	19	2	10.5	0	0
Total	**82**	**22**	**26.8**	**2**	**2.4**

a Includes data within +/- 9 days of Day 84
[Source: Statistical reviewer's analysis]

The inclusion of these data by expanding the window enlarged the treatment effects for each dose compared to the sponsor's analysis. The reason for this is because most of the missing data were on the pitavastatin arms, which the sponsor then treated as if they came from the placebo arm. Further, by including the data, the standard errors were reduced and thus the confidence intervals (CI) are narrower.

- The protocol prespecified analysis was a multiple imputation with jump-to-placebo approach. Patients on the treatment arms were treated as if they were on the placebo arm and that their intermediate measurements were on placebo.

1.3 Collective Evidence

The estimated LS difference and 95% CI in percent change in LDL-C from baseline to week 12 between each pitavastatin arm and placebo are:

- 4 mg versus placebo: -37.1 (-44.4, -29.9)
- 2 mg versus placebo: -28.8 (-35.8, -21.8)
- 1 mg versus placebo: -20.4 (-27.7, -13.0)

Therefore, the results demonstrate that each dose of pitavastatin are superior to placebo in reducing percent change in LDL-C.

1.4 Conclusions and recommendation

The results of the analysis support the hypothesis that patients on the pitavastatin arms experience a greater reduction in percent change in LDL-C compared to patients on placebo. The supplemental NDA 22363 S-015 is approvable from the statistical point of view.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Pitavastatin calcium is a synthetic HMG-CoA reductase inhibitor currently approved for marketing in the United States. It is indicated as an adjunctive therapy to diet in reducing elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein-B (Apo-B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia and mixed dyslipidemia. The proposed label has been updated to extend the indication to pediatrics from 8 to 16 years of age.

2.1.2 History of Drug Development

Livalo was approved in adults in August 2009. (b) (4) In July 2016, the sponsor resubmitted the proposed

pediatric study request to include two clinical studies: 1) a double-blind, randomized, placebo-controlled, parallel-group, 12-week study and 2) a 52-week open-label extension and safety study. In November 2016, FDA submitted a Written Request for these two clinical studies. Included in the Written Request was the need for the studies to take into account an adequate representation of children of ethnic and racial minorities or to provide a description of efforts to do so if they are unable.

2.1.3 Specific Studies Reviewed

One randomized study (NK-104-4.01EU), which only included a subset of the original population was reviewed. This report summarizes the statistical review of the sponsor's methods of the primary and relevant secondary endpoints as well as the results of the reviewer's analyses of these endpoints when addressing missing data.

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission can be accessed at the following link: \\CDSESUB1\evsprod\NDA022363\0145.

The following documents were used to support this review.

Document
Supplemental Clinical Study Report
Clinical Study Report (Original Study)
Statistical Analysis Plan (NK-104-4.01EU Subgroup Analysis)
Statistical Analysis Plan (Original Study)

All results presented in this review were based on data derived from the submitted datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were no issues concerning the submission of data sets and files.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study NK-104-4.01EU was a double-blind, randomized, placebo-controlled, parallel-group, 12-week study. This study evaluated the efficacy and safety of pitavastatin (1mg, 2mg and 4 mg) to placebo in pediatrics with HeFH.

From the original study design, requirements for the inclusion criteria were:

- Male or Female

- Age ≥ 6 and ≤ 16 years
- Fasting LDL-C levels of ≥ 160 mg/dL OR Fasting LDL-C levels of ≥ 130 mg/dL with at least one of the following risk factors:

    - Male
    - A family history of premature cardiovascular disease defined as a myocardial infarction before age 50 in a second-degree relative or before age 60 in a first-degree relative with at least 1 relative (parent, grandparent, or sibling) affected
    - Presence of low HDL-C (<45 mg/dL) or high TG (>150 mg/dL)
    - Presence of high lipoprotein(a) (>75 nmol/L)
    - Presence of type 2 diabetes mellitus diagnosed by treating physician according to current guidances;
    - Presence of hypertension defined as systolic and diastolic blood pressures (SBP and DBP, respectively) above the 95th percentile for age and size

However, to define the subset population, the following additional criteria were used:

- HeFH diagnosed by the Investigator
- Age ≥ 8 and ≤ 16 years
- Baseline LDL-C ≥ 190 mg/dL OR ≥ 160 mg/dL with any of the additional CV risk factors listed above from the original study

From the original study, a total of 106 patients were randomized in a 1:1:1:1 fashion to pitavastatin 1mg, 2mg, 4mg, or placebo. However, to meet the requirements of the Written Request issued by FDA to conduct a study in patients only with HeFH, 82 (77%) patients were included in the subset analysis. There were nine study centers spanning 6 countries. Landmark visits with respect to LDL-C and which were included in the primary efficacy analysis were baseline, week 4, 8, and 12. The primary endpoint was percent change in LDL-C from baseline to week 12. The secondary endpoints included (from baseline to week 12): HDL-C, Non HDL-C, Total Cholesterol, Triglycerides, and Apolipoprotein-B.

