CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022363
Priority or Standard	Priority
Submit Date(s)	11/16/2018
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Division/Office	DMEP/ODEII
Reviewer Name(s)	Primary Reviewer: Iffat Nasrin Chowdhury, MD Team Leader: John Sharretts, MD
Established/Proper Name	Pitavastatin
Trade Name	Livalo
Applicant	Kowa Pharmaceuticals
Dosage Form(s)	1 mg, 2 mg, 4 mg oral tablets
Applicant Proposed Dosing Regimen(s)	Once daily at (b) (4) day, with or without food
Applicant Proposed Indication(s)/Population(s)	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)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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)

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Livalo/Pitavastatin calcium (referred to as pitavastatin hereafter) is a 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitor, otherwise known as a statin.

Pitavastatin is indicated in the adult population as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and Apolipoprotein B (Apo B), as well as increase high-density lipoprotein cholesterol (HDL-C). The dose range for adults is 1 to 4 mg pitavastatin orally once daily at any time of the day with or without food. The recommended starting dose for patients with primary hyperlipidemia and mixed dyslipidemia is 2 mg and the maximum dose is 4 mg.

In response to a Written Request, Kowa Pharmaceuticals submitted two pediatric studies to support an indication in pediatric patients 8 to 16 years of age with heterozygous familial hypercholesterolemia (HeFH), to reduce elevated TC, LDL-C, and Apo B after failing an adequate trial of diet therapy. Kowa Pharmaceuticals also submitted a nonclinical juvenile toxicology study as required by the Written Request.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application contained substantial evidence that pitavastatin is effective for its intended use, treatment of pediatric patients 8-16 years of age with HeFH to reduce LDL-C, TC, and Apo B after failing an adequate trial of diet therapy. The sponsor submitted 2 clinical studies, NK-104-4.01EU and NK-104.4.02EU to support this indication.

Study NK-104-4.01EU was a randomized, double-blind, placebo-controlled study in pediatric patients with high risk hyperlipidemia, excluding homozygous familial hypercholesterolemia, conducted to assess the effectiveness and safety of pitavastatin 1 mg, 2 mg, and 4 mg once daily over 12 weeks of treatment. Although Study NK-104-4.01 enrolled patients 6-17 years of age, this review focused on the population identified in the Written Request, namely pediatric patients (ages ≥ 8 to ≤ 16 years of age) with HeFH, LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL with additional cardiovascular risk factors.

In Study NK-104-4.01EU, pitavastatin, compared to placebo, significantly decreased LDL-C for all three treatment arms. As shown in the following table, pitavastatin 1 mg decreased LDL-C by -20.4 (95% CI, -27.7, -13.0, p<0.001); pitavastatin 2 mg decreased LDL-C by -28.8 (95% CI, -35.8, -21.8, p<0.001); and pitavastatin 4 mg decreased LDL-C by -37.1 (95% CI, -44.4, -29.9, p< 0.001).

Compared to placebo, pitavastatin 1 mg decreased Apo-B by -20.1%; pitavastatin 2 mg decreased Apo B by -25.0%; and pitavastatin 4 mg decreased TC by -27.8%.

Compared to placebo, pitavastatin 1 mg decreased TC by -16.1%; pitavastatin 2 mg decreased TC by -24.5%' and pitavastatin 4 mg decreased TC by -29.7%.

With pitavastatin, changes in HDL-C and TG were not statistically significantly different from placebo.

Furthermore, at Week 12, in the pitavastatin 1 mg arm, 1 out of 20 patients (5%) achieved treatment goal of LDL-C ≤ 130 mg/dL; for pitavastatin 2 mg, 7 out of 24 patients (29%) achieved treatment goal; and for pitavastatin 4 mg, 7 out of 19 patients (37%) achieved treatment goal. No patients in the placebo arm achieved this treatment goal.

Study NK-104-4.02EU was a 52-Week open-label extension study of Study NK-104-4.01EU, which also allowed enrollment of patients who were not previously enrolled in the double-blind study. In total, 85 patients with HeFH who were 8 to 16 years of age were enrolled in the study and the majority of these patients (78.8%) were enrolled directly from the double-blind study.

All patients were assigned to treatment with pitavastatin 1 mg. During the study, patients could be up-titrated to the next dose (based on values at Week 4 and Week 8) in an effort to achieve an optimum LDL-C target of ≤ 110 mg/dL. At the completion of the open-label extension study, 81 of the 85 patients were receiving pitavastatin 4 mg once daily.

Reductions in LDL-C were evident by Week 4 and seemed to reach a plateau by Week 16. At Week 52, LDL-C decreased by 36.62% from Baseline for all patients. Therefore, LDL-C reductions were sustained over 52 weeks and were consistent with results from Study NK-104-4.01.

In Study NK-104-4.02EU, there were clinically meaningful reductions in non-HDL-C (-35%), total cholesterol (-29%), and Apo B (-32%). TG reduction (-9%) and HDL-C improvement (+0.57%) were less impressive, not statistically significant, and not clinically significant.

1.3. Benefit-Risk Assessment

Statins decrease LDL-C by competitively inhibiting the rate-limiting step of cholesterol synthesis in the liver leading to upregulation of hepatic LDL-C receptors. As a class, statins have been shown to reduce risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularization, or stroke) by one-fifth for every 1 mmol/L reduction in LDL-C. (CTT Collaborators, 2005)

Although pitavastatin does not have an indication for cardiovascular risk reduction, pitavastatin is approved for adult patients with primary hyperlipidemia to reduce LDL-C, Apo B, TC, TG and to increase HDL-C.

With this submission, the applicant fulfils a Written Request and proposes to treat pediatric patients with HeFH, 8 to 16 years of age, to reduce LDL-C, Apo B, and TC. Based on evidence from a 12-week well-controlled trial and 52-week open-label extension, I recommend approval of all three doses (1, 2, and 4 mg) of pitavastatin for this pediatric population. However, I recommend that the label identify a "recommended starting dose" of 2 mg for pediatric HeFH based on the improved efficacy starting at pitavastatin 2 mg.

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). Heterozygous FH (HeFH) has a frequency of approximately 1 in 300 to 500 in some populations (Goldberg, 2011). Although ASCVD does not generally manifest until middle age in patients with HeFH, current guidelines advocate statin treatment in addition to diet modifications to be considered as first line therapy in HeFH patients age 8 years and up (Goldberg, 2011), (NHLBI/AAP, 2011) and (European Atherosclerosis Society Consensus Panel, 2015). The treatment goal of lipid lowering therapy in pediatric HeFH is a > 50% reduction in LDL-C or LDL-C ≤130 mg/dL (Daniels, 2011).

Pitavastatin, compared to placebo, significantly decreased LDL-C for all three treatment arms. 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%. LDL-C reductions in the 52-week open label extension were consistent with the 12-week, double-blind, placebo-controlled study.

The safety profile of pitavastatin was consistent with the known safety profile of other statins and includes muscle-related adverse events and liver enzyme abnormalities. Growth and development analysis in the 52-week open-label study were reassuring.

Approval of pitavastatin for the treatment of pediatric patients with HeFH 8-16 years of age is supported by the available evidence of efficacy and safety. Although there are six other statins approved for this population, an individual patient may require trials with several statins before an effective and reasonably tolerated treatment is identified. Given the evidence of benefit and in the context of risks similar to other approved products with similar indication, I recommend approval of this product for the treatment of pediatric patients with HeFH 8-16 years of age. Pitavastatin represents an important new therapy to address the treatment of pediatric HeFH.

Benefit-Risk Integrated Assessment

The risks and benefits of pitavastatin are comparable to other statins, and its availability would provide another option in the armamentarium of drugs already available for treating pediatric patients with HeFH. The balance of risk to benefit is acceptable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Heterozygous familial hypercholesterolemia (HeFH) is a genetic disorder with a prevalence in the white population of about 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 LDL-C levels that are variable and range from 160 mg/dL to >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 with hyperlipidemia. • There are no outcomes data in pediatric populations to determine the optimum age/LDL-C level to initiate statin therapy.	Children and adolescents with HeFH have moderately increased risk of cardiovascular disease[1] due to life-long exposure to high levels of cholesterol. Benefits of lowering LDL-C likely outweigh the risks in this population of patients with HeFH who are ≥8 years old. To date, expert panels of lipidologists and cholesterol management guidelines have not advocated starting statins in children with HeFH younger than age 8.

[1] As categorized by the American Heart Association Expert Panel on Population and Prevention Science

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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+
Benefit	• Pitavastatin (1, 2, and 4 mg) is proposed to be indicated in pediatric patients 8-16 years of age with HeFH, as an adjunctive therapy to diet, to reduce LDL-C, TC, and Apo B. • The efficacy of pitavastatin was established with a randomized, double-blind, placebo-controlled, 12-week study. • Compared to placebo, 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. • In the open-label study, reductions in LDL-C were evident by Week 4 and seemed to reach a plateau by Week 16. At Week 52, LDL-C decreased by 36.62% from Baseline for all patients. • The effect of pitavastatin on CV outcomes has not been determined.	The statin class of drugs, of which pitavastatin is a member, are recommended as first-line therapy by pediatric HeFH management guidelines, after diet and exercise. The pivotal pitavastatin clinical trial was adequate and well-controlled and demonstrated meaningful LDL-C lowering ranging from 20% to 37%, compared to placebo. LDL-C reductions were sustained over 52 weeks of therapy. Pitavastatin is another option in the armamentarium of statin drugs for 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 (≥ 6 years). • The safety profile of pitavastatin, namely muscle symptoms/signs and asymptomatic elevations of ALT/AST, was consistent with the known safety profile of the statin class of drugs and for the pitavastatin adult program. • A detailed safety evaluation focusing on musculoskeletal disorders revealed no cases of rhabdomyolysis, and a low incidence of muscle-related adverse events in pitavastatin treatment arms vs. placebo. • A detailed safety evaluation focusing on liver related adverse events and elevations in ALT/AST revealed no cases of Hy's Law and no ALT/AST ≥3XULN in double blind study and 2 cases of ALT/AST elevations that resolved in the open-label study. • There were no deaths, serious adverse events, or discontinuations due to a treatment emergent adverse event • No obvious safety concerns were identified in growth and development • The safety concerns with statin use are well documented. Healthcare providers are familiar with safety concerns of statins.	Nonclinical data support the administration of pitavastatin in the proposed pediatric population (i.e., ≥ 8 to ≤ 16 years). Muscle symptoms (i.e., pain, soreness, weakness, and/or cramps) or signs (creatine kinase [CK] elevations) are seen with all statins. In placebo-controlled trials, the incidence of these complaints is generally reported at 5%. Asymptomatic elevations in ALT or AST >3 times the upper limit of normal (ULN) are seen with all statins. In most cases, the elevation is most often transient and resolves spontaneously in 70% of cases even if the statin dose is continued unchanged. The general safety profile of pitavastatin was consistent with the safety profile in adults and the know safety profile of statins overall. Analyses of growth measurements, hormones and Tanner staging were reassuring. The safety issues associated with statin class of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		drugs are well known. No new major safety issue related to pitavastatin was identified in this review.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

No patient experience data was submitted as part of the application.

2. Therapeutic Context

2.1. Analysis of Condition

Familial hypercholesterolemia (FH) is a genetic disorder resulting from mutations in several genes involved in LDL-C metabolism. Mutations in the gene encoding for the LDL receptor are the most common cause of FH, but mutations associated with other atherogenic processes (including the Apo B gene as well as gain-of-function mutations in the pro-protein convertase subtilisin/kexin type 9 (PCSK9) gene) can also result in the FH phenotype. Such mutations and defects lead to elevated levels of LDL-C and subsequent premature atherosclerotic cardiovascular disease (Sniderman, 2014).

FH occurs in two forms, homozygous and heterozygous. It is generally believed that among whites, the prevalence of heterozygous FH (HeFH) is about 1/200 to 1/500 and the prevalence of homozygous FH is 1/1,000,000 (Nordestgaard, 2013). Diagnosis of HeFH in patients less than 20 years of age is made if LDL-C is ≥ 160 mg/dL or non-HDL-C ≥ 190 mg/dL in the presence of family history for hypercholesterolemia or premature CHD (Goldberg, 2011). While pediatric patients with HeFH have moderately increased risk of cardiovascular disease (as categorized by the American Heart Association Expert Panel on Population and Prevention Science) due to life-long exposure to high levels of cholesterol, children and adolescents with HeFH are generally asymptomatic. Individuals with untreated HeFH can manifest cardiovascular disease in early to mid-adulthood (Kavey, 2006).

After diet and exercise modification, statins are preferred initial pharmacologic treatment for patients with HeFH. The National Lipid Association Expert Panel suggests that consideration should be given to the introduction of statin treatment at the age of 8 years or older in children with HeFH (Goldberg, 2011). The National Heart, Lung and Blood Institute, with support from American Academy of Pediatrics, recommends pharmacological treatment of children over 8 years of age if LDL-C is over 190 mg/dL (NHLBI/AAP, 2011). The European Atherosclerosis Society Consensus Panel recommends initiating statin treatment at age 8-10 years of age in children with HeFH (Nordestgaard, 2013). A recent Cochrane Review on the use of statins for children with FH recommends that statin treatment should not be started before the age of eight, and that the duration of a delay in the initiation of statin therapy should be based on individual risk stratification (Vuorio, 2013).

2.2. Analysis of Current Treatment Options

The following table summarizes the currently available lipid-lowering options for treating children and adolescents with HeFH. All listed, with the exception of Zetia, have an indication for pediatric patients with HeFH. Zetia has a description of the pediatric trials of HeFH in Section 8 of its labeling.

Table 1: Currently available lipid-lowering agents for children and adolescents with heterozygous familial hypercholesterolemia

Product (s) Name	Relevant Indication	Year of Approval	Dosing and Administration
Crestor/ rosuvastatin	Pediatric patients 8 to 17 years of age with HeFH to reduce LDL-C, TC after failing adequate trial of diet therapy	2009, 2015	5 to 10 mg/day for 8 to < 10 years of age; 5 to 20 mg/day for 10 to 17 years of age
Lescol/ Lescol XL fluvastatin	Reduce elevated TC, LDL-C, and Apo B levels in boys and post-menarchal girls, 10 to 16 years of age, with HeFH after failing an adequate trial of diet therapy	2006	Starting dose 20 mg/day. Dose adjustments, up to a maximum daily dose administered either as Lescol capsules 40 mg twice daily or one Lescol XL 80 mg tablet once daily
Zocor/ simvastatin	Reduce elevated total- C, LDL-C, and apo B levels in boys and post-menarchal girls, 10 to 17 years of age, with HeFH after failing an adequate trial of diet therapy	2002	Starting dose is 10 mg/day; maximum recommended dose is 40 mg/day
Pravachol/ pravastatin	Treat children and adolescent patients ages 8 years and older with HeFH after failing an adequate trial of diet therapy.	2002	Children (ages 8 to 13 years, inclusive): the recommended starting dose is 20 mg once daily; doses greater than 20 mg not studied Adolescents (ages 14 to 18 years): the recommended starting dose is 40 mg once daily; doses greater than 40 mg not studied
Lipitor/ atorvastatin	Reduce elevated total- C, LDL-C, and apo B levels in boys and post-menarchal girls, 10 to 17 years of age, with HeFH after failing an adequate trial of diet therapy	2002	Starting dose: 10 mg once daily; dose range is 10 to 20 mg/day for patients 10 years to 17 years of age
Welchol/ colesevelam	Reduce LDL-C levels in boys and post-menarchal girls, 10 to 17 years of age, with HeFH as monotherapy or in	2009	Recommended dose of Welchol for Oral Suspension, in children 10 to 17 years of age, is one 3.75 gram packet once

Product (s) Name	Relevant Indication	Year of Approval	Dosing and Administration
	combination with a statin after failing an adequate trial of diet therapy		daily
Zetia/ ezetimibe	No indication; trial described in label. In patients with HeFH, 10 to 17 years of age, Zetia co-administered with simvastatin		Patients received co-administered zetia and simvastatin (10mg, 20 mg, or 40 mg)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pitavastatin is approved and marketed in the US for adult patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and to increase high density lipoprotein cholesterol (HDL-C).

