Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 022363, Efficacy Supplement-015
Link to EDR	\\CDSESUB1\evsprod\NDA022363\022363.enx
Submission Date	November 16, 2018
Submission Type	Priority
Brand Name	Livalo®
Generic Name	Pitavastatin
Dosage Form and Strength	Film-coated tablet 1 mg, 2 mg, 4 mg
Route of Administration	Oral
Proposed Indication	(b) (4)
Applicant	Kowa Pharmaceuticals America, Inc.
Clinical Pharmacology Reviewer	Shalini Wickramaratne Senarath Yapa, Ph.D.
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1. Executive Summary

The Applicant, Kowa Pharmaceuticals America, Inc., submitted an efficacy supplement (S-015) for pitavastatin (Livalo®) (NDA 022363, Sequence No. 0145) seeking approval for the following pediatric indication, the treatment of heterozygous familial hypercholesterolemia (HeFH) in children ≥ 8 years to ≤ 16 years of age. The pediatric studies were conducted to satisfy a Written Request (WR) (refer to Appendix I) issued by the Agency for Livalo® to qualify for Pediatric Exclusivity in the United States.

To fulfill the clinical study requirements specified in the WR, the Applicant assessed the efficacy, safety, and pharmacokinetics (PK) of pitavastatin in a subset of the patient population from two previously conducted Phase 3 studies (Studies NK-104-4.01EU and NK-104-4.02EU). The Clinical Pharmacology review focuses on results from Study NK-104-4.01EU, a randomized, double-blind, placebo-controlled study in children and adolescent patients aged ≥ 6 years to < 17 years with high-risk hyperlipidemia, excluding patients with homozygous familial hypercholesterolemia. Patients were eligible to enroll if they had a fasting low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL or LDL-C ≥130 mg/dL in the presence of additional risk factors. To meet the requirements of the WR, the characteristics of the subset of patient population was patients aged ≥ 8 years to ≤ 16 years with HeFH having either a baseline LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL with additional cardiovascular (CV) risk factors. Patients received either pitavastatin 1 mg, 2 mg, 4 mg, or matching placebo once-daily for 12 weeks.

The sample size of the subset of the patient population was 82 patients, and despite the Applicant's efforts to enroll patients with adequate representation from ethnic and racial minority groups, a majority of the patient population were Caucasian and of non-Hispanic or Latino ethnicity.

Pharmacokinetics of pitavastatin and pitavastatin lactone was assessed at trough and 1 hr post-dose at either Week 8 or 12. A dose-dependent increase in plasma concentrations of pitavastatin and pitavastatin lactone was observed at trough and 1 hr post-dose in children and adolescents with HeFH.

Lipid profiles were measured over the 12-week treatment period. At Week 12, a dose-dependent reduction in LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and apolipoprotein B (Apo B) was observed for pitavastatin 1 mg, 2 mg, and 4 mg in children and adolescents with HeFH. The primary efficacy endpoint of the study was the mean percent change in LDL-C from baseline to Week 12 for each treatment group compared to placebo. The differences in least squares (LS) mean percent change in LDL-C between each pitavastatin dose group compared to placebo was statistically significant at Week 12 in children and adolescents with HeFH. Similar results were observed for non-HDL-C, TC, and Apo B. At Week 12, no dose-dependent improvements were observed for high-density lipoprotein cholesterol (HDL-C) and fasting triglyceride (TG) for pitavastatin 1 mg, 2 mg, and 4 mg in children and adolescents with HeFH.

The Applicant fulfilled the requirements specified in the WR, therefore, pediatric exclusivity for Livalo® for the treatment of HeFH in children ≥ 8 years to ≤ 16 years of age will be granted.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the clinical pharmacology information submitted for NDA 022363, Supplement 015 and recommends approval of Livalo® for the treatment of HeFH in children and adolescents ≥ 8 years to ≤ 16 years of age. Recommendations and comments are shown below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Treatment with pitavastatin 1 mg, 2 mg, and 4 mg administered once-daily demonstrated a statistically significant reduction in LDL-C compared to placebo at Week 12 in children and adolescents with HeFH. For further details refer to the Clinical and Statistical reviews by Dr. Chowdhury and Dr. Crackel, respectively. A dose-dependent increase in plasma concentrations of pitavastatin and pitavastatin lactone was observed at trough and 1 hr post-dose at steady-state following administration of pitavastatin 1 mg, 2 mg, and 4 mg in children and adolescents with HeFH.
General dosing instructions	In children and adolescents ≥ 8 years to ≤ 16 years of age with HeFH the proposed dose range is 1 to 4 mg orally once daily at any time of the day with or without food. The proposed recommended starting dose (b) (4) [redacted] The proposed doses and dosing regimen is acceptable from a Clinical Pharmacology perspective.
Labeling	The effectiveness of Livalo® for treatment of HeFH in children and adolescents ≥ 8 years to ≤ 16 years of age has been demonstrated, therefore, the pediatric indication is granted. The clinical pharmacology sections of the label are acceptable.

1.2 Post-Marketing Requirements and Commitments

None.

2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Pitavastatin is a competitive inhibitor of HMG-CoA reductase, which is a rate-determining enzyme involved in the biosynthesis of cholesterol, and thereby inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to the liver is accelerated and plasma TC decreases. Additionally, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low-density lipoproteins[1].

Pitavastatin (Livalo®) has been marketed in the US since August 3rd, 2009, for the treatment of adult patients with primary hyperlipidemia and mixed dyslipidemia.

For pitavastatin, both peak concentrations (C_{max}) and systemic exposure ($AUC_{0\text{-}inf}$) increased in an approximately dose-proportional manner for single doses of Livalo® from 1 to 24 mg once daily. Pitavastatin peak plasma concentrations are achieved approximately 1 hour after oral administration. Pitavastatin exposure (AUC) was not significantly reduced with a high fat meal, however C_{max} decreased by 43%. The principal route of pitavastatin metabolism is glucuronidation via liver UGTs which result in formation of the major metabolite in human plasma, pitavastatin lactone. Minimal metabolism occurs by the CYP450 enzymes. The mean plasma elimination half-life of pitavastatin is approximately 12 hrs. In patients with moderate renal impairment and end-stage renal disease on hemodialysis, pitavastatin exposure ($AUC_{0\text{-}inf}$) is 102% and 86% higher, respectively, and C_{max} is 60% and 40% higher, respectively, than in healthy subjects. In patients with severe renal impairment not on hemodialysis, $AUC_{0\text{-}inf}$ and C_{max} was 36% and 18% higher, respectively, than in healthy subjects. The ratio of pitavastatin C_{max} and $AUC_{0\text{-}inf}$ between patients with moderate hepatic impairment and healthy subjects was 2.7 and 3.8, respectively. The ratio of pitavastatin C_{max} and $AUC_{0\text{-}inf}$ between patients with mild hepatic impairment and healthy subjects was 1.3 and 1.6, respectively[1].