3.2.2 Statistical Methodologies

Protocol specified primary analyses

Sponsor's primary analysis set: All randomized subjects who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least one valid post-baseline lipid measurement.

Reviewer's comment: The sponsor's primary analysis set does not preserve the integrity of randomization as it excludes patients on the basis of events that occur after randomization, however, in this case each subject who received at least 1 dose of study drug also had a valid post-baseline lipid measurement.

Sponsor's primary analysis model: The primary analysis model was a multiple imputation with jump-to-placebo (using intermediate measurements) approach. The model included baseline LDL-C and age as continuous covariates.

Statistical reviewer's primary analyses

From the statistical analysis plan of the original study, the window for data capture of the primary week 12 endpoint was +/- 3 days from day 84. Table 2 below summarizes the distribution of patients whose last measurement (Analysis Relative Day) was captured outside the window. Any measurement captured between Day 81 and Day 87 (inclusive) was used in the primary analysis.

Table 2: **Distribution of patients captured outside prespecified window**

Analysis Relative Day	# of Patients
57	2
80	2
88	2
89	5
90	4
91	1
92	5
93	1
	22

[Source: Statistical reviewer's analysis]

We see that there was a total of 22 patients who were treated as missing in the sponsor's analysis. However, 20 patients had their LDL-C measurement captured within a 9-day span of Day 84. Of these 20 patients, measurements from 18 were captured after Day 84. Due to the relatively tight window and most of the measurements being captured after Day 84, the reviewer used the data from these 20 patients and only considered the 2 patients whose last measurement was captured at Day 57 as missing.

Table 3 below compares the amount of missing data between the sponsor and the reviewer at the week 12 endpoint in each treatment arm. We see that the sponsor's window period of +/- 3 days results in 26.8% missing data, however, by expanding the window period to +/-9 days, missing data are only 2.4%.

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Table 3: Missing Data at Week 12

		Sponsor		Reviewer's	
	Randomized and took at least one dose	**Missing Week 12 data**	**% Missing Week 12 data**	**Missing Week 12 data[a]**	**% Missing Week 12 data[a]**
Pitavastatin 1 mg	20	8	40	1	5
Pitavastatin 2 mg	24	9	37.5	1	4.2
Pitavastatin 4 mg	19	3	15.8	0	0
Placebo	19	2	10.5	0	0
Total	**82**	**22**	**26.8**	**2**	**2.4**

a Includes data within +/- 9 days of Day 84
[Source: Statistical reviewer's analysis]

To provide an unbiased comparison in all randomized patients regardless of adherence to treatment, patients should be followed after treatment discontinuation for the collection of efficacy and safety data. All collected data would then be used in the primary analysis. The preferred method of addressing missing data would be to model patients with missing data after retrieved drop-outs. However, there were no retrieved drop-outs in this study.

Since this was a placebo-controlled study, we can partition and "wash-out" the effect of therapy. The 2 patients with missing data were on the pitavastatin arms (one from 1mg and one from 2mg). Therefore, week 12 measurements from these 2 patients were imputed using a regression model based on completers from the placebo arm, where the known intermediate measurements (from the 2 patients) were not used. One hundred data sets were generated and an analysis of covariance (ANCOVA) with the treatment factor and protocol specified covariates were run on each data set. Point estimates and standard errors were computed and the results were combined to yield a multiple imputation point estimate and standard error.

We sent an information request (IR) to the sponsor asking them to confirm that Table 2 is correct, perform a multiple imputation analysis that includes the data from the 20 patients, and to model a "wash-out" for the 2 missing patients. For the "wash-out" imputation, we asked the sponsor to discard their intermediate measurements and impute their week 12 values as if they came from the placebo arm using only their baseline values (not using the covariate age for the imputation, however using age in the ANCOVA model). We also requested the sponsor to perform the same analysis for the secondary endpoints: HDL-C, Non HDL-C, Total Cholesterol, Triglycerides, and Apolipoprotein-B. The sponsor confirmed that the Table 2 is correct and obtained similar results as the statistical reviewer (see section 3.2.4).