3.2. Summary of Pre-submission/Submission Regulatory Activity

Kowa Research Institute submitted on July 6, 2016, a Proposed Pediatric Study Request (PPSR) for pitavastatin. Two pediatric studies were proposed. 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," proposed 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," was proposed for patients completing the double-blind study as well as for additional eligible patients.

The Agency determined that pediatric information on pitavastatin for the treatment of HeFH children and adolescents was needed. The Agency issued a formal Written Request (WR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), and as amended by the Food and Drug Administration Amendments Act of 2007, to Kowa Research Institute on November 2016.

The WR included a nonclinical study in order to further support the safety evaluation in children younger than 10 years of age. Per the WR, the nonclinical study should evaluate the toxicity of pitavastatin 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 (including effects on myelination).

The WR included a request for the following two clinical studies:

(1) 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 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.
(2) 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.

3.3. Foreign Regulatory Actions and Marketing History

Pitavastatin was first approved in Japan on July 17, 2003. Since then, it has been approved in several countries in Asia, Latin America, Middle East and Europe, as well as Australia and the US. Pitavastatin was approved in the US on August 3, 2009. According to the company's July 2018 PBRER, no regulatory authorities or Marketing Authorization Holders (MAHs) took safety actions for pitavastatin, concerning the withdrawal, revocation, suspension or failure to obtain a renewal of a marketing authorization. Pitavastatin was approved in the EU for pediatric patients.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

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.

4.2. Product Quality

There were no proposed chemistry, manufacturing and controls labeling changes in this submission.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The following is an excerpt from the nonclinical reviewer, Dr. Lydia Haile's report:

The Sponsor assessed the potential effects of pitavastatin on development, growth, behavior and reproduction in juvenile toxicology study in which rats were administered orally with pitavastatin at 1, 7.5 and 15 mg/kg/day from postnatal day (PND) 28 through 56, with a 28 day of treatment-free period. The age of the rats (PND 28) at the start of the study correlates to a human age of approximately 6 years, thus, the study supports the young pediatric age of 6 years. Although the duration of treatment is short (PDN 28-PND 56~ human age 6-12 years), repeat dose rat toxicity studies conducted for the initial NDA approval of pitavastatin in 6-7 week (~ PND 45) rats will fill the gap and covers safety evaluation of pediatric patients > 12 years of age.

There were no treatment related effects on neurobehavioral assessment of functional observational battery (FOB), auditory startle habituation, motor activity, learning/memory, bone growth and sexual maturation (vaginal opening and preputial separation) observed during the dosing and recovery phase. There were small decreases (7-10%) in post weaning mean body weights and mean body weight gains with concomitantly reduced food consumption observed in male rats at 15 mg/kg/day (12-fold the maximum human proposed human dose 4 mg, based on body surface area extrapolation using 20 kg child body weight). Increases in thyroid/parathyroid gland weight with no histologic correlate were seen in all treated males. The primary histological changes were limited to minimal to mild hyperkeratosis, epithelial hyperplasia and/or mixed cell infiltrate in the nonglandular (forestomach) stomach and minimal increases in mitoses and single cell necrosis of hepatocytes with correlative marginal increases (1.3 to 2X) in AST, ALT and ALP were observed at ≥ 7.5 mg/kg/day (6-fold MRHD). In adult rats, the liver, skeletal muscle, forestomach and thyroid glands were identified as target organs of toxicity. Even though, pitavastatin-mediated findings in juvenile rats were comparable to that of the adults, increased hepatocyte mitoses were not a feature of toxicology studies in rats as well as other species. The liver finding is considered to have minimal significance considering the minimal severity of the changes, absence of accompanying proliferative signals (hypertrophy and hyperplasia) and reversibility at the end of drug free period. Rodent forestomach lesions (epithelial hyperplasia and hyperkeratosis) have been reported previously with multiple statins. Although the forestomach changes seem to be mechanism based, extrapolation of the risk to humans is questionable or unlikely considering an important anatomic difference between rodents and humans.

The NOAEL identified in juvenile rat is close to clinical exposure (1-fold maximum human proposed human dose 4 mg, based on body surface area extrapolation using 20 kg child body weight). Based on the absence of age specific and/or human relevant findings in juvenile rats, the assessment of juvenile animal toxicity of pitavastatin is considered adequate and supports the safety of pitavastatin use in the proposed pediatric population.

4.5. Clinical Pharmacology

Please see the clinical pharmacology reviewer report for the complete analysis of pharmacokinetic data. The pharmacokinetic data in the subset analysis included all randomized patients who received at least one dose of study drug and had at least one valid plasma drug concentration.

The following is an excerpt from the sponsor:

The subset analysis demonstrated dose-dependent increases in plasma concentrations of pitavastatin and pitavastatin lactone. Mean plasma concentrations (ng/mL) are summarized in the following table for both pitavastatin and pitavastatin lactone:

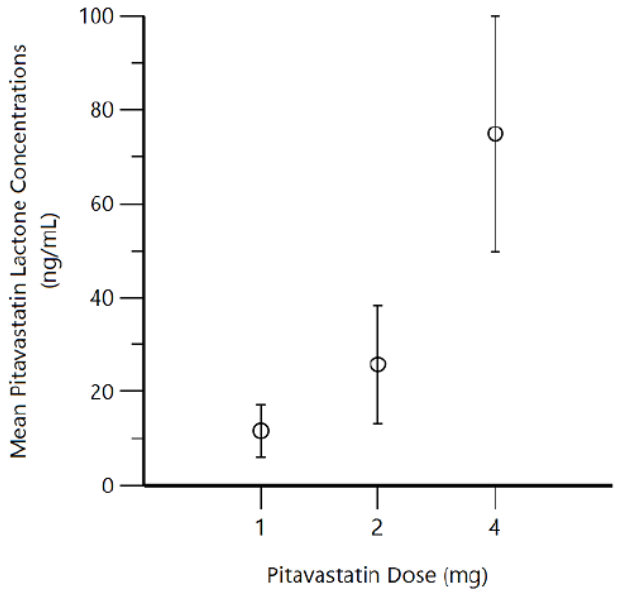
Table 2: Mean Plasma Concentrations (ng/mL) for Pitavastatin and Pitavastatin Lactone

	Pitavastatin		**Pitavastatin Lactone**	
	Trough	**1-hr Post-Dose**	**Trough**	**1-hr Post-Dose**
Pitavastatin 1 mg	NA	13.79	3.29	11.71
Pitavastatin 2 mg	1.31	35.08	8.21	25.82
Pitavastatin 4 mg	3.96	124.79	19.74	74.88

The mean concentration of pitavastatin at the trough measurement was 0.00 ng/mL for the pitavastatin 1 mg dose group, 1.31 ng/mL for the pitavastatin 2 mg dose group, and 3.96 ng/mL for the pitavastatin 4 mg dose group. The mean concentration of pitavastatin at the 1-hour post-dose measurement was 13.79 ng/mL for the pitavastatin 1 mg dose group, 35.08 ng/mL for the pitavastatin 2 mg dose group, and 124.79 ng/mL for the pitavastatin 4 mg dose group.

The following figure is from the clinical pharmacology review and shows the mean plasma concentration of pitavastatin lactone at 1-hour post dose for the three pitavastatin doses.

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



Source: Dr. S. Yapa, clinical pharmacology reviewer, NDA 022363-Supplement-015

The clinical pharmacology team is in agreement with the sponsor that 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.

4.6. Devices and Companion Diagnostic Issues

Not applicable; no companion device or diagnostic is included in this application.

4.7. Consumer Study Reviews

Not applicable; no label comprehension, or other human factors studies were submitted in this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3: Listing of Clinical Trials Reviewed for Indication

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
NK-104-4.01EU	Randomized, Double-Blind, Placebo-Controlled	Pitavastatin 1 mg, 2 mg, 4 mg, or placebo once daily	Percent reduction in LDL-C from baseline over 12 weeks; safety endpoints	12 weeks	82	HeFH children age 8-16 years
NK-104-4.02EU	Open-label extension of Study NK-104-4.01EU	Pitavastatin 1 mg, 2 mg, 4 mg	Percent reduction in LDL-C from baseline over 52 weeks; safety endpoints	52 weeks	85	HeFH children age 8-16 years

5.2. Review Strategy

Reviewers from the various disciplines conducted independent reviews but collaborated on areas requiring clarity. The Clinical review involved the evaluation of study protocols, study reports and analysis of study databases to conduct a safety review of the population specified in the Written Request in Studies NK-104-4.01EU and NK-104-4.02EU. The efficacy review was led by the Statistical team. The Clinical Pharmacology team reviewed the clinical pharmacology data. The Division of Maternal and Pediatric Health was consulted to review growth and development data in Study NK-104-4.02EU. The pharmacology/toxicology team reviewed the juvenile toxicology study.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, 12-Week Study of Pitavastatin in High-Risk Hyperlipidemia in Childhood (Study NK-104-4.01EU)

6.1.1. Study Design, NK-104-4.01EU

Overview and Objective

Primary Objective: To compare the efficacy of pitavastatin 1 mg, 2 mg, and 4 mg once daily to placebo in terms of the percent reduction of LDL-C at Week 12.

Secondary Objective(s):

- To compare the efficacy of pitavastatin 1 mg, 2 mg, and 4 mg once daily to placebo in terms of the change or percent change in secondary lipid parameters in pediatric patients with HeFH over 12 weeks;
- To evaluate pitavastatin exposure at each dose level; and
- To compare the safety and tolerability of pitavastatin 1 mg, 2 mg, and 4 mg once daily to placebo in pediatric patients with HeFH over 12 weeks.

Trial Design

NK-104-4.01EU was a randomized, double-blind, placebo-controlled study in children and adolescent patients with high-risk hyperlipidemia, excluding patients with homozygous familial hypercholesterolemia. The study consisted of an up to 5-week screening/washout period and a 12-week double-blind treatment period. Patients who completed the 12–week treatment period were eligible to enter a 52-week open-label extension study (NK-104-4.02EU).

The supplemental analysis submitted by the sponsor considered the subset population of patients who met the following criteria as outlined in the Agency's Written Request:

- Heterozygous Familial Hypercholesterolemia (HeFH);
- Age ≥ 8 and ≤ 16 years; and
- Baseline LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with additional cardiovascular (CV) risk factors.

Additional CV risk factors (same as the original inclusion criteria) were as follows:

- Male gender;
- A family history of premature cardiovascular disease defined as a myocardial infarction before age 50 in a second-degree relative or before age 60 in a first-degree relative with at least 1 relative (parent, grandparent, or sibling) affected;
- Presence of low HDL-C (< 45 mg/dL) or high TG (> 150 mg/dL);
- Presence of high lipoprotein(a);

- Presence of type 2 diabetes mellitus diagnosed by treating physician according to current guidance; or

- Presence of hypertension defined as systolic and diastolic blood pressures (SBP and DBP, respectively) above the 95th percentile for age and size.

All other inclusion criteria were the same as the original protocol:

- Had not taken any lipid-lowering medications in the 5 weeks prior to screening or in the 4 weeks prior to the lipid qualifying visit at Week -1;

- Had been adherent to an appropriate diet for at least 8 weeks;

- Females who were post-menarche must not have been pregnant or breast feeding and, if sexually active, must have used a reliable form of contraception; and

- Written informed consent

No modifications were made to the exclusion criteria to satisfy the requirements of the Written Request. The exclusion criteria were as follows:

1. Fasting TG >400 mg/dL;

2. Homozygous familial hypercholesterolemia;

3. Other secondary causes of hyperlipidemia (e.g., hypothyroidism, human immunodeficiency virus infection, systemic lupus erythematosus, organ transplantation, previous malignancy, nephrotic syndrome, glycogen storage disease);

4. Previous history of statin intolerance, adverse effects with other statin use, or hypersensitivity to any components of the study drug;

5. Need for non-statin lipid-lowering medications;

6. Apheresis therapy;

7. Use of any concomitant medication that may have interfered with the objectives of the study (see Section 8.1 of the Study Protocol [Appendix 16.1.1]);

8. Type 1 diabetes mellitus;

9. Poorly controlled type 2 diabetes mellitus defined as hemoglobin A1c >9.0% at screening;

10. Severe renal impairment defined as serum creatinine >2.0 mg/dL at screening;
11. Uncontrolled hypertension;
12. Untreated thyroid disease;
13. Severe hepatic impairment, active liver disease, or persistent elevation of alanine transaminase (ALT) or aspartate transaminase (AST) >3 × the upper limit of normal (ULN);
14. Active muscle disease or creatine kinase (CK) >3 × ULN (unless explained by exercise);
15. Screening laboratory values within the following age/gender appropriate reference ranges as assessed by the central laboratory:

    • Hemoglobin <10 g/dL for males or <9 g/dL for females or

    • Alkaline phosphatase >2 × ULN for age;

16. Any other laboratory abnormality that could compromise patient safety because of study participation;
17. Malignancy during the past 5 years;
18. Current smoker or history of drug or alcohol abuse at screening;
19. Hospitalization for any cause within 30 days prior to the administration of study drug;
20. History of major surgery in the 3 months prior to screening;
21. Any medical condition that, in the judgment of the Investigator, would have jeopardized the evaluation of safety and/or constituted a significant safety risk to the patient; or

Study treatments

Pitavastatin 1 mg, 2 mg, and 4 mg tablets for oral administration were round, white, film-coated tablets containing the following excipients: lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose (b) (4), magnesium aluminometasilicate, magnesium stearate, titanium dioxide (b) (4), triethyl citrate (b) (4) and colloidal anhydrous silica. Placebo tablets identical to the pitavastatin 1 mg, 2 mg, and 4 mg tablets were administered for blinding.

Study drug (pitavastatin 1 mg, 2 mg, or 4 mg tablets or matching placebo tablets) was taken orally once daily, with or without food, in the morning. In order to be enrolled in the study,

patients must have been able to swallow tablets; however, if necessary, study drug tablets may have been dissolved in water and taken immediately. At the screening visit, the Investigator was to assess whether the patient would be able to tolerate study drug administration.

Assignment to treatments

Enrollment in the study began in the pitavastatin 1 mg and pitavastatin 2 mg dose groups until sufficient data had been collected to reassure the Data Monitoring Committee that the pitavastatin 4 mg dose group should be opened for enrollment. Within each dose group, patients were randomly assigned in a 3:1 ratio to pitavastatin or placebo.

Blinding

Placebo tablets identical to the pitavastatin 1 mg, 2 mg, and 4 mg tablets were supplied for blinding. Both study drug and placebo were packaged into identical wallet cards containing 35 tablets each. Treatment assignment was not to be unblinded during the study unless it was considered absolutely necessary by the Investigator for the management of an adverse event or other medical emergency. Under such conditions, the Investigator was to contact the Medical Monitor before proceeding with the process of unblinding. The identity of study treatment was to be obtained by contacting IVRS; the reason for unblinding was to be documented in the eCRF. Any patient whose treatment assignment was unblinded was required to discontinue participation in the study. Investigators were also blinded to patient lipid parameters during the treatment phase of the study.