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

For the treatment of primary hyperlipidemia and mixed dyslipidemia in adult patients, the recommended dose of Livalo® is 1 to 4 mg once daily at any time of the day with or without food. The recommended starting dose is 2 mg and the maximum dose is 4 mg. The starting and maintenance doses of Livalo® should be individualized according to patient characteristics, such as goal of therapy and response. For patients with moderate and severe renal impairment, and end-stage renal disease on hemodialysis, the recommended starting dose of Livalo® is 1 mg once daily and the maximum dose is 2 mg once daily[1].

[1] Livalo® (pitavastatin) tablet, US Prescribing Information, Revised: 11/2016

The proposed dose in children and adolescents ≥ 8 years to ≤ 16 years of age with HeFH is 1 to 4 mg orally once daily (b) (4) of the day with or without food. The proposed starting dose and maximum dose is (b) (4) mg and 4 mg, respectively.

2.2.2 Therapeutic Individualization

The Livalo® USPI label specifies that doses of Livalo® should be individualized according to patient characteristics, such as goal of therapy and response. Additionally, after initiation or upon titration of Livalo®, lipid levels should be analyzed after 4 weeks and the dosage adjusted accordingly. This dosing information is applicable to children and adolescents patients ≥ 8 years to ≤ 16 years of age with HeFH.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Proposed labeling by the Applicant (underlined text indicates text to be included):

(b) (4)

8.4 Pediatric Use

(b) (4)

12.3 Pharmacokinetics

(b) (4)

14 CLINICAL STUDIES

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)	19 20 24 19	(b) (4)					

Recommended labeling language by the Reviewer (~~strikeout~~ text indicates text to be deleted and underline text indicates text to be included)

In Section 1 (Indications and Usage) of the revised Livalo® USPI label, the Applicant (b) (4) (b) (4)

12.3 Pharmacokinetics

(b) (4) a dose-dependent increase in pitavastatin plasma concentrations at 1 hour post dose.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Regulatory Background

This submission is under the Priority Review since the studies were conducted to fulfill the WR issued by the Agency (refer to Appendix I). The Applicant is pursuing 6 months of pediatric exclusivity for the proposed pediatric indication based on the new clinical investigations.

To fulfill the clinical study requirements specified in the Agency's WR (Table 1), the Applicant relied on data from two clinical studies that were previously conducted in the EU:

- Study NK-104-4.01EU (Phase 3) was a randomized, double-blind, placebo-controlled study to assess the safety, lipid-lowering benefit, and PK of pitavastatin 1 mg, 2 mg, and 4 mg administered once-daily over 12 weeks in pediatric patients (≥ 6 years and < 17 years of age) with a high risk of CV disease
- Study NK-104-4.02EU (Phase 3) was an open-label extension study to assess the safety and lipid-lowering benefit of pitavastatin 1 mg, 2 mg, and 4 mg administered once daily over 52 weeks of treatment in a pediatric population (≥ 6 years and < 17 years of age) with a high risk of CV disease

In order to fulfill the requirements of the WR, the efficacy, safety, and PK of pitavastatin were assessed in a subset of the patient population from Studies NK-104-4.01EU and NK-104-4.02EU.

The subset of the patient population from Studies NK-104-4.01EU and NK-104-4.02EU were as follows:

- HeFH
- Age ≥8 to 16 years (inclusive)
- Baseline LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with additional CV risk factors

The Clinical Pharmacology review reports the PK and efficacy/pharmacodynamic (PD) results in the pediatric patient population (≥8 to ≤16 years) with HeFH from Study NK-104-4.01EU. Refer to the Clinical Review by Dr. Chowdhury for further details on Study NK-104-4.02EU.

Table 1: Summary of Clinical Study Requirements Outlined in the WR (refer to Appendix 1)

Study	Design	Population	Dosing Regimen/Treatment	Objective(s)/Endpoint(s)
Study 1	Double-blind, randomized, placebo-controlled, 12-week treatment period Randomized to pitavastatin or placebo (3:1 ratio) stratified by age (≥10 years vs. younger) and baseline LDL-C in each dose group Adequate representation of children of ethnic and racial minorities or justification as to why this was unsuccessful	Pediatric patients ≥8 to 16 years (inclusive) of age with HeFH and either LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL with additional CV risk factors n=at least 80 evaluable patients at the efficacy endpoint (Week 12)	3 dose levels of pitavastatin administered orally, once-daily Pitavastatin tablets; Use an age-appropriate formulation	Primary Objective: Efficacy Efficacy Endpoint: • Primary: Mean percent (%) change in LDL-C from baseline to Week 12 for each treatment group compared to placebo • Secondary: -% change in LDL-C from baseline over 12 weeks (Week 4, 8, 12) -Change in non-HDL-C, TC, HDL-C, fasting TG, Apo B from baseline to Week 12 -% change in HDL-C, non-HDL-C, total cholesterol, fasting TG, ApoB from baseline over 12 weeks PK Endpoint: Pitavastatin and pitavastatin lactone concentrations at trough and 1-hour post-dose for each dose level Safety Endpoints
Study 2	52-week, open-label, safety study	Pediatric patients ≥8 to 16 years (inclusive) of age with HeFH and	All patients will be assigned to the lowest dose of pitavastatin studied.	Primary Objective: Safety, tolerability

	Adequate representation of children of ethnic and racial minorities or justification as to why this was unsuccessful	either LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL with additional CV risk factors n=at least 80 evaluable patients Patients who complete Study 1 should be encouraged to enroll in this study and additional patients may be directly enrolled into the study	During the study, the dose of pitavastatin may be up-titrated based on clinically appropriate, protocol defined LDL-C thresholds Pitavastatin tablets, orally, once-daily; Use an age appropriate formulation	

Source: IND 060492 NDA 022363, Written Request – Amendment 1

3.2 Clinical Pharmacology Review Questions

3.2.1 What is the pharmacokinetics of pitavastatin and pitavastatin lactone in children and adolescents ≥ 8 years to ≤ 16 years of age with heterozygous familial hypercholesterolemia?