Protocol specified control of type-I error

From the original study, a sequential testing procedure was applied to the primary endpoints to control the family-wise type 1 error rate as follows:

H_{01}: Superiority in reducing LDL-C at week 12 of Pitavastatin 1mg vs. Placebo

H_{11}: Superiority in reducing LDL-C at week 12 of Pitavastatin 2mg vs. Placebo

H_{21}: Superiority in reducing LDL-C at week 12 of Pitavastatin 4mg vs. Placebo
There was no formal testing for secondary endpoints

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Tables 4 and 5 below describe the analysis populations, patient disposition, demographics and patient characteristics at baseline, and the amount of missing data at week 12. We see from Table 4 that every patient who was randomized had a baseline LDL-C and at least 1 post-baseline measurement.

Table 4: Analysis population

	Pitavastatin 1 mg (N=20[a]) n (%)	Pitavastatin 2 mg (N=24[a]) n (%)	Pitavastatin 4 mg (N=19[a]) n (%)	Placebo (N=19[a]) n (%)	Total (n=82[a]) n (%)
Full Analysis Set (FAS)	20 (100)	24 (100)	19 (100)	19 (100)	82 (100)

a Number of patients who were randomized
[Source: Supplemental CSR Page 30 (2 November 2018) and statistical reviewer's analysis]

It is seen in Table 5 below, that 56.1% of patients were less than 12 years old. Females made up 56.1% of the population and 96.3% of patients were white.

Table 5: Demographics and patient characteristics at baseline – FAS

	Pitavastatin 1 mg (N=20)	Pitavastatin 2 mg (N=24)	Pitavastatin 4 mg (N=19)	Placebo (N=19)	Total (N=82)
Age (years)					
Mean (SD)	11.7 (2.1)	11.4 (2.7)	10.9 (2.2)	11.4 (2.7)	11.4 (2.4)
Age group [n(%)]					
≥ 8 to < 12	9 (45.0)	13 (54.1)	11 (57.9)	13 (68.4)	46 (56.1)
≥ 12 to ≤ 16	11 (55.0)	11 (45.8)	8 (42.1)	6 (31.6)	36 (43.9)
Sex [n(%)]					
Male	9 (45.0)	9 (37.5)	10 (52.6)	8 (42.1)	36 (43.9)
Female	11 (55.0)	15 (62.5)	9 (47.4)	11 (57.9)	46 (56.1)
Race [n(%)]					
White	19 (95.0)	23 (95.8)	19 (100)	18 (94.7)	79 (96.3)
Asian	1 (5.0)	0 (0)	0 (0)	1 (5.3)	2 (2.4)
Black or African American	0 (0)	1 (4.2)	0 (0)	0 (0)	1 (1.2)
Baseline LDL-C (mg/dL)					
Mean (SD)	222.7 (38.6)	226.9 (34.2)	241.6 (50.8)	250.4 (72.2)	234.7 (50.4)
Baseline LDL-C [n(%)]					
≥ 160 to < 190	5 (25.0)	4 (16.7)	3 (15.8)	3 (15.8)	15 (18.3)
≥ 190	15 (75.0)	20 (83.3)	16 (84.2)	16 (84.2)	67 (81.7)

[Source: Supplemental CSR Page 31-34 (2 November 2018) and statistical reviewer's analysis]

3.2.4 Results and Conclusions

Protocol specified and reviewer's analysis of primary endpoint:

Based on the protocol specified analysis, pitavastatin 1mg, 2mg, and 4mg is superior to placebo in reducing percent change in LDL-C at week 12. The estimated LS mean difference and 95% CI in percent change in LDL-C from baseline to week 12 between each pitavastatin arm and placebo are:

- 4 mg versus placebo: -33.8 (-45.0, -22.6)
- 2 mg versus placebo: -22.7 (-37.4, -8.0)
- 1 mg versus placebo: -16.9 (-31.1, -2.7)

The estimated LS mean difference and 95% C.I. based on the reviewer's "wash-out" analysis (which also include data collected within +/- 9 days of Day 84), in percent change in LDL-C from baseline to week 12 between each pitavastatin arm and placebo are:

- 4 mg versus placebo: -37.1 (-44.4, -29.9)
- 2 mg versus placebo: -28.8 (-35.8, -21.8)
- 1 mg versus placebo: -20.4 (-27.7, -13.0)

Both analyses confirm the superiority of pitavastatin in reducing percent change in LDL-C against placebo (Table 6 below).

