Cross-Discipline Team Leader Review

Date	May 16, 2019
From	John Sharretts, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 022363 / S-015
Applicant	Kowa Pharmaceuticals
Date of Submission	November 16, 2019
PDUFA Goal Date	May 16, 2019
Proprietary Name	Livalo
Established or Proper Name	Pitavastatin
Dosage Form(s)	Oral tablets (1 mg, 2 mg, 4 mg)
Applicant Proposed Indication(s)/Population(s)	Adjunctive therapy to diet in pediatric patients 8 to 16 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and Apolipoprotein B (Apo B)
Applicant Proposed Dosing Regimen(s)	Recommended starting dose (b) (4) mg once daily, recommended maximum dose 4 mg once daily
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*Adjunctive therapy to diet in pediatric patients aged 8 years and older with HeFH to reduce elevated TC, LDL-C, and ApoB*
Recommended Dosing Regimen(s) (if applicable)	*Recommended starting dose 2 mg once daily, maximum recommended dose 4 mg once daily*

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Livalo (pitavastatin) is an HMG CoA-reductase inhibitor (statin) indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein (HDL-C) in adult patients with primary hyperlipidemia or mixed dyslipidemia. The applicant submitted this supplemental NDA (sNDA) efficacy supplement including data to fulfill a pediatric Written Request and requesting pediatric exclusivity.

The pivotal clinical trial was a 12-week, randomized, double-blind, placebo-controlled trial to evaluate the effect of three dose levels of pitavastatin versus placebo on LDL-C and other lipid parameters in pediatric patients with high-risk hyperlipidemia, including patients with heterozygous familial hypercholesterolemia (HeFH). To fulfill the Written Request, the applicant submitted a supplemental analysis considering only the subset of the trial population ages 8 to 16 years with HeFH and a baseline LDL-C $\geq$ 190 mg/dL, or LDL-C $\geq$ 160 mg/dL with one additional risk factor. The applicant also submitted analyses of a 12-month single-arm, open-label extension study to support safety and efficacy findings in the pivotal trial.

In the randomized, controlled trial, pharmacokinetic data showed a dose-dependent increase in plasma concentrations of pitavastatin and its major metabolite, pitavastatin lactone, at trough and 1-hour post-dose at steady state. Treatment with pitavastatin resulted in a statistically significant, clinically meaningful effect on the primary endpoint, demonstrating dose-dependent decreases in LDL-C versus placebo. Per the FDA statistical analysis, the estimated least squares (LS) difference and 95% confidence interval (CI) in mean percent change in LDL-C from baseline to Week 12 were:

- 4 mg versus placebo: -37.1 (-44.4, -29.9), p <0.001
- 2 mg versus placebo: -28.8 (-35.8, -21.8), p <0.001
- 1 mg versus placebo: -20.4 (-27.7, -13.0), p <0.001

The trial results provide substantial evidence of effectiveness and support an indication for the treatment of pediatric patients with HeFH to lower LDL-C, TC, and ApoB. The data support a recommended starting dose of 2 mg once daily and maximum dose of 4 mg for pediatric patients with HeFH in labeling. The safety data submitted in support of the supplemental application were consistent with the known safety profile of pitavastatin and the statin class in general. Analyses did not identify any new safety concerns, and the overall benefit-risk assessment remains favorable. The nonclinical data submitted fulfill the Written Request and support approval of the efficacy supplement. The Pediatric Exclusivity Board agreed that the applicant fulfilled the terms of the Written Request. The Pediatric Review Committee (PeRC) agreed with the negotiated labeling for pediatric patients.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Heterozygous familial hypercholesterolemia (HeFH) is a genetic disorder with a prevalence of 1/200 to 1/500 • Several mutations in LDL-C metabolism result in HeFH, but mutations in the gene encoding for the LDL receptor are the most common cause • Phenotype expression results in variable LDL-C levels that range from 160 mg/dL to over 300 mg/dL • Along with elevated levels of LDL-C there is a risk of subsequent premature atherosclerotic cardiovascular disease • Statins have demonstrated CV risk benefit in adult populations • There are no outcomes data in pediatric populations to guide the optimum age at which benefits of drug treatment outweigh potential risks	Children and adolescents with HeFH have moderately increased risk of cardiovascular disease due to life-long exposure to high levels of cholesterol. Benefits of drug treatment to lower LDL-C most likely outweigh risks with increasing age and LDL-C levels in pediatric HeFH patients
Current Treatment Options	• First line treatment is diet and exercise modification • Statins are preferred initial pharmacologic treatment for pediatric patients with HeFH.	Pediatric HeFH guidelines for treatment and management recommend treatment with a statin at age 10 and consideration for treatment at age 8 in selected high-risk patients
Benefit	• The efficacy of pitavastatin in pediatric HeFH patients was established with a randomized, double-blind, placebo-controlled, 12-week study. • Pitavastatin 1 mg decreased LDL-C by -20.4; pitavastatin 2 mg decreased LDL-C by -28.8; and pitavastatin 4 mg decreased LDL-C by -37.1 from baseline to Week 12 versus placebo • The effect of pitavastatin on CV outcomes has not been determined	The statin class of drugs, of which pitavastatin is a member, are first-line therapy after diet and exercise per pediatric HeFH management guidelines. The pivotal pitavastatin clinical trial was adequate and well-controlled and demonstrated meaningful LDL-C lowering ranging from 20% to 37%, compared to placebo Pitavastatin represents an additional option among statin drugs for treatment of children and adolescents with HeFH