In order to maintain overall study blinding, an unblinded (b) (4) statistician was assigned to the Data Monitoring Committee (DMC) without voting power. The unblinded statistician was responsible for the preparation of reports for DMC members and for assistance during the DMC review, but was not involved in the conduct of the clinical study or in the final analysis of the data.

Administrative structure

The study was sponsored by Kowa Research Europe, Ltd. (Kowa) and conducted at 9 clinical sites in Greece, France, Italy, Norway, the Netherlands, and Spain.

(b) (4) a contract research organization, performed project management, clinical monitoring, data management, pharmacovigilance, statistical analysis, and study report preparation.

(b) (4) performed the clinical laboratory analyses. A Data Monitoring Committee (DMC) composed of clinicians with expertise in hyperlipidemia and pediatrics provided study oversight.

Procedures and schedule

The schedule of procedures to be performed during this study is provided below. During the treatment period, lipid and safety assessments were performed every 4 weeks. Pharmacokinetic assessments were performed at either Week 8 or Week 12, depending on patient availability.

Table 4: Schedule of Assessments, Study NK-104-4.01EU

	Washout Period		12-Week Double-Blind Treatment Period			
	Screening/Visit 1[a]	Visit 2[a]	Randomisation/Visit 3	Visit 4	Visit 5	Visit 6[b]
ASSESSMENTS PERFORMED	**Week -5/-1**	**Week -1**	**Week 0**	**Week 4**	**Week 8**	**Week 12/Early Termination**
Confirmation of consent/assent[c]	X					
Review eligibility criteria	X	X	X			
Record demographic information	X					
Record medical/family history[d]	X					
Physical examination	X					X
Electrocardiogram	X					X
Vital signs (including height and weight)	X		X	X	X	X
Genotyping[e]			X			
Serum chemistry[f]	X		X			X
Haematology[g]	X		X			X
Hormones[h]	X		X			X
Liver and muscle enzymes[i]	X	X	X	X	X	X
Serum creatinine	X		X	X	X	X
TSH	X					
Complete lipid profile[j]	X[k]	X	X	X	X	X
Partial lipid profile[j]	X[k]					
Lp(a)	X					X
Pharmacokinetic sampling[l]					X	X[b]
Urinalysis[m]	X		X			X
Pregnancy test[n]	X	X	X	X	X	X
Myoglobin (plasma and urine)[o]	As needed					
Assess menstrual cycle[p]	X	X	X	X	X	X
Dietary counselling	X					
Dietary assessment	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X
Assess adverse events[q]		X	X	X	X	X
Randomisation using IVRS			X			
Dispense study drug[r]			X	X	X	
Drug accountability by tablet count				X	X	X

a. The screening visit (Visit 1) was at Week -1 for patients who were not currently taking lipid-lowering medications and at Week -5 for patients who were required to wash out from lipid-lowering medications. Patients who began to wash out from lipid-lowering medications at Week -5 were to return at Week -1 (Visit 2) for assessment of lipid eligibility criteria. Visit 2 was only required for patients who washed out from lipid-lowering medications at the Screening Visit.
b. With the exception of PK assessments, all Visit 6 procedures were to be completed upon early termination. Laboratory samples collected at an Early Termination Visit were to be identified with Discontinuation Visit labels and pages for early termination were required to be completed.
c. Consent/assent must have been obtained before any protocol-specific procedures were performed.
d. A detailed family history was recorded with an emphasis on cardiovascular and lipid status.
e. For patients without a previous molecular diagnosis, blood samples for genetic testing were collected at Visit 3 (Week 0) to determine the molecular hypercholesterolaemia diagnosis.
f. Serum chemistry parameters included sodium, potassium, chloride, bicarbonate, urea, alkaline phosphatase, bilirubin, total protein, albumin, calcium, phosphate, gamma-glutamyl transferase, lactic dehydrogenase, fasting glucose, HbA_{1c}, and cystatin-C.
g. Haematology parameters included white blood cell count and differential, red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and platelets.
h. Hormone assessments included cortisol, dehydroepiandrosterone sulphate, estradiol (for females only), testosterone (for males only), luteinizing hormone, and follicle-stimulating hormone.
i. Liver enzymes included ALT and AST. Muscle enzymes included creatine kinase.
j. The complete lipid profile consisted of LDL-C, HDL-C, non-HDL-C, TC, TG, Apo A1, and Apo B. The partial lipid profile consisted of all lipid parameters except Apo A1 and Apo B.
k. A complete lipid profile was assessed at the screening visit (Week -1) for patients who were not taking lipid-lowering medications at the time of screening. A partial lipid profile was assessed at the screening visit (Week -5) for patients who were required to wash out from lipid-lowering medications.
l. Blood samples for the evaluation of pitavastatin and pitavastatin lactone concentrations were collected at either Week 8 (Visit 5) or Week 12 (Visit 6), depending on patient availability. On the day of the PK assessment, the daily dose of study drug was administered at the study visit. Pharmacokinetic blood samples were collected at trough and at 1-hour post-dose at the given study visit.
m. Urinalysis parameters included pH, protein, glucose, ketones, blood, nitrates, and specific gravity. If protein was detected, the urinary albumin/creatinine ratio was assessed.
n. Urine pregnancy tests were performed for post-menarche females.
o. Plasma and urine myoglobin were assessed as needed during the study.
p. Monthly menstrual start and stop dates were recorded for post-menarche females. If a female experienced menarche during the study, this was noted.
q. Assessment of adverse events included all SAEs occurring up to 30 days after the final dose of study drug.
r. Patients in the pitavastatin 1 mg and pitavastatin 2 mg dose groups were dispensed their assigned treatment for the duration of the 12-week treatment period. Patients in the pitavastatin 4 mg dose group were dispensed pitavastatin 2 mg (or matching placebo) at Visit 3 and were dispensed pitavastatin 4 mg (or matching placebo) at Visit 4 and Visit 5. All study treatments were dispensed in a double-blind manner.

ALT = alanine aminotransferase; Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; AST = aspartate aminotransferase; HbA_{1c} = haemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; IVRS = Interactive Voice Response System; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); non-HDL-C = non-high-density lipoprotein cholesterol; PK = pharmacokinetic; SAE = serious adverse event; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.
Source: Study Protocol (Appendix 16.1.2)

Source: Study NK-104-4.01EU Suppl Analysis, Table 2, pg. 21/566.

Dietary restrictions/instructions

Patients were required to be on a low-fat, low cholesterol diet for at least 8 weeks. Patients were given dietary counselling at Screening (Week -5) and were required to keep a dietary assessment.

Reviewer Comment: The dietary restrictions were reasonable and in alignment with current guidance on pediatric HeFH management.

Concurrent medications

In general, any medication not excluded by the protocol was permitted. Additionally, the following frequently prescribed medications were permitted by the protocol, provided that the patient had been on a stable dose for at least 4 weeks prior to the screening visit and dosage changes were not anticipated during the study: digoxin/digitoxin; intra-articular, nasal, and inhaled steroids; and topical steroid creams.

Oral contraceptives and thyroid replacement therapy were permitted by the protocol, provided that the patient had been on a stable dose for at least 3 months prior to the screening visit and dosage changes were not anticipated during the study.

The following medications (prescription or over-the-counter) were not to be taken by the patient during the study:

• All hypolipidemic medications affecting lipid measurements;

• Dietary supplements that included plant stanols or sterols;

• Amphetamines, weight loss medications, and amphetamine-derivative agents;

• Anticoagulants;

• Corticosteroids;

• Fusidic acid; and

• Erythromycin, clarithromycin, and cyclosporine.

Treatment compliance

Study drug was dispensed in amounts exceeding the amount required for the period of time until the next visit. Patients were instructed to return all unused study drug at the next visit. Compliance with study drug was assessed by counting unused tablets.

If, at any visit, compliance was not between 80% and 120%, inclusive, the patient was counselled about the importance of compliance with the regimen. Patients were to be questioned as to whether or not non-compliance was due to an inability to swallow the study drug.

Study Endpoints

The primary efficacy endpoint for the supplemental subset analysis was the mean percent change in LDL-C from baseline to Week 12 for each treatment group compared to placebo.

The secondary efficacy endpoints evaluated in the supplemental subset analysis included:

- 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, TC, fasting TG, and Apo B from baseline over 12 weeks of treatment (Week 4, Week 8, and Week 12); and
- Measures of compliance assessed through assessment of diet and counts of used/unused study medication.

PK Assessment

In order to evaluate drug exposure at each dose level of pitavastatin, plasma samples were

collected and analyzed for both pitavastatin and pitavastatin lactone concentrations. Samples were obtained at trough (pre-dose) and 1-hour post-dose at either Visit 5 (Week 8) or Visit 6 (Week 12), depending on subject availability. Only concentration data for subjects included in the subset of the original study population are included in the supplemental analysis presented here.

Statistical Analysis Plan

An independent (supplemental) statistical analysis plan (SAP) was developed to describe the statistical methods used for the analysis outlined in the Written Request.

The Randomized Set for the supplemental analysis included 82 patients: 20 patients in the pitavastatin 1 mg dose group, 24 patients in the pitavastatin 2 mg dose group, 19 patients in the pitavastatin 4 mg dose group, and 19 patients in the placebo group.

All randomized patients who received at least one (1) dose of study drug and were included in the Safety Set.

The Full Analysis Set in the supplemental analysis included the randomized patients who received at least one (1) dose of study drug and had a baseline lipid measurement and at least one (1) valid post-baseline lipid measurement. There were 82 patients in the Full Analysis Set.

The Per-Protocol Analysis Set was summarized for reference but was not utilized in any of the supplemental analysis presented here.

Table 5: Number (%) of Patients, Various Study Datasets, Study NK-104-4.01EU

	Pitavastatin 1 mg n (%)	Pitavastatin 2 mg n (%)	Pitavastatin 4 mg n (%)	Placebo n (%)	Total n (%)
Randomized Set[a]	20 (100.0)	24 (100.0)	19 (100.0)	19 (100.0)	82 (100.0)
Safety Set[b]	20 (100.0)	24 (100.0)	19 (100.0)	19 (100.0)	82 (100.0)
Full Analysis Set[c]	20 (100.0)	24 (100.0)	19 (100.0)	19 (100.0)	82 (100.0)
Per Protocol Analysis Set[d]	18 (90.0)	23 (95.8)	19 (100.0)	18 (94.7)	78 (95.1)
Pharmacokinetics Analysis Set[e]	16 (80.0)	15 (62.5)	17 (89.5)	0 (0.0)	48 (58.5)
Full Analysis Set Patients who were excluded from Per Protocol Analysis	2 (10.0)	1 (4.2)	0 (0.0)	1 (5.3)	4 (4.9)
Low Compliance	1 (5.0)	1 (4.2)	0 (0.0)	1 (5.3)	3 (3.7)
Missing Week 12 endpoint LDL-C	1 (5.0)	1 (4.2)	0 (0.0)	0 (0.0)	2 (2.4)
Prohibited Medications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Study NK-194-4.01EU Suppl Analysis, Abbreviations: LDL-C=low-density lipoprotein cholesterol
a The Randomized Set included all patients randomized in the study
b The Safety Set included all randomized patients who received at least one dose of study drug.
c The Full Analysis Set included all randomized patients who received at least one dose of study drug and had a baseline lipid measurement and at least one valid post-baseline lipid measurement.
d The Per-Protocol Analysis Set included all randomized patients in the Full Analysis Set who completed the 12-week double-blind treatment period without any major deviations from the protocol procedures, and with valid primary efficacy measurement at both baseline and scheduled 12-week visit.
e The Pharmacokinetic Analysis Set included all randomized patients who received at least one dose of study drug and had at least one valid plasma drug concentration

Protocol Amendments

There were no protocol amendments or changes in the conduct of the study as originally planned.

6.1.2. Study NK.104.4.01EU Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted.

Financial Disclosure

The applicant submitted form 3454 with an attachment and certified that they acted with due diligence to obtain from the listed clinical investigators or from the sponsor the information required under 54.4 and no information was received.

Patient Disposition

In total, 82 patients were assigned randomly to study treatment: 20 patients to the pitavastatin 1 mg dose group, 24 patients to the pitavastatin 2 mg dose group, 19 patients to the pitavastatin 4 mg dose group, and 19 patients to the placebo group. Of these pediatric patients included in the supplemental analysis, none withdrew after randomization, and there were no SAEs or clinically significant AEs that precluded patient participation.

Table 6: Patient Disposition, Study NK-104-4.01EU Supplemental Analysis, Randomized Set

	Pitavastatin 1 mg n (%)[a]	Pitavastatin 2 mg n (%)	Pitavastatin 4 mg n (%)	Placebo n (%)	Total n (%)
Randomized	20 (100.0)	24 (100.0)	19 (100.0)	19 (100.0)	82 (100.0)
Completed the Study	20 (100.0)	24 (100.0)	19 (100.0)	19 (100.0)	82 (100.0)
Early Withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent or requested discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE, clinically significant AE, lab abnormality, intercurrent illness, or other medical condition that indicated to the Investigator that continued participation was not in the patient's best interest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Study NK-194-4.01EU Suppl Analysis Abbreviations: AE=adverse event. a Percentages were calculated using the number of randomized patients as the denominator.

Reviewer Comment: It is worth noting that all 82 patients completed the trial and there were no discontinuations due to an adverse event or laboratory abnormality.

Table of Demographic Characteristics

In the study population, 56% (n=46) were female and 44% (n=36) were male. Approximately 96% were Caucasian, 2.4% were Asian, and 1.2% were Black. The overall mean age was 11.4 years. Overall, 28.0% were ≥ 8 to < 10 years old, 65.9% were ≥ 10 to < 16 years old, and 6.1%

were 16 years old.

At baseline, mean height was 152.6 cm, mean weight was 47.0 kg, and mean body mass index (BMI) was 19.6 kg/m2. All patients had a positive diagnosis of HeFH as diagnosed by the Investigator (100%), and the majority of patients as diagnosed by genetic testing (98.8%).

Approximately one-third of patients (39%) were assessed at Tanner stage I. The majority of patients had not taken lipid-lowering medication at screening (59.8%). Overall, the treatment groups were comparable with respect to demographic characteristics.