The PK of pitavastatin and pitavastatin lactone was characterized in Study NK-104-4.01EU.

Study NK-104-4.01EU was a randomized, double-blind, placebo-controlled study in children and adolescent patients aged ≥6 years and <17 years of age with high-risk hyperlipidemia, excluding patients with homozygous familial hypercholesterolemia. Patients were eligible for the study if they had a fasting LDL-C levels ≥160 mg/dL or LDL-C ≥130 mg/dL in the presence of additional risk factors (male, family history of premature CV disease, other lipid abnormalities, and type 2 diabetes). Patients were assigned to 1 of the following groups, pitavastatin 1 mg once-daily or matching placebo, pitavastatin 2 mg once-daily or matching placebo, or pitavastatin 4 mg once-daily or matching placebo. Within each dose group, patients were randomly assigned in a 3:1 ratio to pitavastatin or placebo. Allocation of treatment was stratified based on age (≥6 years and <10 years, ≥10 years and <17 years) and baseline LDL-C (≥130 mg/dL and <160 mg/dL, ≥160 mg/dL) for each dose group. The duration of the treatment period was 12-weeks. Patients in the pitavastatin 4 mg group received pitavastatin 2 mg (or placebo) for the first 4 weeks followed by pitavastatin 4 mg (or placebo) for the remaining 8 weeks. Pitavastatin tablets or matching placebo was taken orally, with or without food, in the morning.

Blood samples to quantify pitavastatin and pitavastatin lactone plasma concentrations were collected at trough and 1 hr post-dose at either Week 8 or Week 12, depending on patient

availability. Given the elimination half-life of pitavastatin in adults is ~12 hr[2], the PK of pitavastatin and pitavastatin lactone at Week 8 or 12 would be at steady-state conditions. Refer to Appendix II for further details on the bioanalytical method for measurement of pitavastatin and pitavastatin lactone concentrations in human plasma.

To fulfill the requirements of the WR, the Applicant assessed the PK of pitavastatin and pitavastatin lactone from a subset of the patient population in Study NK-104-4.01EU:

- HeFH
- Age ≥8 to 16 years (inclusive)
- Baseline LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with additional CV risk factors

The study analysis population for this subset of patient population is presented in Appendix III.

Distribution of race and ethnicity for patients in the Randomized Set is presented in Table 2. A requirement of the WR was that the study had adequate representation of children of ethnic and racial minorities. The Applicant reports that patient recruitment occurred at 9 clinics in 6 European countries in order to encourage diverse enrollment with regard to race and ethnicity. Four of the clinics were in capital cities (most ethnically diverse part of the countries) and another clinic was in a region of known ethnic diversity. Additionally, two of the countries had national screening programs for FH. Despite this effort, a majority of the patient population were Caucasian and of non-Hispanic or Latino ethnicity.

Table 2: Race and Ethnicity Demographics (Randomized Set)

	Pitavastatin 1 mg n=20	Pitavastatin 2 mg n=24	Pitavastatin 4 mg n=19	Placebo n=19	Total n=82
Race – n (%)					
White/Caucasian	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/African or African American	0 (0)	1 (4.2)	0 (0)	0 (0)	1 (1.2)
Multiple Races	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity – n (%)					
Hispanic or Latino	2 (10.0)	3 (12.5)	1 (5.3)	1 (5.3)	7 (8.5)
Not Hispanic or Latino	18 (90.0)	21 (87.5)	18 (94.7)	18 (94.7)	75 (91.5)

Source: Supplemental Clinical Study Report NK-104-4.01EU, Data summarized from Table 5, Page 31

Table 3 presents the mean plasma concentrations of pitavastatin at trough and 1 hr post-dose (collected at either Week 8 or Week 12) for the pitavastatin dose groups in children and adolescents with HeFH. Figure 1 shows the mean plasma concentration of pitavastatin versus pitavastatin dose at the 1 hr post-dose time point. The data shows a dose-dependent increase in plasma concentrations of pitavastatin in children and adolescents with HeFH.

[2] Livalo® (pitavastatin) tablet, US Prescribing Information, Revised: 11/2016

Table 3: Summary of 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

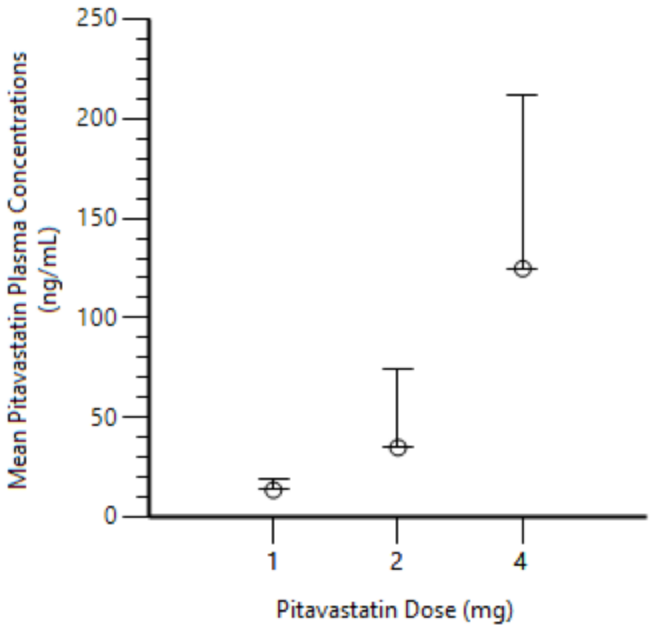

Figure 1: Mean (SD) plasma concentration of pitavastatin at 1 hour post-dose for pitavastatin 1 mg, 2 mg, and 4 mg

Note: Standard deviation is presented as upper error bars

Source: Supplemental Clinical Study Report NK-104-4.01EU, Plot generated by the Reviewer from data presented in Table 26, Page 57

Mean plasma concentrations of pitavastatin lactone at trough and 1 hr post-dose (collected at either Week 8 or Week 12) for the pitavastatin dose groups in children and adolescents with HeFH is presented in Table 4. Figure 2 shows the mean plasma concentration of pitavastatin lactone versus

pitavastatin dose at the 1 hr post-dose time point. The data shows a dose-dependent increase in plasma concentrations of pitavastatin lactone in children and adolescents with HeFH.