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Nonclinical studies support the use of pitavastatin in the age range studied • The safety profile of pitavastatin was consistent with the known safety profile of pitavastatin in adults and statins as a class • There was no evidence of adverse effects on growth or development	Nonclinical data supports the administration of pitavastatin in the proposed pediatric population The general safety findings were consistent with the known safety profile of pitavastatin in adults and statin drugs as a class. There were no new safety issues identified. There were no signals of safety issues specific to pediatric patients, such as effects on growth or development.

2. Background

The purpose of this review is to summarize the basis for the regulatory action for NDA 022363/S-015, an efficacy supplement for LIVALO (pitavastatin) submitted to support a new indication for treatment of pediatric patients with heterozygous familial hypercholesterolemia (HeFH). All reviewers support approval.

Livalo (pitavastatin) is an HMG CoA-reductase inhibitor indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein (HDL-C) in adult patients with primary hyperlipidemia or mixed dyslipidemia. It was first approved in Japan on July 17, 2003, and it was approved in the US on August 3, 2009. At the time of the original US approval, FDA waived the pediatric study requirement under the Pediatric Research Equity Act (PREA) for the approved indications.

populations, and indications. While open to considering evaluation of other high-risk pediatric populations, the Division recommended that the applicant include trials relevant to treatment of elevated LDL-C in patients with HeFH in subsequent submissions.

HeFH is a genetic condition most commonly resulting from mutations in the gene encoding the LDL receptor. Other mutations, including loss-of-function in the gene encoding ApoB and gain-of-function in the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9) may also result in the phenotype. HeFH is associated with elevated LDL-C levels and increased incidence and premature onset of atherosclerotic cardiovascular disease (CVD).[1] Current US guidelines[2] recommend initiating statin therapy in patients 10 years and older with HeFH, following a trial of lifestyle modification, and in selected high-risk patients (LDL-C $\geq$ 190 mg/dL or presence of additional risk factors) starting as early as age 8 years. The optimal age to initiate statins is unknown, and guidelines have attempted to balance the uncertainties of the benefit of starting therapy at younger ages on outcomes later in life and theoretical risks, including effects on neurocognitive development, growth, and pubertal maturation.

[1] Sniderman AD, et al. The Severe Hypercholesterolemia Phenotype: Clinical Diagnosis, Management, and Emerging Therapies. *J Am Coll Cardiol* 2014;63(19):1935-47.

[2] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics* 2011;128 Suppl 5:S213-56.

On July 6, 2016, the applicant submitted a revised PPSR proposing two pediatric studies, a randomized, double blind, placebo-controlled, 4-arm, parallel group study to evaluate the effect of three dose levels (1 mg, 2 mg, and 4 mg daily) versus placebo on LDL-C in patients ages (b) (4) with "high-risk" hyperlipidemia, and a single arm, open-label extension study of patients who completed the randomized trial and additional eligible patients. The applicant had previously completed the studies under a Pediatric Investigation Plan (PIP) with the European Medicines Agency. The majority of patients enrolled in these studies met criteria for a diagnosis of HeFH.

On November 2, 2016, FDA issued a formal Written Request to the applicant for the following studies:

Nonclinical study:

- A nonclinical study in juvenile animals of a pharmacologically relevant species exposed during the period of development appropriate for the intended pediatric age range to evaluate the effects of pitavastatin on neurobehavioral endpoints.

Clinical studies:

- Study 1: A 12- week, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of three dose levels of pitavastatin in pediatric patients ages 8 to 16 years of age with HeFH.
- Study 2: A 52-week safety study of pitavastatin in pediatric patients ages 8 to 16 years with HeFH.

Of note, the clinical analyses requested represent a subset of the study populations that participated in the completed trials, excluding patients younger than 8, older than 16, and patients without HeFH.

On February 26, 2018, the applicant submitted an amendment to the Written Request, requesting to change the deadline for submission of the studies to November 20, 2018. FDA agreed to the change. The applicant submitted a supplemental NDA (sNDA) efficacy supplement including data for all requested studies on November 16, 2018 and requesting pediatric exclusivity on the basis of fulfilling the requirements of the Written Request.

3. Product Quality

The applicant did not submit any new product quality information with this submission.

4. Nonclinical Pharmacology/Toxicology

The applicant submitted data from a 4-week juvenile toxicity study in rats to fulfill one requirement of the Written Request. Refer to the nonclinical review by Dr. Lydia Haile, dated April 01, 2019, for details of the study. Dr. Haile concluded that the results support the use of pitavastatin in the proposed pediatric population. Furthermore, because the toxicity profile in

juvenile rats was similar to that in adult rats (no adverse signals specific to juvenile rats), Dr Haile recommended no labeling changes.

In the study, male and female rats were orally administered pitavastatin at doses of 1, 7.5, and 15 mg/kg/day from post-natal day (PND) 28 through PND 56, followed by a 28-day treatment-free period. The treatment period corresponds to human ages of approximately 6 to 12 years for neurologic and reproductive endpoints. Toxicity studies conducted for the original NDA had been initiated at approximately PND 45, covering the older pediatric age range.