Table 7: Demographic and Baseline Characteristics, Study NK-104-4.01EU

Demographic Parameters	Placebo (N=19) n (%)	Treatment Group			Total (N=82) n (%)
		Pitavastatin 1 mg (N=20) n (%)	Pitavastatin 2 mg (N=24) n (%)	Pitavastatin 4 mg (N=19)	
Sex					
Male	8 (42.1)	9 (45.0)	9 (37.5)	10 (52.6)	36 (43.9)
Female	11 (57.9)	11 (55.0)	15 (62.5)	9 (47.4)	46 (56.1)
Age					
Mean years (SD)	11.4 (2.7)	11.7 (2.1)	11.4 (2.7)	10.9 (2.2)	11.4 (2.4)
Age Group, n (%)					
≥ 8 to < 10 years	5 (26.3)	3 (15.0)	9 (37.5)	6 (31.6)	23 (28.0)
≥ 10 to < 16 years	12 (63.2)	16 (80.0)	13 (54.2)	13 (68.4)	54 (65.9)
16 years	2 (10.5)	1 (5.0)	2 (8.3)	0	5 (6.1)
≥ 8 to < 12 years	13 (68.4)	9 (45.0)	13 (54.2)	11 (57.9)	46 (56.1)
≥ 12 to ≤ 16 years	6 (31.6)	11 (55.0)	11 (45.8)	8 (42.1)	36 (43.9)
Race, n (%)					
White	18 (94.7)	19 (95.0)	23 (95.8)	19 (100.0)	79 (96.3)
Black or African American	0	0	1 (4.2)	0	1 (1.2)
Asian	1 (5.3)	1 (5.0)	0	0	2 (2.4)
Multiple Races	0	0	0	0	0

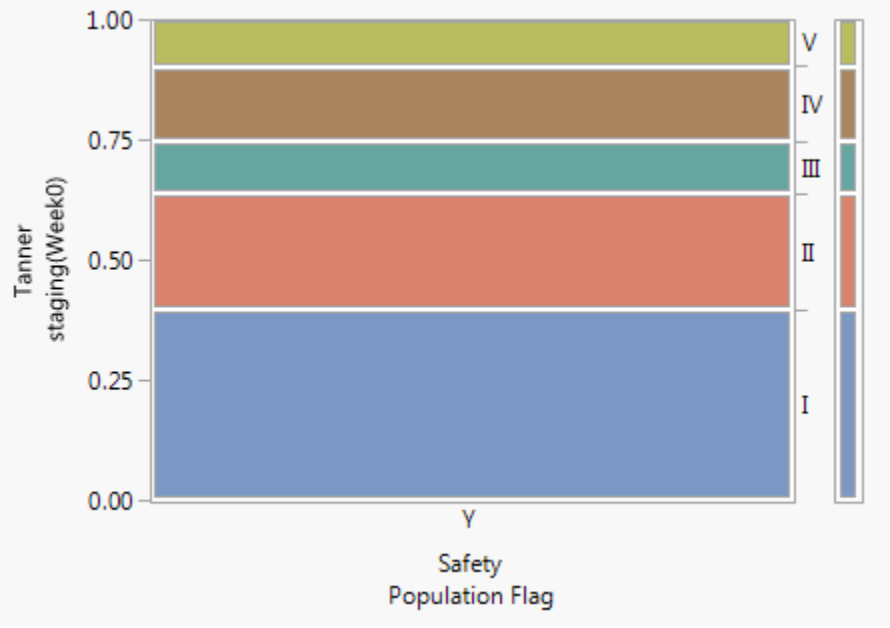
Demographic Parameters	Placebo (N=19) n (%)	Treatment Group			Total (N=82) n (%)
		Pitavastatin 1 mg (N=20) n (%)	Pitavastatin 2 mg (N=24) n (%)	Pitavastatin 4 mg (N=19)	
Ethnicity, n (%)					
Hispanic or Latino	1 (5.3)	2 (10.0)	3 (12.5)	1 (5.3)	7 (8.5)
Not Hispanic or Latino	18 (94.7)	18 (90.0)	21 (87.5)	18 (94.7)	75 (91.5)
Country, n (%)					
France	1 (5.3)	0	0	1 (5.3)	2 (2.4)
Greece	3 (15.8)	4 (20.0)	4 (16.7)	4 (21.1)	15 (18.3)
Italy	2 (10.5)	0	0	9 (47.4)	11 (13.4)
Netherlands	8 (42.1)	8 (40.0)	13 (54.2)	4 (21.1)	33 (40.2)
Norway	4 (21.1)	6 (30.0)	4 (16.7)	0	14 (17.1)
Spain	1 (5.3)	2 (10.0)	3 (12.5)	1 (5.3)	7 (8.5)
Diagnosis by Investigator					
HeFH	19 (100.0)	20 (100.0)	24 (100.0)	19 (100.0)	82 (100.0)
Other	0	0	0	0	0
Diagnosis by Genetic Testing					
HeFH	19 (100.0)	20 (100.0)	23 (95.8)	19 (100.0)	81 (98.8)
Other	0	0	1 (4.2)	0	1 (1.2)
Tanner Staging, n (%)					
I	9 (47.4)	7 (35.0)	10 (41.7)	6 (31.6)	32 (39.0)
II	4 (21.1)	6 (30.0)	5 (20.8)	5 (26.3)	20 (24.4)
III	1 (5.3)	4 (20.0)	3 (12.5)	1 (5.3)	9 (11.0)
IV	3 (15.8)	2 (10.0)	3 (12.5)	5 (26.3)	13 (15.9)
V	2 (10.5)	1 (5.0)	3 (12.5)	2 (10.5)	8 (9.8)
Previous Lipid-lowering Medication at Screening, n (%)					
Yes	10 (52.6)	6 (30.0)	9 (37.5)	8 (42.1)	33 (40.2)
No	9 (47.4)	14 (70.0)	15 (62.5)	11 (57.9)	49

Demographic Parameters	Placebo (N=19) n (%)	Treatment Group			Total (N=82) n (%)
		Pitavastatin 1 mg (N=20) n (%)	Pitavastatin 2 mg (N=24) n (%)	Pitavastatin 4 mg (N=19)	
					(59.8)
Height (cm)					
Mean (SD)	151.3 (14.5)	156.2 (15.1)	152.9 (15.2)	149.9 (13.6)	152.6 (14.6)
Weight (kg)					
Mean (SD)	44.2 (16.7)	52.5 (20.0)	47.9 (16.4)	42.8 (10.2)	47.0 (16.4)

Source: Study NK-194-4.01EU Suppl Analysis, Table 5, pg. 31/566. Abbreviations: BMI=body mass index; FH=familial hypercholesterolemia; SD=standard deviation.
a Percentage was calculated using the number of patients in the column heading in the denominator
Note: Baseline was defined as the randomization visit (Week 0) measurement. If the measurement at this visit was missing, the last measurements prior to the first dose of randomized study drug were used

Reviewer Comment: The population was predominately Caucasian, reflecting the HeFH distribution in the general population. There were more girls than boys enrolled in the study.

Figure 2: Summary of Baseline Tanner Stages in Study NK-104-4.01EU

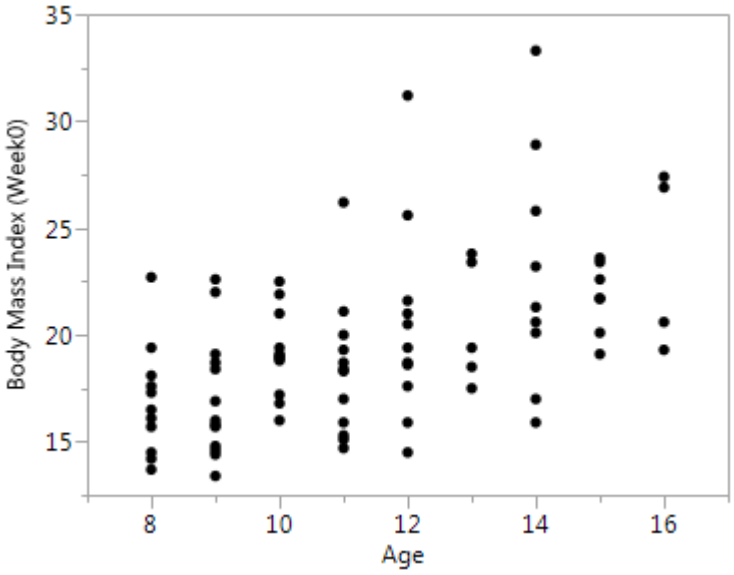


Source: Clinical Reviewer's analysis, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Reviewer Comment: The majority of patients (39%) in the study were Tanner Stage 1. Growth and developmental measurements are better assessed in pre-pubertal children and therefore a relatively meaningful assessment, although not ideal, can be made based on the study population.

The following figure shows the body mass index (BMI) by age.

Figure 3: Body Mass Index by Age, Study NK-104-4.01EU



Source: Clinical Reviewer's analysis, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Reviewer Comment: Only a few patients were overweight or obese as categorized by BMI.

Other Baseline Characteristics

The following table summarizes the baseline lipid parameters in the study population.

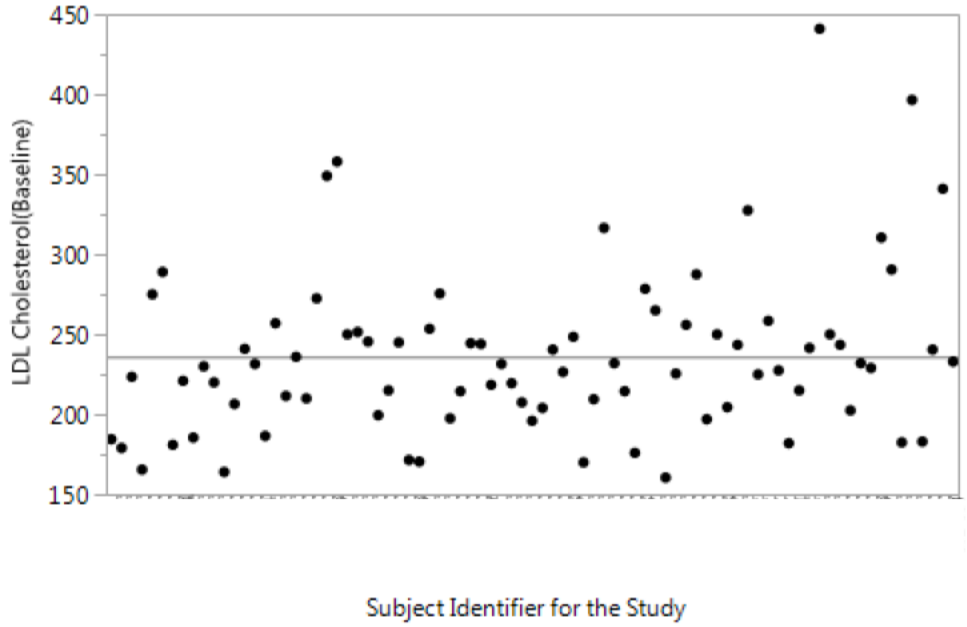
Table 8: Summary of Baseline Lipid Parameters, Study NK-104-4.01EU

	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, pg. 34/566.Abbreviations: Apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; non-HDL-C=non high-density lipoprotein cholesterol; SD=standard deviation; TC=total cholesterol.
a Percentage was calculated using the number of patients in the column heading in the denominator.
Note: Baseline was defined as the average valid values at the qualifying visit (Week -1) and the randomization visit (Week 0). If the lipid value at one visit was missing, the value at the other visit was used as baseline. If the lipid values at both visits were missing, then the last valid lipid value prior to the first dose of randomized study drug was used as baseline.

Reviewer Comment: In the population, 82% had a baseline LDL-C 190 mg/dL or greater, and all patients had LDL-C greater than or equal to 160 mg/dL. Mean lipid parameters were evenly divided amongst the treatment arms.

Figure 4: Scatterplot of Baseline LDL-C, Study NK-104-4.01EU



Source: Clinical Reviewer's analysis, from databases submitted by Sponsor, NDA 022363-Suppl -015.

The mean LDL-C was 235 mg/dL, minimum LDL-C was 160.5 mg/dL, and maximum LDL-C was 441 mg/dL.

Reviewer Comment: All patients in the study were genetically confirmed HeFH, but the scatterplot of baseline LDL-C values shows how phenotype expression is variable and leads to a wide range of LDL-C values (160 mg/dL- 441 mg/dL).

Treatment Compliance

The following table summarizes the exposure and compliance data for Study NK-104-4.01EU.

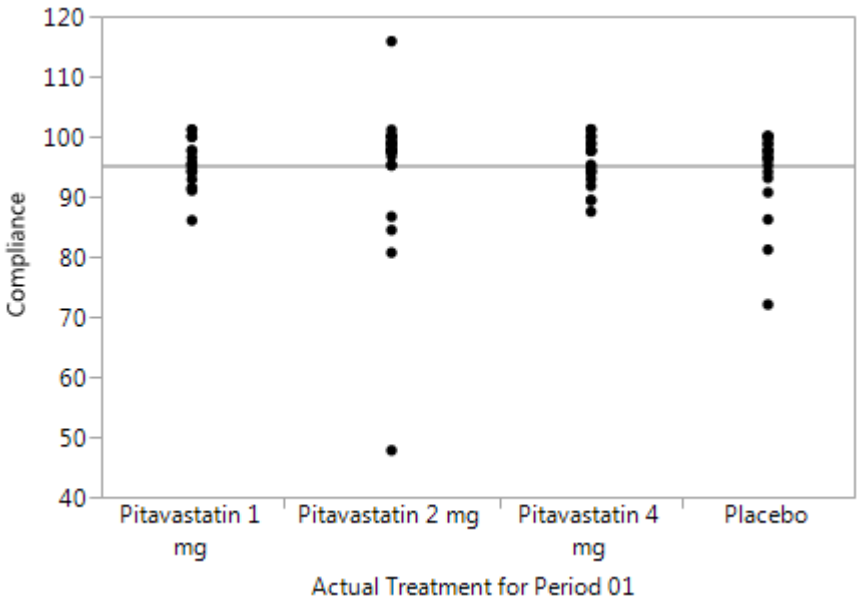
Table 9: Summary of Study Drug Exposure and Treatment Compliance, Study NK-104-4.01EU

	Pitavastatin 1 mg N=20	**Pitavastatin 2 mg N=24**	**Pitavastatin 4 mg N=19**	**Placebo N=19**	**Total N=82**
Exposure[a] (days)					
n	20	24	19	19	82
Mean (SD)	86.1 (3.0)	86.1 (3.2)	84.8 (2.0)	84.9 (2.9)	85.5 (2.9)
Exposure Category-n (%)					
< 28 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 28 to < 57 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 57 to < 85 days	4 (20.0)	4 (16.7)	7 (36.8)	10 (52.6)	25 (30.5)
≥ 85 days	16 (80.0)	20 (83.3)	12 (63.2)	9 (47.4)	57 (69.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Compliance[b] (%)					
n	20	24	19	19	82
Mean (SD)	95.5 (3.9)	95.1 (12.0)	96.2 (3.6)	94.3 (7.3)	95.3 (7.7)
Compliance Category-n (%)					
< 80%	0 (0.0)	1 (4.2)	0 (0.0)	1 (5.3)	2 (2.4)
≥ 80 to ≤ 120%	20 (100.0)	23 (95.8)	19 (100.0)	18 (94.7)	80 (97.6)
> 120%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Study Report NK.104.4.01EUSupplAnalysis Abbreviations: SD=standard deviation a Exposure=date of last dose of study drug – date of first dose of study drug +1.
b Compliance=100 × (total number of tablets taken)/presumed number of tablets taken in the period.

Reviewer Comment: The double-blind treatment period was 12 weeks, or 84 days. The mean study drug exposure was similar, approximately 85.5 days, between the treatment arms.

Figure 5: Summary of Compliance by Treatment Arm, Study NK-104-4.01EU



Source: Clinical Reviewer's analysis, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Reviewer Comment: Compliance was good across the treatment arms, with only 1 patient in pitavastatin 2 mg and 1 patient in placebo who had less than 80% compliance. Therefore, this compliance data supports the efficacy results of the study, that there was a reasonable likelihood of drug effect.

Efficacy Results – Primary Endpoint

The Applicant evaluated lipid endpoints using an analysis of covariance model (ANCOVA), with treatment as a factor and baseline LDL-C and age as covariates. The primary endpoint was the percent change in LDL-C from Baseline to Week 12 Endpoint. Any missing value was imputed using the control-based pattern, whereby the missing response variables obey the distribution of the response variables in the placebo group.

However, the Statistical team found that the control-based pattern of imputation used by the applicant meant that missing patients on the pitavastatin arms were treated as if they were on the placebo arm, including any observed intermediate measurements which are also treated as if on placebo. The Statistical team preferred an analysis that assumes that patients on pitavastatin treatment arms who discontinued experienced a "wash out" of the drug effect by the endpoint and using their intermediate measurements would be therefore be inappropriate since it could partly be explained by the drug. Therefore, to model a "wash-out" of treatment

effect, for patients on pitavastatin treatment arms with missing values, the statistical team used the patients' baseline measurement to impute those missing measurements.