Table 4: Summary of 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

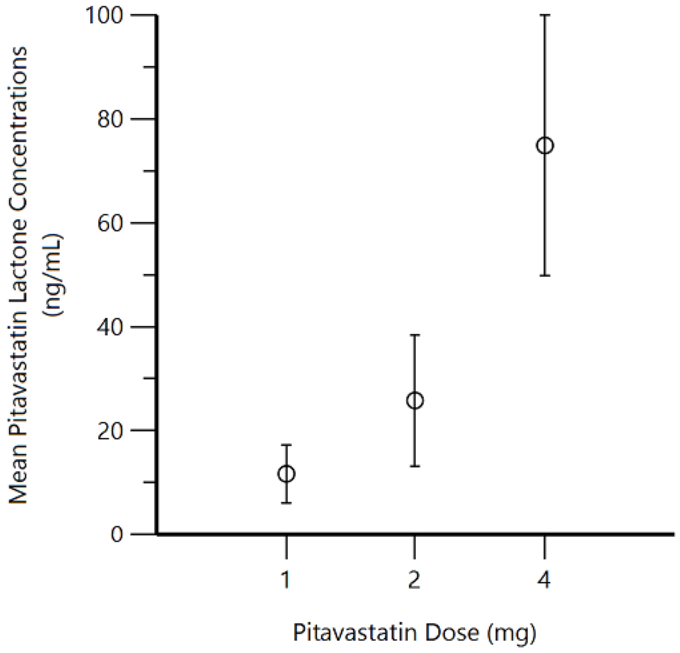

Figure 2: Mean (SD) plasma concentration of pitavastatin lactone at 1 hour post-dose for pitavastatin 1 mg, 2 mg, and 4 mg

Source: Supplemental Clinical Study Report NK-104-4.01EU, Plot generated by the Reviewer from data presented in Table 27, Page 58

3.2.2 What is the efficacy/pharmacodynamics of pitavastatin in children and adolescents ≥ 8 years to ≤ 16 years of age with heterozygous familial hypercholesterolemia?

Lipid profiles for LDL-C, non-HDL-C, TC, Apo B, HDL-C, and fasting TG were assessed following administration of pitavastatin 1 mg, 2 mg, 4 mg or placebo once-daily over the 12-week

treatment period in Study NK-104.4.01EU. Discussed below are the efficacy/PD results in children and adolescents with HeFH reported by the Applicant; for Agency's interpretations of these data refer to the Clinical review by Dr. Chowdhury.

LDL-C

Mean percent change in LDL-C from baseline over the 12 weeks of treatment is shown in Figure 3. Treatment with pitavastatin 1 mg, 2 mg, and 4 mg resulted in a greater percent reduction in LDL-C compared to placebo at Weeks 4, 8, and 12. At each visit, pitavastatin dose groups (1 mg, 2 mg, 4 mg) showed a statistically significant LDL-C reduction versus placebo.

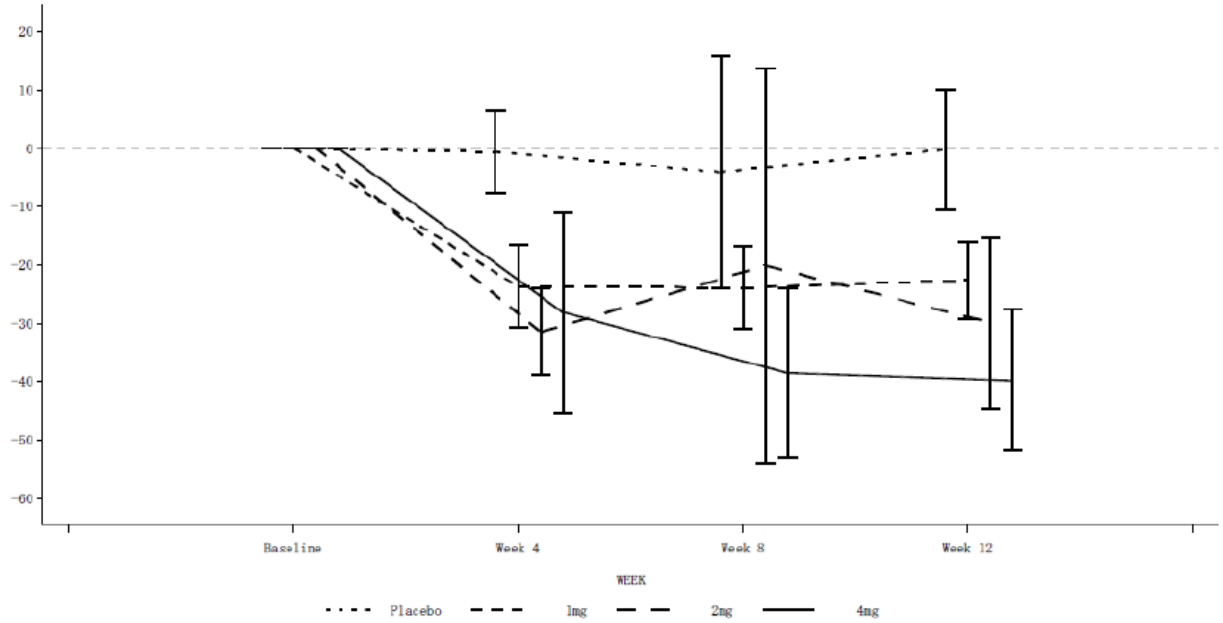

Figure 3: Mean Percent Change (SD) from Baseline Over 12 Weeks of Treatment in LDL-C (mg/dL) for Pitavastatin 1 mg, 2 mg, 4 mg, and Placebo (Full Analysis Set)

y-axis represents percent change in mean LDL-C where all dose groups start at 0% change at baseline

Source: Supplemental Clinical Study Report NK-104-4.01EU, Figure 1, Page 40

The primary efficacy endpoint of the study was the mean percent change in LDL-C from baseline to Week 12 for each treatment group compared to placebo. Table 5 presents the percent change in LDL-C from baseline to Week 12; the data shows a dose-dependent reduction in LDL-C for pitavastatin 1 mg, 2 mg, and 4 mg. The differences in LS mean percent change in LDL-C between each pitavastatin dose group compared to placebo was statistically significant indicating an overall dose-dependent reduction in LDL-C for all pitavastatin dose groups at Week 12 in children and adolescent patients with HeFH.