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Table 6: **Pre-specified primary and statistical reviewer's analysis of LDL-C at week 12**

Sponsor's Primary Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-16.5 (6.13)		
Pitavastatin 2 mg	-22.3 (6.46)		
Pitavastatin 4 mg	-33.4 (4.22)		
Placebo	0.4 (4.04)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-16.9 (7.23)	(-31.1, -2.7)	0.020
Pitavastatin 2 mg vs. Placebo	-22.7 (7.52)	(-37.4, -8.0)	0.003
Pitavastatin 4 mg vs. Placebo	-33.8 (5.71)	(-45.0, -22.6)	< 0.001

Reviewer's Analysis[a]

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-21.4 (2.62)		
Pitavastatin 2 mg	-29.8 (2.37)		
Pitavastatin 4 mg	-38.1 (2.62)		
Placebo	-1.0 (2.64)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-20.4 (3.75)	(-27.7, -13.0)	< 0.001
Pitavastatin 2 mg vs. Placebo	-28.8 (3.58)	(-35.8, -21.8)	< 0.001
Pitavastatin 4 mg vs. Placebo	-37.1 (3.70)	(-44.4, -29.9)	< 0.001

Protocol prespecified analysis is based on multiple imputation (10,000 imputations) with jump-to-placebo using ANCOVA with treatment as a fixed factor and baseline measurement of LDL-C and age as continuous covariates.
The statistical reviewer's analysis is based on multiple imputation (100 imputations) which models a "wash-out" (imputes week 12 LDL-C using only baseline LDL-C) using ANCOVA with the same factors and covariates used by the sponsor
[Source: Supplemental CSR Page 36 (2 November 2018) and statistical reviewer's analysis]

Patient level residual standard deviation

The estimated patient level residual variance and standard deviation from the sponsor's pre-specified analysis is 278.7 and 16.69, respectively. The estimated patient level residual variance and standard deviation from the reviewer's "wash-out" analysis is 128.81 and 11.35, respectively.

Reviewer's note: The assumed standard deviation of 15.0% in the sample size calculation was slightly underestimated with respect to the sponsor's analysis and overestimated with respect to the reviewer's analysis.

Protocol specified and reviewer's analysis of secondary endpoints

Secondary endpoints were not pre-specified; however, they are proposed to be included in the label. Tables 7-11 below display the results of the secondary endpoints for HDL-C, non-HDL, total cholesterol, triglycerides, and apolipoprotein-B. As with the primary endpoint of LDL-C, the sponsor did not include week 12 data that fell outside the window of +/- 3 days and used the same analysis model. Non-HDL-C, total cholesterol, and apolipoprotein-B had significant results for each dosage level while HDL-C and triglycerides were not significant for any dosage level.

- **HDL-C**

Table 7: Pre-specified secondary and statistical reviewer's analysis of HDL-C at week 12

Sponsor's Primary Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	5.7 (4.72)		
Pitavastatin 2 mg	-2.8 (4.24)		
Pitavastatin 4 mg	-1.6 (3.79)		
Placebo	-1.0 (3.56)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	6.6 (5.74)	(-4.6, 17.9)	0.247
Pitavastatin 2 mg vs. Placebo	-1.8 (5.40)	(-12.4, 8.8)	0.740
Pitavastatin 4 mg vs. Placebo	-0.6 (5.13)	(-10.7, 9.4)	0.899

Reviewer's Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	7.2 (3.10)		
Pitavastatin 2 mg	-2.8 (2.69)		
Pitavastatin 4 mg	-1.7 (2.97)		
Placebo	-0.6 (2.95)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	7.8 (4.27)	(-0.6, 16.1)	0.069
Pitavastatin 2 mg vs. Placebo	-2.2 (3.99)	(-10.0, 5.6)	0.58
Pitavastatin 4 mg vs. Placebo	-1.1 (4.19)	(-9.3, 7.1)	0.789

Protocol prespecified analysis is based on multiple imputation (10,000 imputations) with jump-to-placebo using ANCOVA with treatment as a fixed factor and baseline measurement of HDL-C and age as continuous covariates.
The statistical reviewer's analysis is based on multiple imputation (100 imputations) which models a "wash-out" (imputes week 12 HDL-C using only baseline HDL-C) using ANCOVA with the same factors and covariates used by the sponsor
[Source: Supplemental CSR Page 41 (2 November 2018) and statistical reviewer's analysis]

- **Non-HDL-C**

Table 8: Pre-specified secondary and statistical reviewer's analysis of Non HDL-C at week 12

Sponsor's Primary Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-17.3 (5.52)		
Pitavastatin 2 mg	-22.8 (5.74)		
Pitavastatin 4 mg	-31.1 (3.91)		
Placebo	0.7 (3.75)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-18.1 (6.60)	(-31.0, -5.1)	0.006
Pitavastatin 2 mg vs. Placebo	-23.6 (6.78)	(-36.8, -10.3)	0.001
Pitavastatin 4 mg vs. Placebo	-31.9 (5.32)	(-42.3, -21.5)	< 0.001