The Statistical team also found that the applicant's analysis generated a high number of missing data (26.8%) for the primary endpoint. The applicant's method identified 20 of 22 patients as missing if they had missing data within a 9-day span of Day 84. After discussion between the Clinical and Statistical teams, it was decided that a 9-day window for LDL-C value was still reasonable to assume treatment effect. Therefore, these data were included in the analysis. After the inclusion of these data, the results remained unchanged, however, it yielded larger treatment effects, smaller standard errors and narrower confidence intervals.

LDL-C

Using the Statistical team's analysis, the least square (LS) mean percent change in LDL-C at Week 12 was -21.4% for the pitavastatin 1 mg dose group, -29.8% for the pitavastatin 2 mg dose group, -38.1% for the pitavastatin 4 mg dose group, and -1.0% for the placebo group.

The differences in LS mean percent change in LDL-C between each pitavastatin dose group compared to placebo were statistically significant indicating an overall dose-dependent reduction in LDL-C for all dose groups of pitavastatin in pediatric patients with HeFH.

Table 10: Percent Change in LDL-C from Baseline to Week 12, Study NK-104-4.01EU

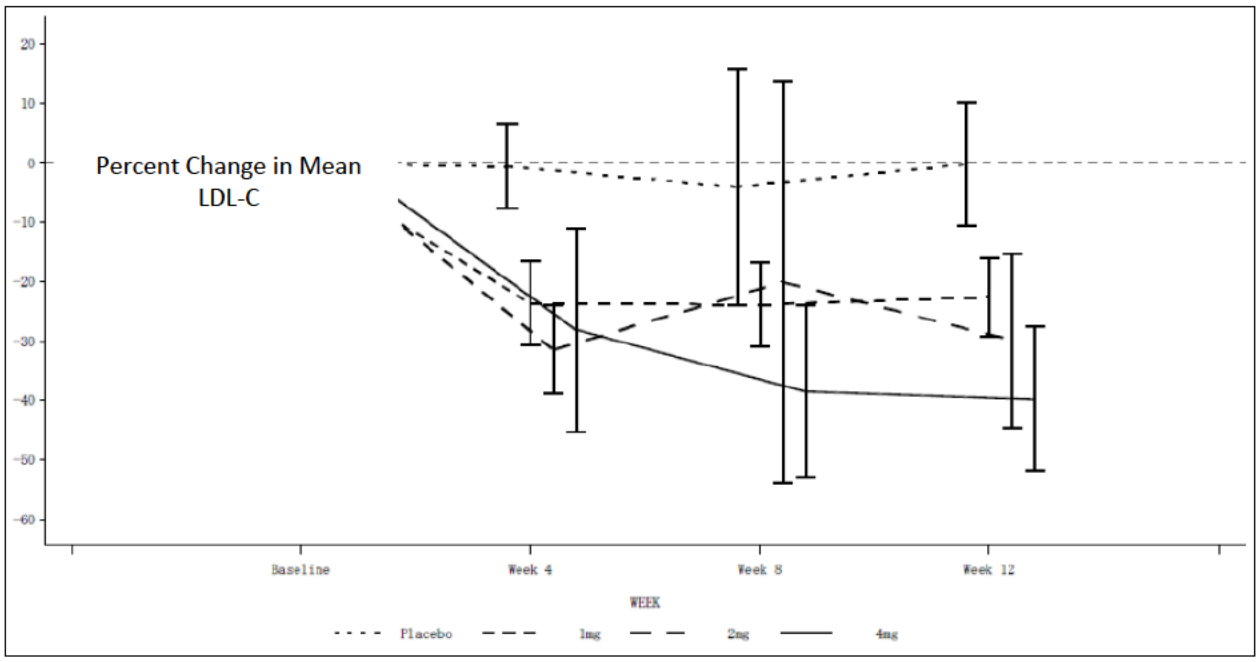
Reviewer's Analysis

Treatment	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg	-21.4 (2.62)	(-26.5, -16.2)	< 0.001
Pitavastatin 2 mg	-29.8 (2.37)	(-34.4, -25.1)	< 0.001
Pitavastatin 4 mg	-38.1 (2.62)	(-43.3, -33.0)	< 0.001
Placebo	-1.0 (2.64)	(-6.2, 4.2)	0.704
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-20.4 (3.75)	(-27.7, -13.0)	< 0.001
Pitavastatin 2 mg vs. Placebo	-28.8 (3.58)	(-35.8, -21.8)	< 0.001
Pitavastatin 4 mg vs. Placebo	-37.1 (3.70)	(-44.4, -29.9)	< 0.001

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

The following figure shows the mean percent change in LDL-C from Baseline at 4-week intervals during the double blind 12-Week study. Pitavastatin 4 mg showed the largest reduction in LDL-C by Week 10 and then the reduction seemed to plateau by Week 12. Pitavastatin 2 mg dose, showed a reduction at Week 4, but then increased at Week 8 and then decreased again at Week 12. All three treatment groups of pitavastatin had statistically significant reduction in LDL-C compared to Placebo.

Figure 6: Mean Percent Change (SD) from Baseline Over 12 Weeks of Treatment in LDL-C, Study NK-104-4.01EU



Source: Study Report NK.104.4.01EUSupplAnalysis , Figure 1, pg. 40/566.

Reviewer Comment: The confidence interval for pitavastatin 2 mg was wide at time point of 8 weeks, which indicated missing data and may account for the variability in LDL-C levels for that dose during the study.

Achievement of Treatment Goal LDL-C ≤ 110 mg/dL and LDL≤ 130 mg/dL

The following table summarizes the number and percent of patients who achieved the LDL-C target goal of ≤ 130 mg/dL and ideal goal of ≤ 110 mg/dL.

At Week 12, in the pitavastatin 1 mg arm, 1 out of 20 patients (5%) achieved treatment goal of LDL-C ≤ 130 mg/dL; for pitavastatin 2 mg, 7 out of 24 patients (29%) achieved treatment goal; and for pitavastatin 4 mg, 7 out of 19 patients (37%) achieved treatment goal. No patients in the placebo arm achieved this treatment goal.

Table 11: Number (%) of Patients Who Achieved LDL-C goal ≤ 130 mg/dL and ≤ 110 mg/dL, Study NK-104-4.01EU

	Placebo (N=19)		**Pitavastatin 1 mg (N=20)**	
	≤ 110 n / N (%)	**≤ 130 n /N (%)**	**≤ 110 n / N (%)**	**≤ 130 n / N (%)**
Week 4	0 / 19 (0.00)	0 / 19 (0.00)	0 / 20 (0.00)	2 / 20 (0.10)
Week 8	0 / 19 (0.00)	1 / 19 (0.053)	1 / 20 (0.05)	2 / 20 (0.10)
Week 12	0 / 19 (0.00)	0 / 19 (0.00)	1 / 20 (0.05)	1 / 20 (0.05)

	Pitavastatin 2 mg (N=24)		**Pitavastatin 4 mg (N=19)**	
	≤ 110 n / N (%)	**≤ 130 n / N (%)**	**≤ 110 n / N (%)**	**≤ 130 n / N (%)**
Week 4	1 / 24 (0.042)	3 / 24 (0.125)	0 / 19 (0.00)	4 / 19 (0.211)
Week 8	0 / 24 (0.00)	2 / 24 (0.083)	4 / 19 (0.211)	7 / 19 (0.368)
Week 12	2 / 24 (0.083)	7 / 24 (0.292)	3 / 19 (0.158)	7 / 19 (0.368)

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Reviewer Comment: Pitavastatin 4 mg was the most effective dose in helping patients to achieve their LDL-C target goal of ≤ 130 mg/dL, a target identified in treatment guidelines for children and adolescents with HeFH. However, since phenotype expression can vary, and some HeFH patients had baseline LDL-C at lower ranges, pitavastatin 1 mg was effective at achieving LDL-C ≤ 130 mg/dL in 5% of patients on that dose.

Efficacy Results – Secondary and other relevant endpoints

HDL-C

As the following table shows, the least square mean percent change in HDL-C was not statistically significantly different at Week 12 for any pitavastatin dose group compared to placebo.

Table 12: Percent Change From Baseline to Week 12 in HDL-C, Study NK-104-4.01EU

Reviewer's Analysis

Treatment	LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	7.2 (3.10)	(1.1, 13.2)	0.021
Pitavastatin 2 mg	-2.8 (2.69)	(-8.1, 2.4)	0.294
Pitavastatin 4 mg	-1.7 (2.97)	(-7.6, 4.1)	0.560
Placebo	-0.6 (2.95)	(-6.4, 5.2)	0.837
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	7.8 (4.27)	(-0.6, 16.1)	0.069
Pitavastatin 2 mg vs. Placebo	-2.2 (3.99)	(-10.0, 5.6)	0.580
Pitavastatin 4 mg vs. Placebo	-1.1 (4.19)	(-9.3, 7.1)	0.789

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Triglycerides

The following table shows that the least square mean percent change in TG was not statistically significantly different at Week 12 for any of the pitavastatin dose groups compared to placebo.

Table 13: Percent Change From Baseline to Week 12 in Triglycerides, Study NK-104-4.01EU

Reviewer's Analysis

Treatment	LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	-12.3 (7.32)	(-26.7, 2.1)	0.093
Pitavastatin 2 mg	-13.6 (7.80)	(-28.9, 1.7)	0.082
Pitavastatin 4 mg	3.5 (7.27)	(-10.7, 17.8)	0.630
Placebo	1.0 (7.19)	(-13.1, 15.1)	0.885
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-13.3 (10.25)	(-33.4, 6.7)	0.193
Pitavastatin 2 mg vs. Placebo	-14.6 (10.67)	(-35.6, 6.3)	0.170
Pitavastatin 4 mg vs. Placebo	2.5 (10.21)	(-17.6, 22.5)	0.809

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Total Cholesterol

The least square mean percent change in TC from Baseline to Week 12 was -16.1% for the pitavastatin 1 mg dose group, -24.5% for the pitavastatin 2 mg dose group, -29.7% for the pitavastatin 4 mg dose group, and -0.7% for the placebo group. The differences in LS mean percent change in TC between each pitavastatin dose group versus placebo at Week 12 were statistically significant.

Table 14: Percent Change From Baseline to Week 12 in Total Cholesterol, Study NK-104-4.01EU

Reviewer's Analysis

Treatment	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg	-16.1 (2.18)	(-20.4, -11.8)	< 0.001
Pitavastatin 2 mg	-24.5 (1.95)	(-28.3, -20.6)	< 0.001
Pitavastatin 4 mg	-29.7 (2.15)	(-33.9, -25.4)	< 0.001
Placebo	-0.7 (2.17)	(-5.0, 3.6)	0.745
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-15.4 (3.11)	(-21.5, -9.3)	< 0.001
Pitavastatin 2 mg vs. Placebo	-23.8 (2.94)	(-29.5, -18.0)	< 0.001
Pitavastatin 4 mg vs. Placebo	-29.0 (3.06)	(-34.9, -23.0)	< 0.001

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Non-HDL-C

The LS mean percent change in non-HDL-C from baseline to Week 12 was -20.9% for the pitavastatin 1 mg dose group, -28.6% for the pitavastatin 2 mg dose group, -35.7% for the pitavastatin 4 mg dose group, and -0.7% for the placebo group. The differences in LS mean percent change in non-HDL-C between each pitavastatin dose group versus placebo at Week 12 were statistically significant.

Table 15: Percent Change From Baseline to Week 12 in non-HDL-C, Study NK-104-4.01EU

Reviewer's Analysis

Treatment	LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	-20.9 (2.66)	(-26.1, -15.7)	< 0.001
Pitavastatin 2 mg	-28.6 (2.40)	(-33.3, -23.9)	< 0.001
Pitavastatin 4 mg	-35.7 (2.67)	(-40.9, -30.5)	< 0.001
Placebo	-0.7 (2.69)	(-6.0, 4.5)	0.785

Treatment Comparison	LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg vs. Placebo	-20.1 (3.82)	(-27.6, -12.7)	< 0.001
Pitavastatin 2 mg vs. Placebo	-27.9 (3.62)	(-35.0, -20.8)	< 0.001
Pitavastatin 4 mg vs. Placebo	-35.0 (3.78)	(-42.4, -27.6)	< 0.001

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Apo B

The LS mean percent change in Apo B from baseline to Week 12 was -20.1% for the pitavastatin 1 mg dose group, -25.0% for the pitavastatin 2 mg dose group, -27.8% for the pitavastatin 4 mg dose group, and -2.5% for the placebo group. The differences in LS mean percent change in Apo B between each pitavastatin dose group versus placebo at Week 12 were statistically significant.

Table 16: Percent Change From Baseline to Week 12 in Apolipoprotein B, Study NK-10404.01EU

Reviewer's Analysis

Treatment	LS Mean (SE)	95% CI	p-value
Pitavastatin 1 mg	-20.1 (2.73)	(-25.5, -14.8)	< 0.001
Pitavastatin 2 mg	-25.0 (2.45)	(-29.8, -20.2)	< 0.001
Pitavastatin 4 mg	-27.8 (2.72)	(-33.2, -22.5)	< 0.001
Placebo	-2.5 (2.74)	(-7.8, 2.9)	0.366
Treatment Comparison	**LS Mean (SE)**	**95% CI**	**p-value**
Pitavastatin 1 mg vs. Placebo	-17.6 (3.91)	(-25.3, -10.0)	< 0.001
Pitavastatin 2 mg vs. Placebo	-22.5 (3.68)	(-29.7, -15.3)	< 0.001
Pitavastatin 4 mg vs. Placebo	-25.3 (3.86)	(-32.9, -17.8)	< 0.001

Source: Statistical team, Dr. R. Crackel, from databases submitted by Sponsor, NDA 022363-Suppl -015.

Reviewer comment: Pitavastatin significantly lowered LDL-C, TC, non-HDL-C, and ApoB across the dose range, but did not meaningfully change HDL-C or TG in this population at any dose. This reviewer recommends lipid parameter values for labeling that represent the best estimate of the true treatment effect, which in this case was the statistical team's analysis.

Durability of Response/ Persistence of Effect

There was significant LDL-C reduction as early as Week 4, which persisted through Week 12. As shown in the LDL-C efficacy tables, LDL-C reductions were consistent across all time points for all age groups.

Additional Analyses Conducted on the Individual Trial

Subgroup efficacy analysis by sex and age group were conducted by the Statistical team. Please see Dr. Roberto Crackel's review for complete report. According to their analysis by sex, each dosage level is superior to placebo in both males and females and there is no significant interaction between sex and treatment within each dosage level. Similarly, subgroup analysis by age (≥8 to < 12 and ≥12 to ≤ 16) showed that each dosage level is superior to placebo in each age category. As with sex, there was no significant interaction between age groups and treatment within each dosage level.

7. Review of Safety (Study NK.104.4.01EU)

7.1. Safety Review Approach

The major safety concern for statins as a class of drugs is muscle toxicity, with the most serious complication being rhabdomyolysis. In 21 clinical trials, with 180,000 person-years follow-up in statin or placebo treated subjects, myopathy (muscle symptoms with CK> 10 x ULN) occurred in 5 subjects per 100,000 person-years and rhabdomyolysis in 1.6 subjects per 100,000 person-years (placebo-corrected) (McKenney and Davidson et al. 2006). During clinical trials with rosuvastatin, 1.0% and 0.4% of the subjects treated with 80mg/day developed myopathy and rhabdomyolysis, respectively, so the 80mg/day dose was not approved.