There was no treatment related mortality or adverse clinical signs at any dose tested. Mean body weight and food consumption were lower at 15 mg/kg/day compared to vehicle control, with full recovery. Reversible microscopic changes in the liver with associated increases in liver enzymes, and reversible nonglandular forestomach changes (hyperkeratosis, epithelial hyperplasia and/or mixed cell infiltrate) occurred at doses $\geq$ 7.5 mg/kg/day. The NOAEL of 1 mg/kg/day was based on the forestomach changes.

Dr. Haile concluded that the toxicology profile was comparable to that in adults. Safety margins were 2x based on human adult exposure at 4 mg daily and are close to the maximum proposed human dose by body surface area extrapolation (1x) using a 20 kg body weight for children. The estimate is conservative, as 20 kg represents approximately the 5th percentile for weight in girls and 3rd percentile in boys at age 8. Furthermore, the toxicities at 7.5 mg/kg/day may not be relevant to humans due to anatomic and functional gastric differences between rats and humans

I concur with Dr. Haile's conclusions. The nonclinical results fulfill the Written Request and support approval of the efficacy supplement, and no labeling changes are required.

5. Clinical Pharmacology

The clinical pharmacology reviewer, Dr. Shalini Wickramaratne Senarath Yapa, concluded that the clinical pharmacology data submitted by the applicant supports approval. Refer to her review, finalized April 02, 2019, for details.

The clinical pharmacology review focused on pharmacokinetic (PK) data and efficacy analyses in Study NK-104-4.01EU. The PK analysis set consisted of all randomized patients who received at least one dose of study drug and had at least one valid plasma drug concentration. In the review, Dr. Wickramaratne Senarath Yapa concluded that the PK data showed a dose-dependent increase in plasma concentrations of pitavastatin and its major metabolite, pitavastatin lactone, at trough and 1-hour post-dose at steady state following administration of pitavastatin 1 mg, 2 mg, and 4 mg. Tables 1 and 2 summarize these PK data.

Table 1: Pitavastatin plasma concentrations (PK analysis set)

Visit Statistics	Pitavastatin 1 mg n=16	Pitavastatin 2 mg n=15	Pitavastatin 4 mg n=17
Week 8/Week 12: Trough			
n/n' [a]	15/0	15/7	16/16
Mean (SD) (ng/mL)	0 (0)[b]	1.31 (2.154)	3.96 (2.886)
CV%	Not calculable	164.0	72.8
Week 8/Week 12: 1 hr post-dose			
n/n' [a]	14/14	13/13	15/15
Mean (SD) (ng/mL)	13.79 (5.516)	35.08 (39.098)	124.79 (87.429)
CV%	40.0	111.4	70.1

[a] n=number of patients who have PK samples; n'= number of patients who have PK sample results above the LLOQ
[b] Concentrations below the lower limit of quantification
Source: Supplemental Clinical Study Report NK-104-4.01EU, Data summarized from Table 26, Page 57

Source: FDA Clinical Pharmacology Review, Table 3

Table 2: Pitavastatin lactone plasma concentrations (PK analysis set)

Visit Statistics	Pitavastatin 1 mg n=16	Pitavastatin 2 mg n=15	Pitavastatin 4 mg n=17
Week 8/Week 12: Trough			
n/n' [a]	15/15	15/15	16/16
Mean (SD) (ng/mL)	3.29 (1.806)	8.21 (9.261)	19.74 (13.428)
CV%	54.9	112.8	68.0
Week 8/Week 12: 1 hr post-dose			
n/n' [a]	14/14	13/13	15/15
Mean (SD) (ng/mL)	11.71 (5.563)	25.82 (12.632)	74.88 (25.116)
CV%	47.5	48.9	33.5

[a]n=number of patients who have PK samples; n'= number of patients who have PK sample results above the LLOQ
Source: Supplemental Clinical Study Report NK-104-4.01EU, Data summarized from Table 27, Page 58

Source: FDA Clinical Pharmacology Review, Table 4

In her review, Dr. Wickramaratne Senarath Yapa the efficacy data showing that treatment with pitavastatin 1 mg, 2 mg, and 4 mg administered once-daily demonstrated a statistically significant, dose-dependent reduction in LDL-C, non-HDL-C, TC, and ApoB compared to placebo at Week 12 in children and adolescents with HeFH. She concluded that the lipid results supported approval of the supplement and the applicant's proposed starting dose and dose range in labeling.

I concur with the overall clinical pharmacology conclusions, but I also agree with revising the recommended starting dose as recommended by the clinical reviewer, Dr. Chowdhury, (b) (4) Clinical efficacy data are discussed in detail in Section 7 of this review.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant submitted two clinical studies in support of efficacy. This section of the review focuses on the efficacy findings relevant to approvability and labeling derived from Study NK-104-4.01EU, the randomized, double-blind, placebo-controlled, 4-arm, parallel-group trial of oral pitavastatin 1 mg, 2 mg, and 4 mg once daily versus placebo. The open-label extension Study NK-104-4.02EU provided supportive data. Refer to the clinical review by Dr. Iffat Chowdhury for details of the clinical program, and the statistical review by Dr. Roberto Crackel for analysis of the statistical methods. Both reviewers recommend approval.