Reviewer's Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-20.9 (2.66)		
Pitavastatin 2 mg	-28.6 (2.40)		
Pitavastatin 4 mg	-35.7 (2.67)		
Placebo	-0.7 (2.69)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-20.1 (3.82)	(-27.6, -12.7)	< 0.001
Pitavastatin 2 mg vs. Placebo	-27.9 (3.62)	(-35.0, -20.8)	< 0.001
Pitavastatin 4 mg vs. Placebo	-35.0 (3.78)	(-42.4, -27.6)	< 0.001

Protocol prespecified analysis is based on multiple imputation (10,000 imputations) with jump-to-placebo using ANCOVA with treatment as a fixed factor and baseline measurement of Non HDL-C and age as continuous covariates.
The statistical reviewer's analysis is based on multiple imputation (100 imputations) which models a "wash-out" (imputes week 12 Non HDL-C using only baseline Non HDL-C) using ANCOVA with the same factors and covariates used by the sponsor
[Source: Supplemental CSR Page 43 (2 November 2018) and statistical reviewer's analysis]

- **Total Cholesterol**

Table 9: Pre-specified secondary and statistical reviewer's analysis of Total Cholesterol at week 12

Sponsor's Primary Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-13.6 (4.70)		
Pitavastatin 2 mg	-19.9 (4.98)		
Pitavastatin 4 mg	-25.9 (3.27)		
Placebo	0.5 (3.13)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-14.1 (5.51)	(-24.8, -3.3)	0.011
Pitavastatin 2 mg vs. Placebo	-20.3 (5.74)	(-31.6, -9.1)	< 0.001
Pitavastatin 4 mg vs. Placebo	-26.4 (4.42)	(-35.1, -17.8)	< 0.001

Reviewer's Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-16.1 (2.18)		
Pitavastatin 2 mg	-24.5 (1.95)		
Pitavastatin 4 mg	-29.7 (2.15)		
Placebo	-0.7 (2.17)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-15.4 (3.11)	(-21.5, -9.3)	< 0.001
Pitavastatin 2 mg vs. Placebo	-23.8 (2.94)	(-29.5, -18.0)	< 0.001
Pitavastatin 4 mg vs. Placebo	-29.0 (3.06)	(-34.9, -23.0)	< 0.001

Protocol prespecified analysis is based on multiple imputation (10,000 imputations) with jump-to-placebo using ANCOVA with treatment as a fixed factor and baseline measurement of Total Cholesterol and age as continuous covariates.
The statistical reviewer's analysis is based on multiple imputation (100 imputations) which models a "wash-out" (imputes week 12 Total Cholesterol using only baseline Total Cholesterol) using ANCOVA with the same factors and covariates used by the sponsor
[Source: Supplemental CSR Page 45 (2 November 2018) and statistical reviewer's analysis]

- **Triglycerides**

Table 10: Pre-specified secondary and statistical reviewer's analysis of Triglycerides at week 12

Sponsor's Primary Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-4.3 (13.48)		
Pitavastatin 2 mg	-3.0 (12.30)		
Pitavastatin 4 mg	-0.3 (11.06)		
Placebo	2.3 (10.21)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-6.6 (16.87)	(-39.7, 26.4)	0.693
Pitavastatin 2 mg vs. Placebo	-5.3 (15.67)	(-36.0, 25.4)	0.735
Pitavastatin 4 mg vs. Placebo	-2.6 (14.99)	(-32.0, 26.8)	0.863

Reviewer's Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-12.3 (7.32)		
Pitavastatin 2 mg	-13.6 (7.80)		
Pitavastatin 4 mg	3.5 (7.27)		
Placebo	1.0 (7.19)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-13.3 (10.25)	(-33.4, 6.7)	0.193
Pitavastatin 2 mg vs. Placebo	-14.6 (10.67)	(-35.6, 6.3)	0.170
Pitavastatin 4 mg vs. Placebo	2.5 (10.21)	(-17.6, 22.5)	0.809

Protocol prespecified analysis is based on multiple imputation (10,000 imputations) with jump-to-placebo using ANCOVA with treatment as a fixed factor and baseline measurement of Triglycerides and age as continuous covariates.
The statistical reviewer's analysis is based on multiple imputation (100 imputations) which models a "wash-out" (imputes week 12 Triglycerides using only baseline Triglycerides) using ANCOVA with the same factors and covariates used by the sponsor
[Source: Supplemental CSR Page 47 (2 November 2018) and statistical reviewer's analysis]

- **Apolipoprotein-B**

Table 11: Pre-specified secondary and statistical reviewer's analysis of Apolipoprotein-B at week 12