Table 5: Percent Change from Baseline to Week 12 in LDL-C (mg/dL) (Full Analysis Set)

Treatment	n[a]	Baseline[b] Mean (SD)	Percent Change From Baseline[c, d]		
			LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	20	222.7 (38.63)	-16.5 (6.13)	(-28.5,-4.5)	0.007
Pitavastatin 2 mg	24	226.9 (34.18)	-22.3 (6.46)	(-35.0,-9.6)	0.001
Pitavastatin 4 mg	19	241.6 (50.76)	-33.4 (4.22)	(-41.7,-25.1)	<0.001
Placebo	19	250.4 (72.21)	0.4 (4.04)	(-7.5,8.3)	0.917
			Difference[c, d]		
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

Source: Post-text Table 14.2.1

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; LDL-C=low-density lipoprotein cholesterol; LS=least squares; SD=standard deviation; SE=standard error; vs=versus.

[a] Only patients with non-missing baseline endpoints were included.

[b] Baseline was defined as the average of the valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at the Week -1 or Week 0 visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, the last valid lipid value prior to the first dose of randomized study drug was used as baseline.

[c] Subjects who discontinued treatment by 12 Weeks were imputed by control-based pattern imputation, whereby the missing response variables obey the distribution of the response variables in the placebo group.

[d] LS means, SE, CI, and p-values were from an ANCOVA model with percent changes in LDL-C as dependent variable, treatment as factor, and baseline LDL-C and age as covariates.

Source: Supplemental Clinical Study Report NK-104-4.01EU, Table 9, Page 36

Non-HDL-C, TC, Apo B

Percent change from baseline to Week 12 for non-HDL-C, TC, and Apo B is presented in Table 6, Table 7, and Table 8, respectively. A dose-dependent reduction in non-HDL-C, TC, and Apo B was observed for pitavastatin 1 mg, 2 mg, and 4 mg. For non-HDL-C, the differences in LS mean percent change between each pitavastatin dose group versus placebo at Week 12 was statistically significant. For TC, the differences in LS mean percent change between each pitavastatin dose group versus placebo at Week 12 was statistically significant. Similarly, for Apo B, the differences in LS mean percent change between each pitavastatin dose group versus placebo at Week 12 was statistically significant. Therefore, for each pitavastatin dose group, the dose-dependent improvements in non-HDL-C, TC, and Apo B at Week 12 was statistically significant relative to placebo in children and adolescents with HeFH.

Table 6: Percent Change from Baseline to Week 12 in non-HDL-C (mg/dL) (Full Analysis Set)

Treatment	n[a]	Baseline[b] Mean (SD)	Percent Change From Baseline[c, d]		
			LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	20	239.3 (40.47)	-17.3 (5.52)	(-28.1,-6.5)	0.002
Pitavastatin 2 mg	24	246.9 (36.20)	-22.8 (5.74)	(-34.1,-11.6)	<0.001
Pitavastatin 4 mg	19	257.2 (51.27)	-31.1 (3.91)	(-38.8,-23.5)	<0.001
Placebo	19	267.6 (74.54)	0.7 (3.75)	(-6.6,8.1)	0.844
			Difference[c, d]		
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

Source: Post-text Table 14.2.3

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares; non-HDL-C=non-high-density lipoprotein cholesterol, SD=standard deviation; SE=standard error; vs.=versus.

[a] Only patients with non-missing baseline endpoints were included.

[b] Baseline was defined as the average of the valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at the Week -1 or Week 0 visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, the last valid lipid value prior to the first dose of randomized study drug was used as baseline.

[c] Subjects who discontinued treatment by 12 Weeks were imputed by control-based pattern imputation, whereby the missing response variable obeys the distribution of the response variable in the placebo group.

[d] LS means, SE, CI, and p-values were from an ANCOVA model with percent changes in non-HDL-C as dependent variable, treatment as factor, and baseline non-HDL-C and age as covariates.

Source: Supplemental Clinical Study Report NK-104-4.01EU, Table 15, Page 43

Table 7: Percent Change from Baseline to Week 12 in TC (mg/dL) (Full Analysis Set)

Treatment	n[a]	Baseline[b] Mean (SD)	Percent Change From Baseline[c, d]		
			LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	20	293.2 (42.36)	-13.6 (4.70)	(-22.8,-4.4)	0.004
Pitavastatin 2 mg	24	299.5 (34.64)	-19.9 (4.98)	(-29.6,-10.1)	<0.001
Pitavastatin 4 mg	19	308.4 (51.00)	-25.9 (3.27)	(-32.4,-19.5)	<0.001
Placebo	19	321.2 (70.39)	0.5 (3.13)	(-5.7,6.6)	0.881
			Difference[c, d]		
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

Source: Post-text Table 14.2.4

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; TC=total cholesterol; LS=least squares; SD=standard deviation; SE=standard error; vs.=versus.

[a] Only patients with non-missing baseline endpoints were included.

[b] Baseline was defined as the average of the valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at the Week -1 or Week 0 visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, the last valid lipid value prior to the first dose of randomized study drug was used as baseline.

[c] Subjects who discontinued treatment by 12 Weeks were imputed by control-based pattern imputation, whereby the missing response variable obeys the distribution of the response variable in the placebo group.

[d] LS means, SE, CI, and p-values were from an ANCOVA model with percent changes in TC as dependent variable, treatment as factor, and baseline TC and age as covariates.