Statins have also been associated with elevated liver transaminases. Asymptomatic elevated liver transaminase >3 x ULN occur in <1% of patients on low and intermediate doses of statins and 2 to 3% at high doses (McKenney and Davidson et al. 2006). The mechanism of action of the statin mediated liver enzyme elevation has not been elucidated; however, modest elevations do not appear to signal risk for significant liver injury, even with continued statin treatment.

Lastly, as these are studies in pediatric patients, growth and development data will be reviewed by Division of pediatrics and Maternal Health (DPMH).

7.2. Review of the Safety Database

7.2.1. Overall Exposure

For the supplemental analysis Safety Set, mean exposure to study drug was 86.1 days for the pitavastatin 1 mg dose group, 86.1 days for the pitavastatin 2 mg dose group, 84.8 days for the pitavastatin 4 mg dose group, and 84.9 days for the placebo group.

Table 17: Summary of Study Drug Exposure and Treatment Compliance, Safety Set, Study NK-104-4.01EU

	Pitavastatin 1 mg N=20	Pitavastatin 2 mg N=24	Pitavastatin 4 mg N=19	Placebo N=19	Total N=82
Exposure[a] (days)					
n	20	24	19	19	82
Mean (SD)	86.1 (3.0)	86.1 (3.2)	84.8 (2.0)	84.9 (2.9)	85.5 (2.9)
Exposure Category-n (%)					
< 28 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 28 to < 57 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 57 to < 85 days	4 (20.0)	4 (16.7)	7 (36.8)	10 (52.6)	25 (30.5)
≥ 85 days	16 (80.0)	20 (83.3)	12 (63.2)	9 (47.4)	57 (69.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Compliance[b] (%)					
n	20	24	19	19	82
Mean (SD)	95.5 (3.9)	95.1 (12.0)	96.2 (3.6)	94.3 (7.3)	95.3 (7.7)
Compliance Category-n (%)					
< 80%	0 (0.0)	1 (4.2)	0 (0.0)	1 (5.3)	2 (2.4)
≥ 80 to ≤ 120%	20 (100.0)	23 (95.8)	19 (100.0)	18 (94.7)	80 (97.6)
> 120%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Study Report NK.104.4.01EUSupplAnalysis , Table 7, pg. 35/566. Abbreviations: SD=standard deviation a Exposure=date of last dose of study drug – date of first dose of study drug +1.b Compliance=100 × (total number of tablets taken)/presumed number of tablets taken in the period.

Reviewer Comment: Exposure and compliance were similar in the pitavastatin treatment groups vs. placebo.

7.2.2. Relevant characteristics of the safety population:

Refer to Section 6.1.2 for demographic and other baseline characteristics of the population.

7.2.3. Adequacy of the safety database:

The size of the safety database was adequate and followed the recommendation in the Written Request of at least 80 patients. The duration of double-blind treatment, 12 weeks, and the patient demographic, HeFH children and adolescents > 8 years of age and ≤ 16 years of age also

followed the Written Request requirements.

7.3. Adequacy of Applicant's Clinical Safety Assessments

The safety evaluations were followed as outlined in the pediatric Written Request. Namely, the Written Request stated that:

- 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 examination (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 rhabdomyolysis.

7.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues in data quality or the quality of the overall submission that had an effect on the safety review.

7.3.2. Categorization of Adverse Events

All adverse events were coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 15 and was considered adequate on review of sample coding.

7.3.3. Routine Clinical Tests

A safety laboratory panel was done at various time points during the trial and included:

Hematology: white blood cell count and differential, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelets [Screening, Week 0, and Week 12]

Serum chemistry: sodium, potassium, chloride, bicarbonate, urea, alkaline phosphatase, bilirubin, total protein, albumin, calcium, phosphate, gamma-glutamyl transferase, lactic dehydrogenase, fasting glucose, HbA1c, and cystatin-C. [Screening, Week 0, and Week 12]

Liver and muscle enzymes: ALT/AST and creatine kinase [Screening, Week 0, Week 4, Week 8, and Week 12]

Urinalysis parameters included pH, protein, glucose, ketones, blood, nitrates, and specific gravity. If protein was detected, the urinary albumin/creatinine ratio was assessed. [Screening, Week 0, and Week 12]

Other safety evaluations included physical examinations, ECG, assessment of sexual maturation (including assessments of height, sexual maturation, and Tanner staging) and adverse events.

Hormone assessment included cortisol, DHEAS, estradiol (girls), testosterone (boys), LH, and FSH at Screening, Week 0, and Week 12.

Tanner staging assessment occurred at Weeks 0 and 12.

Pitavastatin and pitavastatin lactone concentrations were collected at either Week 8 (Visit 5) or Week 12 (Visit 6), depending on patient availability. On the day of the PK assessment, the daily dose of study drug was administered at the study visit. Pharmacokinetic blood samples were collected at trough and at 1-hour post-dose at the given study visit.

7.4. Safety Results

7.4.1. Deaths

No deaths were reported in the trial.

7.4.2. Serious Adverse Events

There were no serious adverse events in the trial.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patients were discontinued from the study due to a treatment emergent adverse event.

7.4.4. Significant Adverse Events

Musculoskeletal adverse events

During the 12-week study, there were four patients (two patients on pitavastatin 1 mg, one patient on pitavastatin 2 mg, and one patient on pitavastatin 4 mg) who had an adverse event in the System Organ Class (SOC) Musculoskeletal and Connective Tissue Disorder compared to no patients in the placebo group. These 4 patients had 6 occurrences of these TEAEs.

There was one patient with “blood creatine phosphokinase increased” in the Investigations SOC who was on pitavastatin 2 mg during the 12-week study phase.

Table 18: Summary of Musculoskeletal and Connective Tissue Disorder and Creatine Kinase Increase, Study NK-104-4.01EU

	Placebo N=19, (%) [number of occurrences]	Pitavastatin 1 mg N=20, (%) [number of occurrences]	Pitavastatin 2 mg N=24, (%) [number of occurrences]	Pitavastatin 4 mg N=19, (%) [number of occurrences]	Total N=82, (%) [number of occurrences]
SOC/Musculoskeletal and Connective Tissue Disorder	0	2 (10%)[2]	1 (4.2%)[2]	1(5.3%)[2]	4 (4.9%)[6]
Arthralgia	0	0	1 (4.2%)[2]	0	1 (1.2%)[2]
Musculoskeletal pain	0	0	0	1 (5.3%)[1]	1 (1.2%)[1]
Mylagia	0	0	0	1 (5.3%)[1]	1 (1.2%)[1]
Pain in Extremity	0	1 (5.0%)[1]	0	0	1 (1.2%)[1]
Musculoskeletal stiffness	0	1 (5.0%)[1]	0	0	1(1.2%)[1]
SOC/ Investigations					
Blood Creatine Phosphokinase Increased					
	0	0	1 (4.2%)	0	1 (1.2%)

Source: Applicant response to Information request, 11 March 2019.

Patient Narratives

Patient ID# (b) (6) 13-year-old male on pitavastatin 2 mg, reported TEAE of arthralgia, mild in severity, and lasting 17 days (b) (6) treatment was required (ibuprofen 400 mg given), but study drug was not interrupted, and patient recovered. This patient also reported increased AST, mild in severity; lasting 29 days (b) (6) AST was increased to 49 U/L (normal range 0-40 U/L). Patient also reported increased CK at the same time, mild in severity; lasting 29 days (b) (6) CK was increased to 490 U/L (normal range 25-300 U/L). CK increased to <2XULN. This CK increase was reported as "Blood Creatine Phosphokinase Increased". Study drug administration was interrupted. Patient recovered. Patient again reported arthralgia on (b) (6) mild in severity, study drug interrupted, and patient recovered.

Reviewer Comment on Patient ID# (b) (6) *Arthralgia occurred on positive re-challenge of study drug (pitavastatin 2 mg), suggesting possible relatedness to drug. AST and CK increases were not clinically meaningful and both laboratory changes were reversible.*

Patient ID# (b) (6) 14-year-old male on pitavastatin 1 mg, reported musculoskeletal (neck) stiffness, lasting 9 days (b) (6) treatment required (paracetamol 500 mg), and patient recovered. Study drug was not discontinued.

Reviewer Comment on Patient ID# (b) (6) *This case less likely to be drug-related and may be a self-limited injury. The neck stiffness was short in duration, and patient recovered with analgesia and without study drug (pitavastatin 1 mg) discontinuation.*

Patient ID# (b) (6) 12-year-old male on pitavastatin 1 mg, reported pain in right leg, mild in severity, and lasting 46 days (b) (6) no action was taken, and patient recovered.

Reviewer Comment on Patient ID# (b) (6) *This adverse event is possibly related to drug due to temporal association with the drug.*

Patient ID (b) (6) 10-year-old male on pitavastatin 4 mg, reported musculoskeletal (shoulder) pain, lasting 5 days, related to a fall, (b) (6) treatment required, use of shoulder splint, patient recovered. Patient also reported pain in legs (myalgia) lasting 8 days (b) (6) CK was checked, but was within normal limits, and patient recovered.

Reviewer Comment on Patient ID (b) (6) *This patient had shoulder pain related to a fall, that was not drug-related. The short-duration myalgia may also have been a self-limited injury.*

Reviewer Comment: Treatment Emergent AEs that mapped to Musculoskeletal and Connective Tissue Disorders occurred with all doses of pitavastatin but did not occur with Placebo,

suggesting that these AEs are drug-related. The incidence of these events was 6.35% in the combined pitavastatin treatment arms vs. placebo. However, of the 4 patients with AEs in the Musculoskeletal SOC, 2 patients may not be drug-related adverse events. Because the study population was small, it was not possible to determine if these AEs were dose-related. However, from adult pitavastatin placebo-controlled trials, myalgia is reported at slightly higher frequencies with increasing dose of pitavastatin. There were no cases suggestive of myopathy or rhabdomyolysis, and no events resulted in permanent discontinuation of study drug.

Skeletal Muscle Biochemistry

There was one patient on pitavastatin 1 mg who reportedly had an elevated CK ≥3XULN to < 5XULN. No other patients had CK elevations during the study.

Table 19: CK Elevations, Study NK-104-4.01EU, Safety Set

CK Elevations	Placebo N=19, (%)	Pitavastatin 1 mg N=20, (%)	Pitavastatin 2 mg N=24, (%)	Pitavastatin 4 mg N=19, (%)	Total N=82, (%)
>=3XULN to <5XULN	0(0.0)	1(5.0)	0(0.0)	0(0.0)	1(1.2)
>=5XULN to <10XULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=10XULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Applicant response to Information request, 11 March 2019.

Patient ID# (b) (6) had an increased creatine kinase on Visit 5 (b) (6) of 1097 U/L (normal range 25-300 U/L). No other reported AE associated with this laboratory increase. The next CK lab value on (b) (6) was normal at 44 U/L.

Reviewer Comment: For comparison of musculoskeletal AEs in the open-label extension (see Section 9). In that study, 6 out of 85 patients reported an AE that mapped to the Musculoskeletal and Connective Tissue SOC. However, on further review, 3 of the 6 may not have been study drug related. There were no events suggestive of myopathy or rhabdomyolysis. Consistent with the 12-week trial, the incidence of musculoskeletal adverse events potentially attributable to pitavastatin was low.

Hepatic adverse events

Patient ID# (b) (6) - 13-year-old male on pitavastatin 2 mg, reported AE of increased AST to 49 U/L (normal range 0-40 U/L) on (b) (6) and AST of 46 U/L on (b) (6) Corresponding ALT not increased on those visit days, while CPK was mildly elevated. (See narrative above).

Hepatic Biochemistry

None of the subjects met the criteria for Hy's Law.[2] The following plot is of ALT elevations (x-axis) vs. bilirubin elevations (y-axis), which shows a few ALT levels > 1XULN but < 2XULN for patients in treatment arm

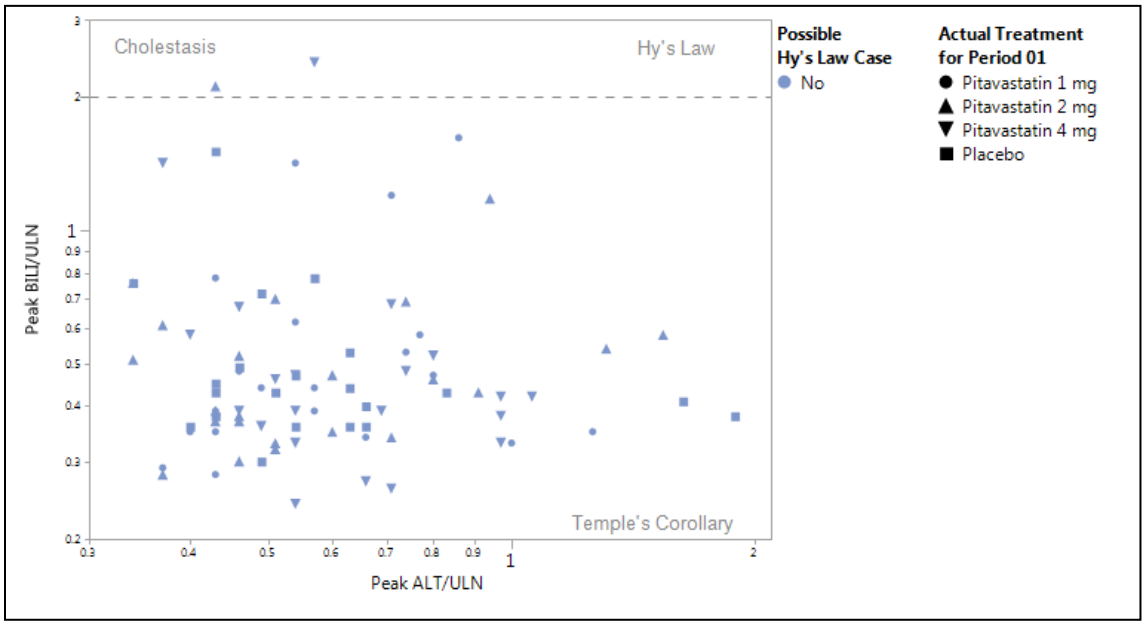


Figure 7: Peak ALT vs Peak Total Bilirubin, Safety Set, Study NK-104-4.01EU

[2] ALT ≥3×ULN or AST ≥3×ULN and total bilirubin ≥2×ULN without initial findings of cholestasis (serum alkaline phosphatase [ALP] activity >2 x ULN) No other reason can be found to explain the combination of increased AT and total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

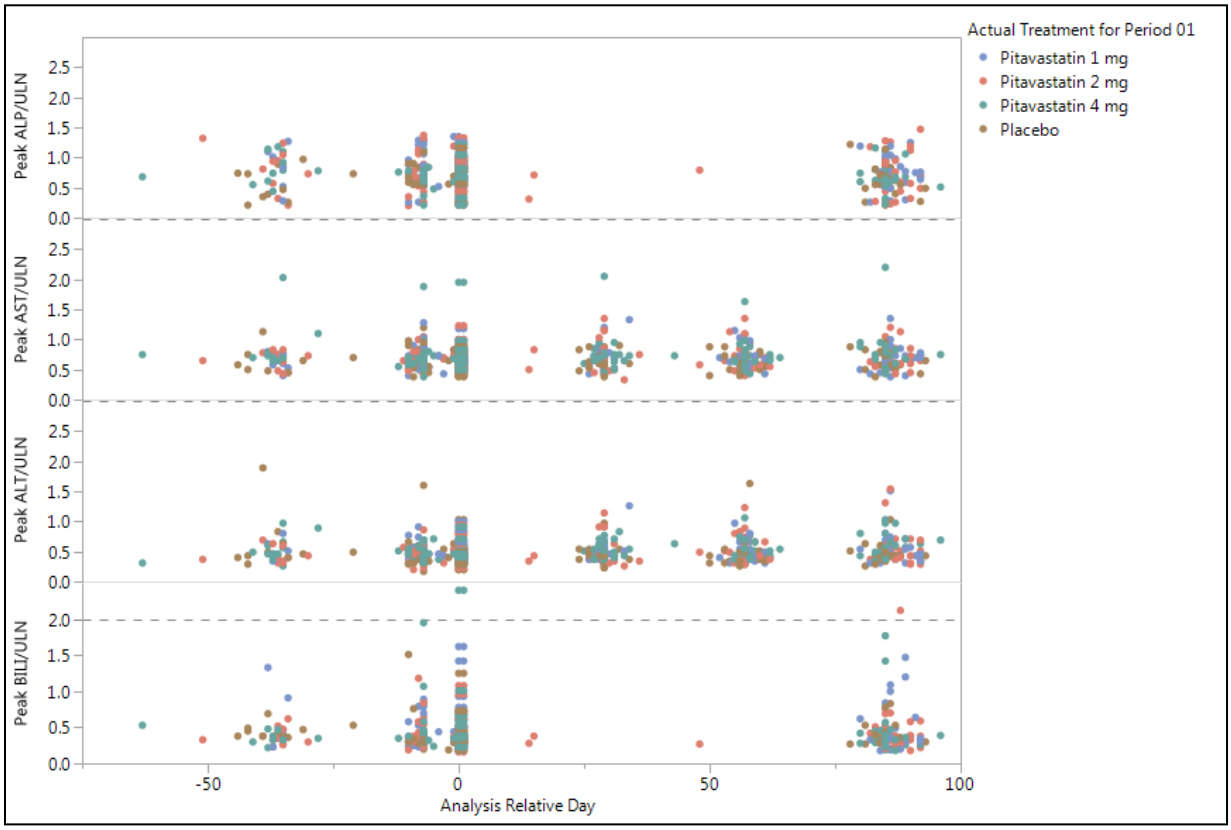


Figure 8: Peak Liver Laboratory Test per Patient by Study Day, Study NK-104-4.01EU

Overall, as seen in the figure above, most patients in the 12- week double blind study had liver enzyme levels that were clustered around 0.5-1.0 XULN. There were no ALT/AST elevations ≥ 3XULN during this treatment period. The following table summarizes the ALT/AST elevations.