Sponsor's Primary Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-15.7 (5.02)		
Pitavastatin 2 mg	-18.1 (5.00)		
Pitavastatin 4 mg	-25.0 (3.88)		
Placebo	-1.0 (3.68)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-14.7 (6.15)	(-26.7, -2.6)	0.017
Pitavastatin 2 mg vs. Placebo	-17.0 (6.09)	(-29.0, -5.1)	0.005
Pitavastatin 4 mg vs. Placebo	-24.0 (5.28)	(-34.3, -13.6)	< 0.001

Reviewer's Analysis

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-20.1 (2.73)		
Pitavastatin 2 mg	-25.0 (2.45)		
Pitavastatin 4 mg	-27.8 (2.72)		
Placebo	-2.5 (2.74)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-17.6 (3.91)	(-25.3, -10.0)	< 0.001
Pitavastatin 2 mg vs. Placebo	-22.5 (3.68)	(-29.7, -15.3)	< 0.001
Pitavastatin 4 mg vs. Placebo	-25.3 (3.86)	(-32.9, -17.8)	< 0.001

Protocol prespecified analysis is based on multiple imputation (10,000 imputations) with jump-to-placebo using ANCOVA with treatment as a fixed factor and baseline measurement of Apolipoprotein-B and age as continuous covariates.
The statistical reviewer's analysis is based on multiple imputation (100 imputations) which models a "wash-out" ((imputes week 12 Apolipoprotein-B using only baseline Apolipoprotein-B) using ANCOVA with the same factors and covariates used by the sponsor
[Source: Supplemental CSR Page 49 (2 November 2018) and statistical reviewer's analysis]

3.3 Evaluation of Safety

Table 12 below displays the number and percentage rates of the most common adverse reactions as proposed in the product label by treatment group.

Table 12: Adverse events by treatment arm

Adverse Reaction	Pitavastatin 1 mg (n=20)	Pitavastatin 2 mg (n=24)	Pitavastatin 4 mg (n=19)	Placebo (n=19)
Any TEAE [n(%)]	14 (70)	14 (58.3)	7 (36.8)	10 (52.6)
Nasopharyngitis [n(%)]	3 (15)	6 (25)	2 (10.5)	5 (26.3)
Influenza [n(%)]	0	0	2 (10.5)	2 (10.5)
Abdominal pain [n(%)]	2 (10)	2 (8.3)	0	1 (5.3)
Vomiting [n(%)]	0	0	1 (5.3)	2 (10.5)
Abdominal discomfort [n(%)]	0	0	0	2 (10.5)
Headache [n(%)]	5 (25)	5 (20.8)	1 (5.3)	2 (10.5)

[Source: Supplemental CSR Page 62 (2 November 2018)]

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender and Age

This section summarizes results from the analysis of the primary efficacy endpoint within subgroup levels. The subgroups explored are:

- Sex (Male; Female)
- Age (8 to < 12 years; 12 to ≤16 years)

4.1.1 Subgroup analyses results

Table 13 below summarizes the sample sizes for sex and age group by treatment.

Table 13: Sample sizes for Sex and Age group

	Pitavastatin 1 mg (N=20)	Pitavastatin 2 mg (N=24)	Pitavastatin 4 mg (N=19)	Placebo (N=19)
Sex				
Male	9	9	10	8
Female	11	15	9	11
Age group				
≥ 8 to < 12	9	13	11	13
≥ 12 to ≤ 16	11	11	8	6

[Source: Supplemental CSR Page 31-34 (2 November 2018) and statistical reviewer's analysis]

Tables 14 and 15 show the results of the subgroup analysis for sex and age, respectively. From Table 14, we can see that each dosage level is superior to placebo in both males and females and that there is no significant interaction between sex and treatment within each dosage level. Similarly, from Table 15, we see that each dosage level is superior to placebo in each age category.

As with sex, there is no significant interaction between age groups and treatment within each dosage level.

Table 14: Reviewer's subgroup analysis for Sex

Males

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-19.7 (3.87)		
Pitavastatin 2 mg	-28.0 (4.03)		
Pitavastatin 4 mg	-36.1 (3.63)		
Placebo	2.5 (4.09)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-22.2 (5.69)	(-33.4, -11.1)	< 0.001
Pitavastatin 2 mg vs. Placebo	-30.5 (5.78)	(-41.8, -19.1)	< 0.001
Pitavastatin 4 mg vs. Placebo	-38.5 (5.44)	(-49.2, -27.9)	< 0.001