Source: Supplemental Clinical Study Report NK-104-4.01EU, Table 17, Page 45

Table 8: Percent Change from Baseline to Week 12 in Apo B (mg/dL) (Full Analysis Set)

Treatment	n[a]	Baseline[b] Mean (SD)	Percent Change From Baseline[c, d]		
			LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	20	136.3 (20.00)	-15.7 (5.02)	-25.6,-5.9	0.002
Pitavastatin 2 mg	24	142.7 (22.74)	-18.1 (5.00)	-27.9,-8.3	<0.001
Pitavastatin 4 mg	19	144.2 (25.09)	-25.0 (3.88)	-32.6,-17.4	<0.001
Placebo	19	150.7 (36.68)	-1.0 (3.68)	-8.3,6.2	0.776
Treatment Comparison			**Difference[c, d]**		
			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

Source: Post-text Table 14.2.7.
Abbreviations: ANCOVA=analysis of covariance; Apo B=apolipoprotein B, CI=confidence interval; LS=least squares; SD=standard deviation; SE=standard error; vs.=versus.

[a] Only patients with non-missing baseline endpoints were included.
[b] Baseline was defined as the average of the valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at the Week -1 or Week 0 visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, the last valid lipid value prior to the first dose of randomized study drug was used as baseline.
[c] Subjects who discontinued treatment by 12 Weeks were imputed by control-based pattern imputation, whereby the missing response variable obeys the distribution of the response variable in the placebo group.
[d] LS means, SE, CI, and p-values were from an ANCOVA model with percent changes in Apo B as dependent variable, treatment as factor, and baseline Apo B and age as covariates.

Source: Supplemental Clinical Study Report NK-104-4.01EU, Table 21, Page 49

HDL-C and Fasting TG

Percent change from baseline to Week 12 for HDL-C and fasting TG are presented Table 9 and Table 10, respectively. No dose-dependent improvement in HDL-C and fasting TG was observed for pitavastatin 1 mg, 2 mg, and 4 mg. The differences in LS mean percent change in HDL-C and fasting TG between each pitavastatin dose group versus placebo at Week 12 was not statistically significant in the children and adolescent with HeFH.

Table 9: Percent Change from Baseline to Week 12 in HDL-C (mg/dL) (Full Analysis Set)

Treatment	n[a]	Baseline[b] Mean (SD)	Percent Change From Baseline[c, d]		
			LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	20	54.0 (13.99)	5.7 (4.72)	(-3.6,14.9)	0.229
Pitavastatin 2 mg	24	52.6 (12.44)	-2.8 (4.24)	(-11.1,5.5)	0.515
Pitavastatin 4 mg	19	51.2 (8.22)	-1.6 (3.79)	(-9.0,5.8)	0.670
Placebo	19	53.6 (10.94)	-1.0 (3.56)	(-7.9,6.0)	0.786
			Difference[c, d]		
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

Source: Post-text Table 14.2.2
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; HDL-C=high-density lipoprotein cholesterol, LS=least squares; SD=standard deviation; SE=standard error; vs.=versus.

[a] Only patients with non-missing baseline endpoints were included.
[b] Baseline was defined as the average of the valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at the Week -1 or Week 0 visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, the last valid lipid value prior to the first dose of randomized study drug was used as baseline.
[c] Subjects who discontinued treatment by 12 Weeks were imputed by control-based pattern imputation, whereby the missing response variable obeys the distribution of the response variable in the placebo group.
[d] LS means, SE, CI, and p-values were from an ANCOVA model with percent changes in HDL-C as dependent variable, treatment as factor, and baseline HDL-C and age as covariates.

Source: Supplemental Clinical Study Report NK-104-4.01EU, Table 13, Page 41

Table 10: Percent Change from Baseline to Week 12 in Fasting TG (mg/dL) (Full Analysis Set)

Treatment	n[a]	Baseline[b] Mean (SD)	Percent Change From Baseline[c, d]		
			LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	20	83.2 (28.64)	-4.3 (13.48)	(-30.8,22.1)	0.748
Pitavastatin 2 mg	24	100.2 (52.41)	-3.0 (12.30)	(-27.1,21.1)	0.807
Pitavastatin 4 mg	19	77.8 (20.96)	-0.3 (11.06)	(-22.0,21.4)	0.979
Placebo	19	86.0 (33.38)	2.3 (10.21)	(-17.7,22.3)	0.821
			Difference[c, d]		
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

Source: Post-text Table 14.2.5.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares; SD=standard deviation; SE=standard error; TG=triglycerides, vs.=versus.

[a] Only patients with non-missing baseline endpoints were included.
[b] Baseline was defined as the average of the valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at the Week -1 or Week 0 visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, the last valid lipid value prior to the first dose of randomized study drug was used as baseline.
[c] Subjects who discontinued treatment by 12 Weeks were imputed by control-based pattern imputation, whereby the missing response variable obeys the distribution of the response variable in the placebo group.
[d] LS means, SE, CI, and p-values were from an ANCOVA model with percent changes in fasting TG as dependent variable, treatment as factor, and baseline TG and age as covariates.

Source: Supplemental Clinical Study Report Study NK-104-4.01EU, Table 19, Page 47

3.2.3 How does the pharmacokinetics and pharmacodynamics of Livalo® in children and adolescents ≥ 8 years to ≤ 16 years of age with heterozygous familial hypercholesterolemia compare to that in adults?

In children and adolescents aged ≥ 8 to ≤ 16 years with HeFH, a dose-dependent increase in plasma concentrations of pitavastatin was observed at steady-state (trough and 1 hr post-dose) for pitavastatin doses from 1 to 4 mg once-daily. In adults, pitavastatin exposure (C_{max}, $AUC_{0\text{-}inf}$) increased in an approximately dose-proportional manner for pitavastatin single doses from 1 to 24 mg once-daily[3]. In children and adolescents with HeFH, for LDL-C, the mean percent change from baseline to Week 12 was -16.5%, -22.3%, and -33.4% for pitavastatin 1 mg, 2 mg, and 4 mg, respectively, and the adjusted (for placebo) mean percent change from baseline to Week 12 was -16.9%, -22.7%, and -33.8% for pitavastatin 1 mg, 2 mg, and 4 mg, respectively. In adult patients with primary hypercholesterolemia, the adjusted mean percent change from baseline to Week 12 for LDL-C was -32%, -36%, and -43% for pitavastatin 1 mg, 2 mg, and 4 mg, respectively[3].