Study NK-104-4.01EU
This was a 12-week, randomized, double-blind, placebo-controlled trial to evaluate the effect of three dose levels of pitavastatin versus placebo on LDL-C and other lipid parameters in pediatric patients with HeFH. The study consisted of a 5-week screening and washout period and a 12-week double-blind treatment period. The original trial included patients as young as 6 years of age, patients without a diagnosis of HeFH, and patients with LDL as low as 130 mg/dL with additional CV risk factors.

The supplemental analysis submitted to fulfill the Written Request considered only the subset of the trial population ages 8 to 16 with HeFH. Patients had a baseline LDL-C $\geq$ 190 mg/dL or LDL-C $\geq$ 160 mg/dL with one additional risk factor (male, HDL-C $\leq$ 45 mg/dL, TG $\geq$ 150 mg/dL, elevated lipoprotein(a) [Lp(a)], type 2 diabetes mellitus, hypertension, or family history of premature CVD) and were not on any lipid-lowering therapy within 5 weeks prior to screening. Key exclusion criteria were fasting TG $\geq$ 400 mg/dL, homozygous familial hypercholesterolemia (HoFH), type 1 diabetes mellitus, severe renal impairment (defined as serum creatinine > 2.0 mg/dL), and current apheresis therapy.

The primary efficacy endpoint was the mean percent change in LDL-C from baseline to Week 12 for each treatment group versus placebo. Key secondary endpoints were the mean percent change in other lipid parameters (HDL-C, non-HDL-C, TC, TG, and ApoB). The major PK endpoints were the concentrations of pitavastatin and its major metabolite, pitavastatin lactone, at trough (pre-dose) and 1-hour post-dose at steady state. Refer to Dr. Chowdhury's review for details of the study design.

The Full Analysis set included patients who received at least one dose of study drug and at least one valid, post-baseline lipid measurement. In the supplemental analysis, all randomized patients met these two criteria, and thus none were excluded from efficacy analyses. The primary analysis was an analysis of covariance (ANCOVA) model with treatment as a fixed factor and baseline LDL-C and age as covariates, using control-based (jump-to-placebo) imputation of missing values. Analyses of the key secondary efficacy endpoints used a similar approach. Refer to Dr. Crackel's review for details of the statistical analysis plan.

Results:
The applicant conducted the site at 9 study sites in 6 countries in Europe (France, Greece, Italy, Netherlands, Norway, and Spain). The original trial population consisted of 106 patients. The analyses conducted to meet the requirements of the written request included 82 (77%) of these patients, including 81 with genetically confirmed HeFH diagnosis.

Demographics
In the analysis population, 46 (46%) of patients were female, and 96% were Caucasian. Demographic characteristics were similar among treatment arms. Although the incidence of HeFH is higher in certain White, non-Hispanic populations due to a founder effect (Finns, Icelanders, Christian Lebanese, French Canadians, and South African Afrikaners and Ashkenazi Jews)[3], non-White and Hispanic HeFH patients were likely underrepresented in this trial compared to the overall US population.[4] It is important to consider whether the trial results are generalizable to the US population.

Historically, underrepresentation of US racial and ethnic minorities has been a limitation of clinical trials across the statin drug class. More specifically, there is very limited clinical trial experience for pitavastatin in Black or African American and Hispanic patients. In adult Phase 3 trials, each group represented fewer than 1% of participants (Asian patients were better represented).[5] Nonetheless, there is evidence from other programs that statins lower LDL-C[6] and improve CV outcomes[7] in non-White patients. While it is plausible that the LDL-lowering effect of pitavastatin is different (either greater or lesser) in less-studied populations, dose titration addresses individual variation to some extent. From a public health standpoint, the larger concern, ultimately, is that non-white pediatric patients with HeFH most likely remain underdiagnosed[4] and undertreated in clinical practice. Because patients may need to try more than one statin to balance efficacy and tolerability, pitavastatin potentially represents an additional option to address unmet need among pediatric patients with HeFH.

Baseline characteristics
Baseline characteristics were similar among treatment arms. The mean age of participants was 11.4 years, and 32 (39.0%) subjects were Tanner Stage I at baseline. Mean height was 153 cm, mean weight was 47.0 kg, and mean body mass index (BMI) was 19.6%. Approximately 40% had previously used lipid-lowering medications. Mean baseline LDL-C was 234.7 mg/dL overall and 250.4 mg/dL in the placebo arm. Mean TC, non-HDL-C, and ApoB were also slightly higher in placebo, consistent with the LDL-C findings. Mean HDL-C and TG were similar across arms. Table 3 summarizes baseline lipid parameters.