Table 20: AST/ALT Elevations, Safety Set, Study NK-104-4.01EU

ALT Elevations	Placebo N=19, (%)	Pitavastatin 1 mg N=20, (%)	Pitavastatin 2 mg N=24, (%)	Pitavastatin 4 mg N=19, (%)	Total N=82, (%)
>=3XULN to <5XULN	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)
>=5XULN to <10XULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=10XULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AST Elevations	Placebo N=19, (%)	Pitavastatin 1 mg N=20, (%)	Pitavastatin 2 mg N=24, (%)	Pitavastatin 4 mg N=19, (%)	Total N=82, (%)
>=3XULN to <5XULN	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0(0.0)
>=5XULN to <10XULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=10XULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Reviewer Comment: For comparison of the liver enzyme abnormalities in the open-label extension, see Section 9. In that study 1 out of 85 patients had ALT/AST elevations that was >3XULN and another patient had ALT/AST elevation that was nearly >3XULN. Consistent with the 12-week trial, the incidence of liver enzyme abnormalities potentially attributable to pitavastatin was low.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The overall incidence of TEAEs was 54.9% (45 patients) who reported any TEAE. The incidence of TEAE by treatment arm was 70.0% (14 patients) for the pitavastatin 1 mg dose group, 58.3% (14 patients) for the pitavastatin 2 mg dose group, 36.8% (7 patients) for the pitavastatin 4 mg dose group, and 52.6% (10 patients) for the placebo group.

The most common system organ classes of TEAEs were infections and infestations (23 [28.0%] patients), gastrointestinal disorders (14 [17.1%] patients), and nervous system disorders (13 [15.9%] patients).

Overall, the most commonly reported preferred terms of TEAEs in the study were the following:

- Nasopharyngitis (3 [15.0%] patients in the pitavastatin 1 mg dose group, 6 [25.0%] patients in the pitavastatin 2 mg dose group, 2 [10.5%] patients in the pitavastatin 4 mg dose group, and 5 [26.3%] patients in the placebo group);
- Headache (5 [25.0%] patients in the pitavastatin 1 mg dose group, 5 [20.8%] patients in the pitavastatin 2 mg dose group, 1 [5.3%] patient in the pitavastatin 4 mg dose group, and 2 [10.5%] patients in the placebo group);
- Abdominal pain (2 [10.0%] patients in the pitavastatin 1 mg dose group, 2 [8.3%] patients in the pitavastatin 2 mg dose group, and 1 [5.3%] patients in the placebo group);
- Influenza (2 [10.5%] patients in the pitavastatin 4 mg dose group, and 2 [10.5%] patients in the placebo group);
- Vomiting (1 (5.3%) patient in the pitavastatin 4 mg dose group and 2 [10.5%] patients in the placebo group), and
- Abdominal discomfort (2 [10.5%] patients in the placebo group).

No other TEAE occurred in more than two (2) patients in any treatment group.

Table 21: Summary of Treatment Emergent Adverse Events (≥2 Patients in Any Treatment Group by System Organ Class and Preferred Term, Study NK-104-4.01EU

MedDRA System Organ Class Preferred Term	Pitavastatin 1 mg N=20 n (%)	Pitavastatin 2 mg N=24 n (%)	Pitavastatin 4 mg N=19 n (%)	Placebo N=19 n (%)	Total N=82 n (%)
Patient with any TEAE[a]	14 (70.0)	14 (58.3)	7 (36.8)	10 (52.6)	45 (54.9)
Infections and Infestations	4 (20.0)	8 (33.3)	4 (21.1)	7 (36.8)	23 (28.0)
Nasopharyngitis	3 (15.0)	6 (25.0)	2(10.5)	5 (26.3)	16 (19.5)
Influenza	0 (0.0)	0 (0.0)	2 (10.5)	2 (10.5)	4 (4.9)
Gastrointestinal Disorders	3 (15.0)	6 (25.0)	1 (5.3)	4 (21.1)	14 (17.1)
Abdominal Pain	2 (10.0)	2 (8.3)	0 (0.0)	1 (5.3)	5 (6.1)
Vomiting	0 (0.0)	0 (0.0)	1 (5.3)	2 (10.5)	3 (3.7)
Abdominal Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	2 (2.4)
Nervous System Disorders	5 (25.0)	5 (20.8)	1 (5.3)	2 (10.5)	13 (15.9)
Headache	5 (25.0)	5 (20.8)	1 (5.3)	2 (10.5)	13 (15.9)

Abbreviations: MedDRA= Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.a Treatment-emergent adverse events during the double-blind period were defined as those adverse events that had a start date on or after the first dose of randomized study drug.

Reviewer Comment: To analyze by a different method, this reviewer combined the three pitavastatin treatment arms in the table above to compare to placebo.

Nasopharyngitis – All pitavastatin doses - 11/ 63= 17.5% vs. 5/ 19= 26.3% placebo

Influenza- All pitavastatin doses- 2 / 63 = 3.17% vs. 2/19= 10.5% placebo

Abdominal pain – All pitavastatin doses - 4 /63= 6.4% vs. 1/19= 5.3% placebo

Abdominal discomfort- All pitavastatin doses- 0 vs. 2/19= 10.5% placebo

Vomiting- All pitavastatin doses- 1/63= 1.6% vs. 2/19= 10.5% placebo

Headache- All pitavastatin doses- 11/63= 17.5% vs. 2/19= 10.5% placebo

Combining abdominal pain and abdominal discomfort, the incidence is higher in placebo (15.8%) than in pitavastatin. When all doses of pitavastatin are compared to placebo, only headache incidence is slightly higher than placebo. However, the placebo group is a very small comparator group (n=19) and only one more patient with headache in placebo would have tilted the incidence toward placebo. Therefore, none of these adverse events are recommended for listing in pitavastatin labeling because these AEs are not significantly higher incidence than placebo.

7.4.6. Laboratory Findings

Hematology

No notable changes in percent change from Baseline to Week 12 were observed for any hematology parameters.

Chemistry

No clinically meaningful patterns were identified in the percent change from Baseline to Week 12 clinical chemistry parameters.

7.4.7. Vital Signs

No clinically important differences in mean changes in systolic blood pressure, diastolic blood pressure, or heart rate from baseline to Week 12 were noted.

Table 22: Change from Baseline to Week 12/Early Termination, Study NK-104-4.01EU

Parameter Statistic	Pitavastatin 1 mg N=20	Pitavastatin 2 mg N=24	Pitavastatin 4 mg N=19	Placebo N=19	Total N=82
Systolic BP, mmHg					
Baseline[a] mean (SD)	112.4 (11.5)	106.1 (9.4)	104.2 (11.4)	103.9 (10.2)	106.7 (10.9)
Week 12/ET mean (SD)	111.5 (7.1)	108.7 (12.2)	105.7 (5.5)	104.4 (9.9)	107.7 (9.5)
Mean (SD) change	-1.0 (8.5)	2.6 (11.5)	1.5 (10.2)	0.5 (8.5)	1.0 (9.8)
Diastolic BP, mmHg					
Baseline mean (SD)	64.8 (8.1)	61.3 (7.1)	60.8 (8.1)	64.9 (8.0)	62.9 (7.9)
Week 12/ET mean (SD)	66.2 (7.8)	65.8 (7.0)	63.8 (7.6)	64.7 (8.1)	65.2 (7.5)
Mean (SD) change	1.4 (7.1)	4.5 (9.0)	3.0 (8.0)	-0.2 (7.2)	2.3 (8.0)
Heart rate, bpm					
Baseline mean (SD)	71.0 (13.2)	71.0 (11.9)	74.4 (11.0)	75.1 (9.2)	72.7 (11.4)
Week 12/ET mean (SD)	73.7 (12.6)	73.7 (11.8)	76.1 (10.7)	72.3 (10.2)	73.9 (11.3)
Mean (SD) change	2.7 (8.3)	2.6 (13.5)	1.6 (7.9)	-2.7 (9.8)	1.2 (10.4)

Source: Study Report NK.104.4.01EUSupplAnalysis , Table 41, pg. 72/566. Abbreviations: BP=blood pressure; bpm=beats per minute; ET=early termination; SD=standard deviation a Baseline was defined as the randomization visit (Week 0) measurement. If the measurement at this visit was missing, the last measurement prior to the first dose of randomized study drug was used.

No clinically important differences in mean changes in height or weight from baseline to Week 12 were noted.

Table 23: Change from Baseline to Week 12/Early Termination in Height and Weight, Study NK-104-4.01EU

Parameter Statistic	Pitavastatin 1 mg N=20	Pitavastatin 2 mg N=24	Pitavastatin 4 mg N=19	Placebo N=19	Total N=82
Height, cm					
Baseline[a] mean (SD)	156.2 (15.1)	152.9 (15.2)	149.9 (13.6)	151.3 (14.5)	152.6 (14.6)
Week 12/ET mean (SD)	157.4 (14.9)	154.1 (15.2)	151.2 (13.9)	152.3 (14.4)	153.8 (14.5)
Mean (SD) change	1.3 (0.9)	1.2 (1.4)	1.3 (1.2)	1.0 (1.1)	1.2 (1.2)
Weight, kg					
Baseline mean (SD)	52.55 (20.01)	47.85 (16.44)	42.79 (10.21)	44.24 (16.74)	46.99 (16.43)
Week 12/ET mean (SD)	54.01 (20.67)	49.05 (16.40)	44.30 (10.41)	45.07 (16.50)	48.24 (16.60)
Mean (SD) change	1.47 (1.30)	1.20 (1.68)	1.51 (1.31)	0.84 (1.19)	1.25 (1.40)

Source: Source: Study Report NK.104.4.01EUSupplAnalysis , Table 42, pg. 72/566. Abbreviations: BP=blood pressure; bpm=beats per minute; ET=early termination; SD=standard deviations Baseline was defined as the randomization visit (Week 0) measurement. If the measurement at this visit was missing, the last measurement prior to the first dose of randomized study drug was used.

7.4.8. Electrocardiograms (ECGs)

7.4.9. QT

Not applicable.

7.4.10. Immunogenicity

Not applicable.

7.5. Safety Analyses by Demographic Subgroups

The following table summarizes all TEAE by the subgroup males. There were a total of 4 male patients who reported a TEAE in Musculoskeletal and Connective Tissue Disorders.

Table 24: Summary of All Treatment Emergent Adverse Events by Subgroup Males, Safety Set, Study NK-104-4.01EU

MedDRA 【System Organ Class】 Preferred Term	Placebo (N=8)	1mg (N=9)	2mg (N=9)	4mg (N=10)	Total (N=36)
Total Events	5(62.5) [8]	8(88.9) [15]	5(55.6) [12]	5(50.0) [11]	23(63.9) [46]
【EAR AND LABYRINTH DISORDERS】	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(10.0) [1]	1(2.8) [1]
EAR PAIN	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(10.0) [1]	1(2.8) [1]
【GASTROINTESTINAL DISORDERS】	0(0.0) [0]	2(22.2) [2]	2(22.2) [2]	1(10.0) [1]	5(13.9) [5]
ABDOMINAL PAIN	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
ABNORMAL FAECES	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
APHTHOUS STOMATITIS	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
NAUSEA	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
VOMITING	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(10.0) [1]	1(2.8) [1]
【GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS】	1(12.5) [2]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	2(5.6) [3]
CHEST PAIN	1(12.5) [2]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(2.8) [2]
PYREXIA	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
【INFECTIONS AND INFESTATIONS】	4(50.0) [6]	3(33.3) [4]	3(33.3) [4]	3(30.0) [4]	13(36.1) [18]
GASTROENTERITIS	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
INFLUENZA	2(25.0) [3]	0(0.0) [0]	0(0.0) [0]	2(20.0) [2]	4(11.1) [5]

MedDRA 【System Organ Class】 Preferred Term	Placebo (N=8)	1mg (N=9)	2mg (N=9)	4mg (N=10)	Total (N=36)
NASOPHARYNGITIS	3(37.5) [3]	2(22.2) [2]	3(33.3) [3]	2(20.0) [2]	10(27.8) [10]
VIRAL UPPER RESPIRATORY TRACT INFECTION	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
PSEUDOCROUP	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
【INJURY, POISONING AND PROCEDURAL COMPLICATIONS】	0(0.0) [0]	1(11.1) [1]	1(11.1) [2]	1(10.0) [1]	3(8.3) [4]
CHILBLAINS	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
FALL	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(10.0) [1]	1(2.8) [1]
TENDON RUPTURE	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
WOUND	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
【INVESTIGATIONS】	0(0.0) [0]	0(0.0) [0]	1(11.1) [2]	0(0.0) [0]	1(2.8) [2]
ASPARTATE AMINOTRANSFERASE INCREASED	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
BLOOD CREATINE PHOSPHOKINASE INCREASED	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(2.8) [1]
【MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS】	0(0.0) [0]	2(22.2) [2]	1(11.1) [2]	1(10.0) [2]	4(11.1) [6]
ARTHRALGIA	0(0.0) [0]	0(0.0) [0]	1(11.1) [2]	0(0.0) [0]	1(2.8) [2]
MUSCULOSKELETAL PAIN	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(10.0) [1]	1(2.8) [1]
MYALGIA	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(10.0) [1]	1(2.8) [1]
PAIN IN EXTREMITY	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
MUSCULOSKELETAL STIFFNESS	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
【NERVOUS SYSTEM DISORDERS】	0(0.0) [0]	2(22.2) [3]	0(0.0) [0]	1(10.0) [1]	3(8.3) [4]
HEADACHE	0(0.0) [0]	2(22.2) [3]	0(0.0) [0]	1(10.0) [1]	3(8.3) [4]

MedDRA 【System Organ Class】 Preferred Term	Placebo (N=8)	1mg (N=9)	2mg (N=9)	4mg (N=10)	Total (N=36)
【RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS】	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(10.0) [1]	2(5.6) [2]
RHINORRHOEA	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	1(10.0) [1]	2(5.6) [2]
【SKIN AND SUBCUTANEOUS TISSUE DISORDERS】	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]
PRURITUS	0(0.0) [0]	1(11.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.8) [1]

The following table summarizes all TEAE by subgroup females. Of the 46 female patients in the 12-week, double blind study, there were no reported TEAEs in the Musculoskeletal and Connective Tissue Disorders.