[3] Livalo® (pitavastatin) tablet, US Prescribing Information, Revised: 11/2016

4. Appendices

4.1 Appendix I: Written Request – Amendment 1

REVISED WRITTEN REQUEST, AMENDMENT 1

BACKGROUND:

There are two proposed pediatric studies. The first study (hereafter, Study 1), titled, "A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, 12-Week Study of Pitavastatin in High-Risk Hyperlipidemia in Childhood," proposes to investigate pitavastatin in the treatment of pediatric patients with high-risk hyperlipidemia (excluding homozygous hyperlipidemia). An open-label extension period, outlined in a separate protocol (hereafter, Study 2), titled, "A 52-Week Open-Label Extension and Safety Study of Pitavastatin in High-Risk Hyperlipidemia in Childhood," is proposed for patients completing the double-blind study as well as for additional eligible patients.

Familial hypercholesterolemia (FH) is a genetic disorder resulting in a deficient or defective LDL receptor associated with elevated cholesterol levels and premature atherosclerotic cardiovascular disease (ASCVD) with a frequency of about 1 in 300 to 500 in some populations.[1] Total cholesterol
concentrations in heterozygous FH patients (HeFH) are typically in the range of 350 to 550 mg/dL. Although ASCVD does not generally manifest until middle age in patients with HeFH, in addition to diet modifications, current guidelines advocate statin treatment in HeFH patients to be considered from age 8 years and up.[2,3,4] Neonates are not included in this written request because HeFH is not diagnosed at this age.

To obtain needed pediatric information on pitavastatin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  In order to further support the safety evaluation in children younger than 10 years of age, you should evaluate the toxicity of pitavastatin, a lipophilic statin, in juvenile animals of a pharmacologically relevant species exposed during the period of development appropriate for the intended pediatric age range. This toxicity study should evaluate the effects of pitavastatin on neurobehavioral endpoints (including learning and memory) and should include a complete histopathologic evaluation of the central and peripheral nervous systems

[1] 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 Hyperchoesterolemia. *J of Clinical Lipidology* 2011; 5, S1-S8.
[2] Goldberg AC, Toth P, 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. Journal of Clinical Lipidology 2011;5:S1-S8.
[3] Expert Panel on Ingetrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics 2011; 128; S213-S256.
[4] European Atherosclerosis Society Consensus Panel. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *European Heart Journal* 2015; 36: 2425-2437.

(including effects on myelination). The results of this study will inform whether your existing clinical trial in pediatric patients with HeFH included adequate safety monitoring, especially for patients younger than 10 years.

- *Clinical studies:*

Study 1: A double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of three dose levels of pitavastatin in pediatric patients who are 8 to 16 years (inclusive) of age with heterozygous familial hypercholesterolemia (HeFH). The trial must consist of a screening/washout period and a 12-week double-blind treatment period. Study endpoints must include safety, lipid-lowering, and PK profile of pitavastatin.

Study 2: A 52-week safety study of pitavastatin in pediatric patients who are 8 to 16 years (inclusive) of age with HeFH; blinding of treatment assignment is not required. This study will include patients who have completed Study 1, described above, but may also include eligible pediatric patients who were not enrolled in Study 1. All patients enrolled in the study will be assigned to treatment with the lowest dose of pitavastatin studied. During the study, the dose of pitavastatin may be up-titrated based on clinically appropriate, protocol-defined LDL-C thresholds.

- *Objective of Study 1*: The primary objective of this study is to compare the efficacy of pitavastatin to placebo with regard to percentage reduction in LDL-C from baseline to Week 12 in pediatric patients with HeFH.

- *Objective of Study 2*: The primary objective of this study is to assess the safety and tolerability of pitavastatin in pediatric patients with HeFH over a period of at least 52 weeks.

- *Patients to be Studied (Studies 1 & 2):*

    - Age group in which study(ies) will be performed: Patients ages ≥ 8 years to 16 years (inclusive). (Younger patients may be included in the same study if required by other global regulatory authorities.)

    - Number of patients to be studied: A sufficient number of patients must be randomized to Study 1 to provide for at least 80 evaluable patients (8 to 16 years, inclusive, with HeFH and either LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL with additional CV risk factors) at the efficacy endpoint (Week 12). Randomization to pitavastatin or placebo (in a 3:1 ratio) must be stratified by age (≥10 years vs. younger) and baseline LDL-C in each dose group. All patients who complete Study 1 should be encouraged to enroll in Study 2; additional patients (8 to 16 years, inclusive, with HeFH) may be enrolled directly into Study 2 to provide for at least 80 evaluable patients ≥ 8 years of age. A sufficient number of patients to characterize the safety in patients younger than 12 years of age must be enrolled.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - *Pharmacokinetic Endpoints (Study 1):*
    The pharmacokinetic endpoints for Study 1 must include pitavastatin and pitavastatin lactone concentrations at trough and 1-hour postdose at each dose level.

  - *Efficacy Endpoints (Study 1):*
    The primary efficacy endpoint for Study 1 will be the mean percent change in LDL-C from Baseline to Week 12 for each treatment group compared to placebo. Secondary endpoints must include the change in lipid and lipoprotein parameters from Baseline to Week 12 in non-HDL-C, total cholesterol, HDL-C, fasting triglycerides, and Apo B. Measures of compliance with diet and study medication must be assessed through dietary assessment and counts of unused study medication, respectively.