Females

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-22.7 (3.58)		
Pitavastatin 2 mg	-30.8 (2.96)		
Pitavastatin 4 mg	-40.4 (3.82)		
Placebo	-3.6 (3.49)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-19.1 (5.00)	(-28.9, -9.3)	< 0.001
Pitavastatin 2 mg vs. Placebo	-27.3 (4.59)	(-36.3, -18.3)	< 0.001
Pitavastatin 4 mg vs. Placebo	-36.9 (5.17)	(-47.0, -26.7)	< 0.001

Interaction p-value[a]

Pitavastatin 1 mg = 0.824

Pitavastatin 2 mg = 0.658

Pitavastatin 4 mg = 0.680

a The p-value for the interaction between sex and treatment was averaged over 100 data sets.
[Source: Statistical reviewer's analysis]

Table 15: Reviewer's subgroup analysis for Age group

Age ≥ 8 to < 12 years

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-24.5 (4.12)		
Pitavastatin 2 mg	-38.2 (3.80)		
Pitavastatin 4 mg	-39.7 (3.97)		
Placebo	-4.9 (3.58)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-19.6 (5.05)	(-29.5, -9.7)	< 0.001
Pitavastatin 2 mg vs. Placebo	-33.4 (4.48)	(-42.1, -24.6)	< 0.001
Pitavastatin 4 mg vs. Placebo	-34.9 (4.53)	(-43.7, -26.0)	< 0.001

Age ≥ 12 to ≤ 16 years

Treatment	**LS Mean (SE)**		
Pitavastatin 1 mg	-17.9 (3.80)		
Pitavastatin 2 mg	-19.6 (4.50)		
Pitavastatin 4 mg	-37.8 (4.32)		
Placebo	7.9 (5.92)		
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-25.8 (5.93)	(-37.4, -14.1)	< 0.001
Pitavastatin 2 mg vs. Placebo	-27.5 (5.75)	(-38.8, -16.3)	< 0.001
Pitavastatin 4 mg vs. Placebo	-45.8 (6.25)	(-58.0, -33.5)	< 0.001

Interaction p-value[a]

Pitavastatin 1 mg = 0.157

Pitavastatin 2 mg = 0.423

Pitavastatin 4 mg = 0.437

a The p-value for the interaction between age and treatment was averaged over 100 data sets
[Source: Statistical reviewer's analysis]

4.1.2 Shrinkage analyses results

The reviewer performed a shrinkage analyses for sex and age group by dosage level. A shrinkage analysis allows for different treatment effects and obtains more precise estimates of those effects by removing variability, thus, obtaining more narrow confidence/credible intervals. Tables 16 and 17 below display the results of the analyses.

Table 16: Reviewer's shrinkage subgroup analysis for Sex

	Before Shrinkage Estimates		After Shrinkage Estimates	
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**LS Mean (SE)**	**95% CI**
Males				
Pitavastatin 1 mg vs. Placebo	-22.2 (5.69)	(-33.4, -11.1)	-20.5 (3.91)	(-28.3, -12.9)
Pitavastatin 2 mg vs. Placebo	-30.5 (5.78)	(-41.8, -19.1)	-28.5 (3.82)	(-35.7, -20.9)
Pitavastatin 4 mg vs. Placebo	-38.5 (5.44)	(-49.2, -27.9)	-37.7 (3.88)	(-44.7, -29.7)
Females				
Pitavastatin 1 mg vs. Placebo	-19.1 (5.00)	(-28.9, -9.3)	-20.3 (3.79)	(-27.7, -12.8)
Pitavastatin 2 mg vs. Placebo	-27.3 (4.59)	(-36.3, -18.3)	-28.2 (3.69)	(-36.1, -21.5)
Pitavastatin 4 mg vs. Placebo	-36.9 (5.17)	(-47.0, -26.7)	-37.5 (3.85)	(-44.7, -30.0)

[Source: Statistical reviewer's analysis]

Table 17: Reviewer's shrinkage subgroup analysis for Age group

Treatment Comparison	**Before Shrinkage Estimates**		**After Shrinkage Estimates**	
Age ≥ 8 to < 12 years	**LS Mean (SE)**	**95% CI**	**LS Mean (SE)**	**95% CI**
Pitavastatin 1 mg vs. Placebo	-19.6 (5.05)	(-29.5, -9.7)	-21.8 (3.89)	(-29.5, -14.3)
Pitavastatin 2 mg vs. Placebo	-33.4 (4.48)	(-42.1, -24.6)	-31.4 (3.75)	(-38.7, -24.2)
Pitavastatin 4 mg vs. Placebo	-34.9 (4.53)	(-43.7, -26.0)	-38.1 (3.70)	(-45.4, -30.8)
Age ≥ 12 to ≤ 16 years	**LS Mean (SE)**	**95% CI**	**LS Mean (SE)**	**95% CI**
Pitavastatin 1 mg vs. Placebo	-25.8 (5.93)	(-37.4, -14.1)	-22.3 (4.01)	(-30.1, -14.3)
Pitavastatin 2 mg vs. Placebo	-27.5 (5.75)	(-38.8, -16.3)	-30.8 (3.93)	(-38.4, -23.1)
Pitavastatin 4 mg vs. Placebo	-45.8 (6.25)	(-58.0, -33.5)	-39.2 (4.05)	(-47.0, -31.0)