---

[3] Austin MA, et al. Genetic Causes of Monogenic Heterozygous Familial Hypercholesterolemia: A HuGE Prevalence Review. *Am J Epidemiol*. 2004; 160 (5):407–420.
[4] Belay B, et al. Underrepresentation of non-White Children in Trials of Statins in Children with Heterozygous Familial Hypercholesterolemia. *Ethn Dis*. 2009;19(2):166-71.
[5] FDA Clinical Review. NDA 022363. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022363s000_MedR_P1.pdf
[6] FDA Clinical Review. NDA 20702. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020702_s000.pdf
[7] Albert MA, et al. Race, ethnicity, and the efficacy of rosuvastatin in primary prevention: The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Am Heart J*. 2011; 162:106-114.e2

Table 3: Baseline Lipid Parameters (NK-104-4.01EU, FAS)

	Pitavastatin 1 mg N=20	Pitavastatin 2 mg N=24	Pitavastatin 4 mg N=19	Placebo N=19	Total N=82
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)
LDL-C Category-n (%)[a]					
≥ 160 to < 190 mg/dL	5 (25.0)	4 (16.7)	3 (15.8)	3 (15.8)	15 (18.3)
≥ 190 mg/dL	15 (75.0)	20 (83.3)	16 (84.2)	16 (84.2)	67 (81.7)
Total	20	24	19	19	82
HDL-C (mg/dL)					
Mean (SD)	54.0 (14.0)	52.6 (12.4)	51.2 (8.2)	53.6 (10.9)	52.8 (11.5)
Total Cholesterol (mg/dL)					
Mean (SD)	293.2 (42.4)	299.5 (34.6)	308.4 (51.0)	321.2 (70.4)	305.1 (50.5)
Non-HDL-C (mg/dL)					
Mean (SD)	239.3 (40.5)	246.9 (36.2)	257.2 (51.3)	267.6 (74.5)	252.2 (51.8)
Triglycerides (mg/dL)					
Mean (SD)	83.2 (28.6)	100.2 (52.4)	77.8 (21.0)	86.0 (33.4)	87.6 (37.3)
Apo B (mg/dL)					
Mean (SD)	136.3 (20.0)	142.7 (22.7)	144.2 (25.1)	150.7 (36.7)	143.3 (26.5)

Source: Study Report NK.104.4.01EUSupplAnalysis, Table 6.

Primary Efficacy Endpoint

Treatment with pitavastatin resulted in statistically significant, clinically meaningful, dose-dependent decreases in LDL-C versus placebo, and the trial results support an indication for the treatment of pediatric patients with HeFH. The FDA statistical analysis provides the best estimate of the treatment effect and is the appropriate analysis to include in labeling, whereas the applicant's primary analysis underestimates the true treatment effect.

In the FDA Statistical review, Dr. Crackel concluded that all three doses of pitavastatin are superior to placebo in reducing LDL-C. The estimated least squares (LS) difference and 95% confidence interval (CI) in mean percent change in LDL-C from baseline to Week 12 for each pitavastatin arm versus placebo were:

- 4 mg versus placebo: -37.1 (-44.4, -29.9), p <0.001
- 2 mg versus placebo: -28.8 (-35.8, -21.8), p <0.001
- 1 mg versus placebo: -20.4 (-27.7, -13.0), p <0.001

The results provide substantial evidence of effectiveness. Strengths of the analysis include the randomized, blinded, controlled design in a rare disease population, and the finding of dose-dependent reduction in LDL-C from baseline, and clear separation of the 95% CI from placebo

with highly significant nominal *p*-values. LDL-C has previously served as the basis for full approval of indications for pediatric HeFH. Per the FDA analysis, there was little missing data, as nearly all patients completed the trial on study drug and had an available LDL-C value at or shortly beyond 12 weeks. Observed changes in other lipid parameters, discussed later in this section of the review, were consistent with the primary endpoint. Limitations include the use of a single trial to support effectiveness, and the lack of racial and ethnic diversity in the study population, discussed previously. FDA had previously agreed to use of a single trial to support efficacy as part of the Written Request, and the robust findings mitigate this limitation to some extent.

The results of Dr. Crackel's analysis differ in magnitude from the results of the applicant's pre-specified analysis of the primary endpoint. In the applicant's analysis, pitavastatin treatment at the doses of 1 mg, 2 mg, and 4 mg daily demonstrated LDL-C reductions of 16.9%, 22.7%, and 33.8%, respectively, versus placebo. In the statistical review, Dr. Crackel identified several key limitations of the applicant's primary analysis that affect these estimates of the treatment effect. The applicant's analysis had a large amount of missing data for the primary endpoint (26.8%), because the prespecified window for laboratory collection at week 12 (Day 84 +/- 3 days) excluded 2 patients with laboratory collection at Day 80 (11 weeks, 3 days) and 18 patients with collection after Day 87. Additionally, the applicant used a control-based (jump-to-placebo) model to impute missing data, a method that implausibly assumes that the LDL response of patients in the active treatment arms with missing data would have behaved similarly to patients on placebo. Refer to Dr. Crackel's review for discussion of the limitations of such an analysis.

In his analysis, Dr. Crackel expanded the Week 12 analysis window, thus capturing available data and reducing missingness for the primary endpoint to just 2 patients (2.4%). He used a washout imputation for missing values, which assumes that LDL-C levels for patients with missing data would return to near baseline. Refer to the statistical review for further details of this analysis. Dr. Crackel used similar methods to analyze secondary lipid endpoints, summarized in Table 4. The results of the primary and secondary analyses support an indication to reduce LDL-C, TC, and ApoB in pediatric patients with HeFH. Pitavastatin did not demonstrate a meaningful effect on HDL-C or TG, but the mean values of these parameters were normal at baseline (Refer to Table 3).