  - *Safety Endpoints (Study 1 and Study 2):*
    - Safety outcomes must include incidence and severity of adverse events, clinical laboratory measures (including assessment of liver-related chemistries such as ALT, AST, alkaline phosphatase, bilirubin, and albumin; creatine kinase; serum creatinine and urinalysis; adrenal, gonadal, and pituitary hormones), vital signs, and physical examiniation (including height, weight, and Tanner staging).
    - All adverse events must be monitored until symptom resolution or until the condition stabilizes.
    - A Data Monitoring Committee (DMC) must be included because of the possibility of rhabdomyolyis. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known Drug Safety concerns and monitoring:*
  Pitavastatin labeling includes a warning for the risk of myopathy/rhabdomyolysis and liver enzyme abnormalities. Effects on liver and muscle should be prospectively monitored by blood chemistries, as described above, at least every 4 weeks during Study 1 and at the following timepoints during Study 2: Baseline, Week 4, Week 8, Week 12, Week 16, Week 28, Week 40 and Week 52/Early Termination. The protocol must include stopping criteria relevant to these risks.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

    - *dosage form*: Tablet
    - *route of administration*: Oral
    - *regimen*: Once daily

      Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

    - you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
    - the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
    - you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1

  The primary null hypothesis is that each dose of pitavastatin is equal to placebo with respect to the primary endpoint, LDL-C change from baseline at Week 12. The alternative hypothesis is that each dose of pitavastatin and placebo are different with respect to the primary efficacy endpoint.

  The primary analysis population must be all patients randomized who have received at least 1 dose of the study drug. With respect to the primary efficacy analysis, we are interested in estimating the treatment effect based on the de facto (intent-to-treat) estimand, i.e., the difference in LDL-C change in all randomized patients regardless of adherence to treatment or use of rescue. You should include provisions to limit missing data through study design and education of investigators and patients, and conduct analyses using methods to account for missing data for the primary and key secondary efficacy analyses in a fashion consistent with what the measurements would have been, had they been collected. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, and these post-treatment data should be included in the primary analysis.

  Secondary efficacy objectives must include comparisons between each dose of pitavastatin and placebo with respect to the following parameters:

  - Percent change in LDL-C from baseline over 12 weeks of treatment (Week 4, Week 8, and Week 12)
  - Percent changes in HDL-C, non-HDL-C, total cholesterol, fasting triglycerides, and Apo B from baseline over 12 weeks of treatment

  A total sample size of 80 patients (age ≥ 8 years) should provide both sufficient safety follow-up and at least 90% power under the assumption that treatment difference=25% and standard deviation=15%.

  Sensitivity analyses should be included to study the limitations of the primary analysis. For each sensitivity analysis, you should describe what limitation(s) of the data or assumption(s) of the primary analysis are being evaluated and how the sensitivity analysis achieves this. We also expect sensitivity analyses to address the potential effect of missing data on the reliability of results regardless of the extent of the missing data. The use of LOCF is not appropriate for handling missing data because it relies on the strong, untestable, and implausible assumption that outcomes remain constant after

patients drop out and, as a single-imputation approach, it does not take into account the statistical uncertainty in the imputation process.

Study 2:

At least 80 patients (ages 8 to 16 years, inclusive, with HeFH) should be treated with pitavastatin in this 52-week, open-label safety study. Descriptive data must be provided for safety endpoints (see above). The analysis must also include a descriptive summary of the efficacy results by age group.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that pitavastatin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for

Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before November 30, 2018. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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/s/

MARY T THANH HAI
05/30/2018

4.2 Appendix II: Bioanalytical Method for Measurement of Pitavastatin and Pitavastatin Lactone in Human Plasma

Pitavastatin and pitavastatin lactone concentrations in human plasma were measured using a previously validated method which consisted of a liquid-liquid extraction by tert-butyl methyl ether followed by a liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis of the extracts. The validation of the LC-MS/MS method was reviewed by the Agency during the initial review cycle for NDA 022363 and therefore not discussed further in this review (for further details refer to the Clinical Pharmacology review by Dr. Lau dated July 17th, 2009).

All clinical samples for Study NK-104-4.01EU that were included in the PK Analysis Set were analyzed within validated stability periods. Further information about the validated long-term stability periods are outlined below:

- The validated long-term stability period for pitavastatin and pitavastatin lactone was up to 122 days and 364 days, respectively, at -80˚C (data submitted with this supplement)
- The validated long-term stability period for pitavastatin and pitavastatin lactone was demonstrated for 28 days at -20˚C (data reviewed during the initial review cycle). Some clinical study samples however were stored at -20˚C for more than 28 days (for 49 days). The Applicant conducted additional long-term stability assessments at -20˚C for 49, 61, and 66 days and the acceptance limits were not met for the specified durations (data submitted with this supplement). Therefore, the Applicant excluded clinical study samples that were stored for more than 28 days at -20˚C from the PK Analysis Set.

Analysis of clinical samples from Study NK-104-4.01EU for measurement of pitavastatin and pitavastatin lactone was performed using three quality control (QC) samples and in some runs diluted QC samples were also included; the accuracy and precision of the QC samples were within the acceptance limits. Pharmacokinetic samples were re-analyzed as part of the incurred sample reproducibility assessment, and results of the incurred sample reanalysis met the acceptance criteria.

4.3 Appendix III: Study NK-104-4.01EU, Study Analysis Population

Table AIII-1 presents the study analysis population for the subset of the patient population (HeFH, age ≥8 to 16 years (inclusive), baseline LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with additional CV risk factors) in Study NK-104-4.01EU. Reasons for excluding patients from the PK Analysis Set are as follows: placebo treatment, patient or parent refused blood draws for PK, not taking study drug day before the visit, not bringing study drug to the visit, subject not fasting.

Table AIII-1: Study Analysis Population

	Pitavastatin 1 mg n (%)	Pitavastatin 2 mg n (%)	Pitavastatin 4 mg n (%)	Placebo n (%)	Total n (%)
Randomized Set[a]	20 (100)	24 (100)	19 (100)	19 (100)	82 (100)
Completed the Study	20 (100)	24 (100)	19 (100)	19 (100)	82 (100)
Full Analysis Set[b]	20 (100)	24 (100)	19 (100)	19 (100)	82 (100)
PK Analysis Set[c]	16 (80)	15 (62.5)	17 (89.5)	0 (0)	48 (58.5)

[a] Includes all patients randomized in the study

[b] Includes all randomized patients who received at least 1 dose of study drug and had a baseline lipid measurement and at least 1 valid post-baseline lipid measurement

[c] Includes all randomized patients who received at least 1 dose of study drug and had at least 1 valid plasma drug concentration

Source: Supplemental Clinical Study Report NK-104-4.01EU, Data obtained from Table 3 and 4, Page 29-30

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