[Source: Statistical reviewer's analysis]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The major statistical issue was the amount of missing data (26.8%) that was present in the sponsor's analysis for the primary endpoint. While the sponsor's primary analysis method demonstrated that each dose of pitavastatin was superior to placebo, it was found upon review that 20 of the 22 patients who were considered missing had data within a 9-day span of Day 84. Upon discussion with the clinical reviewer, it was agreed upon that these data should be included in the analysis. After the inclusion of these data, the results remained unchanged, however, it yielded larger treatment effects, smaller standard errors and narrower confidence intervals.

Another statistical issue was the method of imputing missing week 12 measurements. The sponsor used a jump-to-placebo approach, meaning that patients on the pitavastatin arms were treated as if they were on the placebo arm, including that their observed intermediate measurements are treated as having occurred on placebo. Since we wish to assume that the patients who have discontinued

will have experienced a "wash out" of the drug effect by the endpoint, using their intermediate measurements are inappropriate since it can partly be explained by the drug. Therefore, to model a "wash-out" of treatment effect, missing week 12 values from those on the pitavastatin arms were imputed using only the patients baseline measurement.

We sent an IR to the sponsor and asked them to confirm that Table 2 is correct, perform an analysis that includes the data from the 20 patients and to model a wash-out for the 2 missing patients. The sponsor confirmed that the table is correct and obtained similar results as the statistical reviewer.

5.2 Collective Evidence

In response to a Written Request from FDA, the sponsor submitted the results from an analysis that utilized a subset of the original study population that was more relevant to pediatric patients with HeFH. While the analysis was post-hoc, there remains strong evidence that each dosage level of pitavastatin is superior to placebo in reducing percent change in LDL-C in pediatrics from 8 to 16 years old with HeFH. Further, there appears to be no outstanding safety issues.

5.3 Conclusions and Recommendations

The results of the sponsor's analysis and the statistical reviewer's analysis of the primary endpoint demonstrate that each dosage of pitavastatin is superior to placebo in reducing percent change in LDL-C in pediatrics ages from 8 to 16 with HeFH. Therefore, I recommend approval in regard to the primary endpoint, however, whether secondary endpoints should appear in the label will require further discussion.

5.4 Labeling Recommendations

Below is the sponsor's proposed wording and table of results in the product label and the statistical reviewer's recommended table. Since 20 of the 22 measurements that were not used by the sponsor were within a 9-day span of the endpoint, the statistical reviewer is recommending reporting the results from the reviewer's analysis which uses these data for the primary and secondary endpoints. Further, since secondary endpoints were not pre-specified and HDL-C and Triglycerides were not statistically significant, discussion with the clinical team will be required to decide if they should be reported in the label.

- *Sponsor's recommended text and table for the Livalo label:*

14.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

(b) (4)

Table 10. (b) (4) Response in Pediatric Patients with Heterozygous Familial Hypercholesterolemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	Non-HDL-C
(b) (4)							

- *Statistical reviewer's recommended table for the Livalo label:*

Table 10. (b) (4) Response in Pediatric Patients with Heterozygous Familial Hypercholesterolemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C[a]	Apo-B[a]	TC[a]	TG[a]	HDL-C[a]	Non-HDL-C[a]
Placebo	19	-1.0	-2.5	-0.7	1.0	-0.6	-0.7
LIVALO 1mg	20	-21.4	-20.1	-16.1	-12.3	7.2	-20.9
LIVALO 2mg	24	-29.8	-25.0	-24.5	-13.6	-2.8	-28.6
LIVALO 4mg	19	-38.1	-27.8	-29.7	3.5	-1.7	-35.7

a LS means were obtained by multiple imputation which models a "wash-out" using ANCOVA with treatment as a fixed factor and baseline measurement of the parameter and age as continuous covariates

6 Appendix

Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different and related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. Below is the model used in the analysis for sex and age group by dosage levels:

$$Y_i \sim N(\mu_i, \sigma_i^2), i = 1, 2$$

$$\mu_i \sim N(\mu, \tau^2), i = 1, 2$$

$$\mu \sim N(0, 10000), \quad \tau^{-2} \sim Half\ N(0, 1)$$

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