I agree with Dr. Crackel's analyses and recommend inclusion of these data in Section 14 – *Clinical Trials Experience* of labeling. The inclusion of available patient data in place of protocol-defined "missing" values, and the use of a more appropriate imputation method for missing data ultimately provide a more accurate estimate of the true treatment effect than the applicant's analyses.

Table 4: [redacted] Response in Pediatric Patients with Heterozygous Familial Hypercholesterolemia: Mean percent change from baseline at Week 12 [redacted]

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

Source: FDA Statistical Review, Table 10

Analysis of Dosing

In the clinical review, Dr. Chowdhury recommended that the starting dose for pediatric patients with HeFH in labeling should be 2 mg once daily. She noted that only one patient in the 1 mg treatment arm achieved LDL-C level less than 130 mg/dL. The finding is not surprising, considering that the majority of enrolled patients had an LDL-C greater than 190 mg/dL at baseline, requiring a greater than 30% reduction from baseline to achieve target versus the mean reduction in LDL-C of 21% with the 1 mg dose. Published US guidelines recommend an LDL-C target of <130 mg/dL (or 50% decrease from baseline)[8] in pediatric patients with HeFH.

Dr. Chowdhury also relied on data from Study NK-104-4.02EU, the single-arm, open-label, extension study of patients with high-risk hyperlipidemia who participated in the randomized trial (and additional patients meeting eligibility criteria). In this study, all patients (including those treated at other dose levels in the randomized trial) initiated treatment at 1 mg daily, with protocol-specified dose titration targeting LDL-C less than or equal to 110 mg/dL. Of the 85 patients enrolled, 76 (89.4%) completed the trial on treatment and 9 discontinued prematurely. Among the completers, 73 of 76 (96.1%) were taking pitavastatin 4 mg daily, 3 patients (3.9%) were taking 2 mg daily, and no patients completed the study at the 1 mg dose level. Mean LDL-C reduction at Week 52 per the applicant's analysis was 36.6%.

Collectively, these data support Dr. Chowdhury's recommended starting dose. The applicant's proposed [redacted]

8. Safety

The safety data submitted in support of the application were consistent with the known safety profile of pitavastatin and the statin class in general. Analyses did not identify any new safety

[8] Goldberg AC, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol.* 2011;5(3):133-140.

concerns. Although analyses were inadequate to definitively exclude subtle effects, there were no unexpected changes in assessments of growth and development.

This section considers clinical safety data from Study NK-104-4.01EU, the 12-week randomized, placebo controlled clinical trial, and Study NK-104-4.02EU, the 52-week, single-arm, open-label extension study. The Safety population consisted of all randomized patients who received at least one dose of study drug. All randomized patients met this criterion, and thus no patients were excluded from safety analyses.

Dr. Chowdhury primarily considered the safety database for patients included in the supplemental analysis (n=82), conducted to fulfill the terms of the pediatric Written Request. Out of concern for introduction of ascertainment bias due to exclusion of patients after randomization from the supplemental analyses, I have repeated several analyses, including investigations of adverse events (AEs) and laboratory results, on the full Safety Sets of both the randomized, controlled trial (n=106) and the open-label extension (n=112).

Exposure
Overall, the safety database was adequate to conduct a review. The applicant provided the data outlined in the Written Request to support safety. Exposure was similar among the four arms of the randomized trial, with a mean of 84 days in the full Safety Set. Median exposure of the 112 subjects in the open-label extension was 342 days.

General Safety Topics
In the supplemental safety set of the randomized trial there were no major safety findings, including no deaths, no serious adverse events (SAEs), or withdrawals due to an AE. Refer to the clinical review for details.

In the full safety set, one patient treated with pitavastatin 2 mg experienced an SAE of *Facial bones* fracture related to a skiing accident. The patient discontinued study drug and withdrew from the study. The investigator assessed the AE as not related to study drug.

One additional patient (b) (6) treated with pitavastatin 4 mg withdrew due to TEAEs of *Pyrexia* and *Rash generalized*. The patient was a 7-year old female with a history of allergic asthma who developed fever 38.3 C and rash, which began on the face and became generalized, beginning on Study Day 12. Treatment included betamethasone and cetirizine. She discontinued study drug on Day 15, and the AE resolved on Day 18. The patient withdrew from the study on Day 36. The investigator assessed the relationship to study drug as Improbable. From the available narrative, the event appears to be possibly related.

In the full safety set of the open-label extension, one patient (b) (6) withdrew due to a TEAE of *Rash pruritic*, assessed as possibly drug-related. Assessment of the rash events is challenging due to limited information in the narratives. Hypersensitivity reactions are currently described in labeling for Livalo.

In the supplemental analysis, 45 patients (54.9%) experienced 95 TEAEs. The number of events and the percentage of patients experiencing at least one event, summarized in Table 5

varied considerably among arms. In the full Safety Set, 60 patients (56.6%) experienced 116 TEAEs. The number and percent of patients experiencing an event and the total events, while still variable, was more consistent across arms. Notably, up to 35% of events were excluded from individual arms in the supplemental Safety Set, potentially introducing ascertainment bias (decreased ascertainment of events) in those arms.

The most frequent TEAE PTs were *Nasopharyngitis*, *Headache*, *Abdominal pain*, and *Influenza*. Among the most common TEAEs, only Headache occurred more frequently on pitavastatin than placebo, and the incidence decreased with dose (23.1%, 18.5%, 3.8% with pitavastatin 1 mg, 2 mg, and 4 mg, respectively, versus 7.9% with placebo in the full Safety Set).

Table 5: Treatment Emergent AEs (NK-104.4.01EU, Supplemental Safety Set)

Arm	Placebo	1 mg	2 mg	4 mg	Total
N	19	20	24	19	82
Patients with at least one TEAE	10 (53%)	14 (70%)	14 (42.6%)	7 (36.8%)	45 (54.9%)
Total Events	20	25	37	13	95

Source: FDA Cross-Discipline Team Leader from dataset ADAE

Table 6: Treatment Emergent AEs (NK-104-4.01EU, Full Safety Set)

Arm	Placebo	1 mg	2 mg	4 mg	Total
N	27	26	27	26	106
Patients with at least one TEAE	15 (55.6%)	18 (69.2%)	16 (59.3%)	11 (42.3%)	60 (56.6%)
Total Events	31	36	39	20	126

Source: FDA Cross-Discipline Team Leader from dataset ADAE

Musculoskeletal Events

Dr. Chowdhury did not identify any new safety concerns in her review of musculoskeletal adverse events and musculoskeletal-related laboratory values. Musculoskeletal symptoms are commonly reported with statin use. In clinical trials, about 12% of patients report myalgias or other muscle symptoms associated with statin use, a rate similar to placebo. The incidence of severe creatinine kinase (CK) elevations greater than ten times the upper limit of normal (10x ULN) is 0.2%, and rhabdomyolysis is exceedingly rare (0.03%).[9]

In the supplemental Safety Set, Dr. Chowdhury noted an apparent imbalance in TEAEs from the System Organ Classification (SOC) *Musculoskeletal and Connective Tissue Disorders* between the pitavastatin arms and placebo. Refer to her review for details, including narratives

[9] Harsh VG et al. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J.* 2014;168(1):6-15.

of all events. Table 7 summarizes these events. In my review of the full analysis set, summarized in Table 8, one additional patient in the placebo arm experienced a TEAE in this SOC, meaning that the imbalance in pitavastatin patients with events versus placebo was less pronounced.

Among the musculoskeletal TEAEs in the randomized trial, only one, the second occurrence of *Arthralgia* in Patient (b) (6) treated with pitavastatin 2 mg, resulted in interruption of study drug. The event resolved, the patient resumed study drug, and ultimately completed the study. The investigator assessed the events as possibly related.

One patient in the 2 mg arm experienced an AE of *Blood creatinine phosphokinase increased* (< 2x ULN) in the *Investigations* SOC, a finding of unclear clinical significance.

Table 7: TEAEs – Musculoskeletal and Connective Tissue Disorders (NK 104-4.01EU Supplemental Safety Set)

Arm	Placebo	1 mg	2 mg	4 mg	Total
N	19	20	24	19	82
Patients with at least one TEAE	0	2 (10%)	1 (4.2%)	1(5.3%)	4 (4.9%)
Total Events	0	2	2	2	6

Source: FDA Cross-Discipline Team Leader from dataset ADAE

Table 8: TEAEs – Musculoskeletal and Connective Tissue Disorders (NK 104-4.01EU Full Safety Set)

Arm	Placebo	1 mg	2 mg	4 mg	Total
N	27	26	27	26	106
Patients with at least one TEAE	1 (3.7%)	2 (7.7%)	1 (3.7%)	1 (3.8%)	5 (4.7%)
Total Events	1	2	2	2	7

Source: FDA Cross-Discipline Team Leader from dataset ADAE

Musculoskeletal events in the open-label extension were consistent with the randomized trial. From my analysis, 12 patients experienced 17 events in the Musculoskeletal and Connective Tissue Disorders SOC, including:

- 4 events of *Myalgia* in 3 patients
- 3 events of *Back pain* in 3 patients
- 2 events of *Pain in extremity* in 2 patients
- 2 events of *Muscle spasms* in 2 patients
- 2 events of *Arthralgia* in 2 patients

Most events resolved without action taken on the study drug, and none resulted in permanent discontinuation of study drug. Refer to Dr. Chowdhury's review for representative narratives.

Musculoskeletal-related laboratory findings were unremarkable. In my analysis of the full Safety Set of the randomized trial, one patient assigned to pitavastatin 1 mg daily experienced creatinine kinase (CK) $\geq$ 3x ULN, but < 5x ULN. In the Full Safety Set of the open-label extension, 32 patients experienced an elevation in CK greater than or equal to the upper limit of normal, and one patient experienced CK $\geq$ 3x but < 5x ULN. Overall, these mild elevations of CK do not represent a clinically significant finding. Dr. Chowdhury previously reviewed these narratives in her review.

Musculoskeletal adverse reactions are a known safety issue with statins, including pitavastatin. In the two pediatric studies, no patients experienced a clinical syndrome consistent with a severe musculoskeletal reaction, such as myopathy or rhabdomyolysis. No patients experienced a musculoskeletal TEAE requiring permanent discontinuation of study drug, even though some case narratives suggested the reported AEs were at least possibly related to study drug. The findings are consistent with the known safety profile of pitavastatin in adults and statins overall.

Hepatic Events
Dr. Chowdhury did not identify any new safety issues in her review of liver-related TEAEs and laboratory values. Liver enzyme elevations are described in current labeling. Overall, about 1 to 3% of patients treated with statins experience AST/ALT elevations greater than 3x ULN per approved statin labeling.

One patient in the randomized trial experienced an AST elevation < 2x ULN categorized as a TEAE. In the open-label extension, one patient experienced an ALT elevation < 3x ULN, and one patient experienced an ALT elevation > 3x but < 5x ULN, categorized as TEAEs. Dr. Chowdhury included patient narratives for these cases in her review. I did not identify any additional hepatic TEAEs in my review of the full Safety Sets of the randomized trial or the open-label extension. I did not identify any additional AST/ALT elevations $\geq$ 3x ULN in my review of the full laboratory databases of these studies.

Other Safety Issues
In both the randomized, controlled trial and the open-label extension, there were no clinically significant increases of shifts of any Laboratory or Vital signs parameters. Refer to Dr. Chowdhury's review for details and additional safety analyses.

Growth and Development
Dr. Chowdhury concluded that there was no evidence of adverse effects on growth or development in either the clinical trial or the open-label extension. The applicant provided tables summarizing height and weight velocity and *z*-scores calculated using US Centers for Disease Control normative data. Mean annual height and weight velocity *z*-scores were near zero, indicating that growth in the study population was comparable to CDC normative data. Shift tables summarizing Tanner Stage data demonstrated no changes in any treatment arm in the 12-week randomized, controlled trial.

Safety Summary

In summary, these data did not identify any new safety concerns with pitavastatin. The findings were consistent with the know safety profile described in current labeling. I agree with Dr. Chowdhury's recommendation that the labeling state only that the safety findings in pediatric patients with HeFH were consistent with those observed in the adult population.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

DMEP consulted the Division of Pediatric and Maternal Health (DPMH) to review the applicant's evaluation of growth (height and weight) and sexual maturation. The DPMH reviewer, Dr. Elizabeth Durmowicz, also reviewed the published literature for long-term data on growth and pubertal development in pediatric patients exposed to statins since DPMH's previous review in 2015.

DPMH concluded that the applicant's analyses did not provide meaningful information due to limitations of the data collection. For the current dataset, DPMH recommended analyzing growth data (including weight and height *z*-scores at 12 months) among patients who were Tanner Stage I at baseline from the full analysis set, including patients down to age 6. The applicant provided these analyses, and the results were reassuring, as pediatric growth was comparable to normative data. Refer to Section 8 – *Safety: Growth and Development* for additional details.

Refer to the Efficacy and Safety Sections of this review for discussion of the scientific data.

DMEP presented the application to the Pediatric Exclusivity Board on March 27, 2019. The board agreed that the applicant fulfilled the terms of the Written Request. See the Pediatric Exclusivity Determination Checklist for additional information.

DMEP presented the application to the Pediatric Review Committee (PeRC) on April 10, 2019. The PeRC agreed with the proposed indication for pediatric patients aged 8 and older with HeFH, and labeling, including the revised starting dose recommended by the Division of 2 mg once daily pending final conclusions from the safety review.

11. Other Relevant Regulatory Issues

An OSI audit was not requested based on the rationale that there was no specific efficacy or safety concern after review of site-specific data. There were no data integrity issues and no issues with respect to monitoring of the clinical trials.

Refer to Section 10 for discussion of pediatric exclusivity.

12. Labeling

Prescribing Information
The applicant and the Division have agreed on labeling changes related to this supplement.

- INDICATIONS AND USAGE:
  - Expands the indications for LIVALO to include use as an adjunctive therapy to diet in Pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated TC, LDL-C, and Apo B.
- DOSAGE AND ADMINISTRATION:
  - Recommended pediatric starting dose is 2 mg once daily, and maximum recommended dose is 4 mg once daily
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - No changes to Contraindications or Warnings and Precautions
  - ADVERSE REACTION will state that the safety profile in pediatric patients with HeFH is similar to that observed in the adult population
- USE IN SPECIFIC POPULATION:
  - Briefly describes the clinical program to support the new indication
- CLINICAL STUDIES section:
  - Describes the clinical program to support the new indication, including a statement that LIVALO significantly reduced plasma LDL-C, non-HDL-C, TC, and Apo-B compared to placebo in the randomized trial, and that the effect was dose-dependent. Section clarifies that there was no dose-dependent improvement in HDL-C or fasting TG. Efficacy results are presented in a table.

Other Labeling
Not applicable

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Not applicable

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Not applicable

14. Recommended Comments to the Applicant

None

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/

JOHN M SHARRETTS
05/16/2019 12:55:16 PM

WILLIAM H CHONG
05/16/2019 02:58:38 PM
I agree with Dr. Sharretts' assessment. This memorandum also serves as the Division's Decisional memorandum.