Table 25: Summary of All Treatment Emergent Adverse Events, by Subgroup Female, Safety Set, Study NK-104-4.01EU

MedDRA 【System Organ Class】 Preferred Term	Placebo (N=11)	1mg (N=11)	2mg (N=15)	4mg (N=9)	Total (N=46)
Total Events	5(45.5) [12]	6(54.5) [10]	9(60.0) [25]	2(22.2) [2]	22(47.8) [49]
【GASTROINTESTINAL DISORDERS】	4(36.4) [6]	1(9.1) [1]	4(26.7) [6]	0(0.0) [0]	9(19.6) [13]
ABDOMINAL DISCOMFORT	2(18.2) [2]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	2(4.3) [2]
ABDOMINAL PAIN	1(9.1) [2]	1(9.1) [1]	2(13.3) [3]	0(0.0) [0]	4(8.7) [6]
DENTAL CARIES	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
FAECES HARD	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
NAUSEA	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
VOMITING	2(18.2) [2]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	2(4.3) [2]
【GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS】	0(0.0) [0]	1(9.1) [1]	2(13.3) [2]	1(11.1) [1]	4(8.7) [4]
FATIGUE	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
INFLUENZA LIKE ILLNESS	0(0.0) [0]	1(9.1) [1]	0(0.0) [0]	1(11.1) [1]	2(4.3) [2]
PYREXIA	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
【INFECTIONS AND INFESTATIONS】	3(27.3) [4]	1(9.1) [1]	5(33.3) [7]	1(11.1) [1]	10(21.7) [13]
GASTROENTERITIS	1(9.1) [1]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	2(4.3) [2]
LARYNGITIS	1(9.1) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(2.2) [1]
NASOPHARYNGITIS	2(18.2) [2]	1(9.1) [1]	3(20.0) [3]	0(0.0) [0]	6(13.0) [6]
PHARYNGITIS	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(11.1) [1]	1(2.2) [1]

MedDRA 【System Organ Class】 Preferred Term	Placebo (N=11)	1mg (N=11)	2mg (N=15)	4mg (N=9)	Total (N=46)
RHINITIS	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
UPPER RESPIRATORY TRACT INFECTION	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
RESPIRATORY TRACT INFECTION	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
【INJURY, POISONING AND PROCEDURAL COMPLICATIONS】	0(0.0) [0]	2(18.2) [4]	0(0.0) [0]	0(0.0) [0]	2(4.3) [4]
JOINT DISLOCATION	0(0.0) [0]	1(9.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.2) [1]
PROCEDURAL PAIN	0(0.0) [0]	1(9.1) [1]	0(0.0) [0]	0(0.0) [0]	1(2.2) [1]
POST-TRAUMATIC PAIN	0(0.0) [0]	1(9.1) [2]	0(0.0) [0]	0(0.0) [0]	1(2.2) [2]
【NERVOUS SYSTEM DISORDERS】	2(18.2) [2]	3(27.3) [3]	5(33.3) [9]	0(0.0) [0]	10(21.7) [14]
HEADACHE	2(18.2) [2]	3(27.3) [3]	5(33.3) [7]	0(0.0) [0]	10(21.7) [12]
HYPOAESTHESIA	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
SYNCOPE	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
【RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS】	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]
OROPHARYNGEAL PAIN	0(0.0) [0]	0(0.0) [0]	1(6.7) [1]	0(0.0) [0]	1(2.2) [1]

Reviewer Comment: No females reported a TEAE in the Musculoskeletal and Connective Tissue Disorders SOC, as compared to 4 male patients who reported a TEAE to this SOC. The sample size is too small to conclude that males are more likely to have TEAEs in this SOC.

Regarding TEAEs reported to the Investigations SOC, only 1 male patient compared to 0 female patients reported a TEAE to this SOC. This one male patient reported both a TEAE of aspartate aminotransferase increased and blood creatine phosphokinase increased.

In reports not shown in this review, TEAEs were also summarized by age group ≥8 to < 10 years of age and ≥ 10 to ≤ 16 years of age. These analyses showed that all the TEAEs reported to the Musculoskeletal and Connective Tissue Disorder and Investigations SOC were in the older age group of ≥ 10 to ≤ 16 years of age.

7.6. Specific Safety Studies/Clinical Trials

7.7. Additional Safety Explorations

7.7.1. Human Carcinogenicity or Tumor Development

Not applicable

7.7.2. Human Reproduction and Pregnancy

Not applicable

7.7.3. Pediatrics and Assessment of Effects on Growth

As expected, shift table for changes in Tanner Staging for the 12-week double blind study showed no changes in the 3 months of the study for any of the treatment arms. Please refer to Section 9.8.3 for review of the pediatric growth data for the open-label study NK-104-4.02EU. Additionally the Division of Pediatrics and Maternal Health was consulted to provide an assessment of the pediatric growth data, particularly in the 52 week study.

7.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

7.8. NK.104.4.01EU Original Protocol

7.8.1. Additional Safety Tables

The following study shows the incidence of treatment emergent adverse events by SOC and PT from the original protocol.

Table 26: All Treatment Emergent Adverse Events, Original Protocol, Study NK-104-4.01EU

System Organ Class Preferred Term	Placebo (N=27) n (%)	Pitava 1 mg (N=26) n (%)	Pitava 2 mg (N=27) n (%)	Pitava 4 mg (N=26) n (%)	Total (N=106) n (%)
Subjects with any TEAE	15 (55.6)	18 (69.2)	16 (59.3)	11 (42.3)	60 (56.6)
EAR AND LABYRINTH DISORDERS	1 (3.7)	0 (0.0)	0 (0.0)	1 (3.8)	2 (1.9)
EAR PAIN	1 (3.7)	0 (0.0)	0 (0.0)	1 (3.8)	2 (1.9)
GASTROINTESTINAL DISORDERS	6 (22.2)	6 (23.1)	6 (22.2)	2 (7.7)	20 (18.9)
ABDOMINAL PAIN	2 (7.4)	3 (11.5)	2 (7.4)	0 (0.0)	7 (6.6)
ABDOMINAL DISCOMFORT	3 (11.1)	1 (3.8)	0 (0.0)	1 (3.8)	5 (4.7)
VOMITING	3 (11.1)	0 (0.0)	0 (0.0)	1 (3.8)	4 (3.8)
NAUSEA	0 (0.0)	1 (3.8)	1 (3.7)	0 (0.0)	2 (1.9)
ABNORMAL FAECES	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
APHTHOUS STOMATITIS	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
BOWEL MOVEMENT IRREGULARITY	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
DENTAL CARIES	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
DIARRHOEA	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
ENTERITIS	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
FAECES HARD	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
GINGIVAL PAIN	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3.7)	2 (7.7)	2 (7.4)	2 (7.7)	7 (6.6)
PYREXIA	0 (0.0)	1 (3.8)	1 (3.7)	1 (3.8)	3 (2.8)
INFLUENZA LIKE ILLNESS	0 (0.0)	1 (3.8)	0 (0.0)	1 (3.8)	2 (1.9)
CHEST PAIN	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

System Organ Class Preferred Term	Placebo (N=27) n (%)	Pitava 1 mg (N=26) n (%)	Pitava 2 mg (N=27) n (%)	Pitava 4 mg (N=26) n (%)	Total (N=106) n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
FATIGUE	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
INFECTIONS AND INFESTATIONS	8 (29.6)	7 (26.9)	8 (29.6)	5 (19.2)	28 (26.4)
NASOPHARYNGITIS	6 (22.2)	4 (15.4)	6 (22.2)	2 (7.7)	18 (17.0)
INFLUENZA	2 (7.4)	0 (0.0)	0 (0.0)	2 (7.7)	4 (3.8)
GASTROENTERITIS	1 (3.7)	1 (3.8)	1 (3.7)	0 (0.0)	3 (2.8)
BRONCHITIS	1 (3.7)	0 (0.0)	0 (0.0)	1 (3.8)	2 (1.9)
UPPER RESPIRATORY TRACT INFECTION	0 (0.0)	1 (3.8)	1 (3.7)	0 (0.0)	2 (1.9)
VIRAL UPPER RESPIRATORY TRACT INFECTION	0 (0.0)	2 (7.7)	0 (0.0)	0 (0.0)	2 (1.9)
GASTROENTERITIS VIRAL	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
LARYNGITIS	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
PAROTITIS	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
PHARYNGITIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
PSEUDOCROUP	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
RESPIRATORY TRACT INFECTION	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
RHINITIS	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (3.7)	3 (11.5)	2 (7.4)	1 (3.8)	7 (6.6)
CHILLBLAINS	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
FACIAL BONES FRACTURE	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
FALL	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
JOINT DISLOCATION	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)

System Organ Class Preferred Term	Placebo (N=27) n (%)	Pitava 1 mg (N=26) n (%)	Pitava 2 mg (N=27) n (%)	Pitava 4 mg (N=26) n (%)	Total (N=106) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
LIGAMENT SPRAIN	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
POST-TRAUMATIC PAIN	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
PROCEDURAL PAIN	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
TENDON RUPTURE	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
WOUND	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
INVESTIGATIONS	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
ASPARTATE AMINOTRANSFERASE INCREASED	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
METABOLISM AND NUTRITION DISORDERS	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
DECREASED APPETITE	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3.7)	2 (7.7)	1 (3.7)	1 (3.8)	5 (4.7)
ARTHRALGIA	1 (3.7)	0 (0.0)	1 (3.7)	0 (0.0)	2 (1.9)
MUSCULOSKELETAL PAIN	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
MUSCULOSKELETAL STIFFNESS	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
MYALGIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
PAIN IN EXTREMITY	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
NERVOUS SYSTEM DISORDERS	2 (7.4)	6 (23.1)	5 (18.5)	1 (3.8)	14 (13.2)
HEADACHE	2 (7.4)	6 (23.1)	5 (18.5)	1 (3.8)	14 (13.2)

System Organ Class Preferred Term	Placebo (N=27) n (%)	Pitava 1 mg (N=26) n (%)	Pitava 2 mg (N=27) n (%)	Pitava 4 mg (N=26) n (%)	Total (N=106) n (%)
NERVOUS SYSTEM DISORDERS					
HYPOAESTHESIA	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
SYNCOPE	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
PSYCHIATRIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
NIGHTMARE	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	1 (3.8)	2 (7.4)	1 (3.8)	4 (3.8)
RHINORRHOEA	0 (0.0)	1 (3.8)	0 (0.0)	1 (3.8)	2 (1.9)
COUGH	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
OROPHARYNGEAL PAIN	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (3.7)	1 (3.8)	0 (0.0)	2 (7.7)	4 (3.8)
PRURITUS	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)
RASH	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
RASH GENERALISED	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)
SKIN IRRITATION	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.9)

Reviewer Comment: Data from the original protocol which included HeFH patients age 6-17, shows the incidence of musculoskeletal and connective tissue AEs was similar in pitavastatin and placebo, approximately 1/27 (3.7%) in placebo vs. 4/79 (5.0%) in combined pitavastatin arms.

8. Review of Relevant Individual Trials Used to Support Efficacy

8.1. A 52-Week Open-Label Extension and Safety Study of Pitavastatin Calcium in High-Risk Hyperlipidemia in Childhood (Study NK-104-4.02EU)

8.1.1. Study Design

The Applicant conducted a supplemental analysis of Study NK-104-4.02EU to comply with the Agency's Written Request. The Written Request modified the age parameters (≥8 year to ≤16 years) and restricted the population to only pediatric patients with HeFH. In all other ways, the supplemental analysis was the same as the original protocol.

Overview and Objective

The primary objective of the supplemental analysis for Study NK-104-4.02EU was to evaluate the safety and tolerability of pitavastatin 1 mg, 2 mg, and 4 mg once daily in pediatric patients with HeFH over a period of 52 weeks.

The secondary objective was to assess the persistence of efficacy with pitavastatin over 52 weeks by measuring lipid parameters over time.

Trial Design

Study NK-104-4.02EU was a 52-week, open-label study in patients with high risk hyperlipidemia who were on an appropriate diet and had elevated LDL-C. This study included patients who completed the 12-week, double-blind study NK-104-4.01EU, but was also open for enrollment by eligible children and adolescents who were not enrolled in the double-blind study.

Patients who completed the double-blind study NK-104-4.01EU were automatically eligible to participate in this open-label study. For these patients, Visit 1 (Week 0) for this extension study was performed at the same visit as the last visit of the preceding double-blind study.

All patients enrolled in the study were assigned to treatment with pitavastatin 1 mg once daily. During the study, the dose of pitavastatin may have been up-titrated in an effort to achieve an optimum LDL-C treatment target of ≤110 mg/dL. The decision to up-titrate the dose of pitavastatin was based on LDL-C values at Week 4 and Week 8.

The following criteria were used to determine if a patient's dosage should be up-titrated:

- Patients with a fasting LDL-C >110 mg/dL at Week 4 were contacted by phone approximately 1 week after the study visit and instructed to up-titrate their daily dose to 2 mg. Patients who required up-titration were asked to return to the site at Week 8. Patients with a fasting LDL-C ≤110 mg/dL at Week 4 continued to take pitavastatin 1 mg and returned to the site at Week 16.
- Patients with a fasting LDL-C >110 mg/dL at Week 8 were contacted by phone approximately 1 week after the study visit and instructed to up-titrate their daily dose to 4 mg. Patients who required up-titration were asked to return to the site at Week 12. Patients with a fasting LDL-C ≤110 mg/dL at Week 8 continued to take pitavastatin 2 mg and returned to the site at Week 16.

Patients remained on their highest titrated dose of pitavastatin for the remainder of the study. Patients who were unable to tolerate a particular dose of pitavastatin or who developed predefined laboratory test abnormalities may have had their dose down-titrated to the next lowest dose as long as they continued to have an LDL-C <130 mg/dL. Patients who were unable to achieve an LDL-C value <130 mg/dL were to be withdrawn from the study, at the discretion of the Investigator, if it was thought that they would receive better treatment outside of the trial.

During the treatment period, lipid and safety assessments were performed at Week 4, Week 8 (if applicable), Week 12 (if applicable), Week 16, Week 28, Week 40, and Week 52 or Early Termination (ET).

Inclusion Criteria

- HeFH diagnosed by the Investigator (not a specific inclusion in the original study population; however, homozygous FH was excluded);
- Age ≥ 8 and ≤ 16 years, inclusive (original study population included children ≥ 6 years)
- Baseline LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with additional CV risk factors (original study population included subjects with baseline LDL ≥ 160 mg/dL or ≥ 130 mg/dL with additional CV risk factors)

Additional CV risk factors were:

Male gender;

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

Other Inclusion Criteria

- Must not have taken any lipid-lowering medications in the 5 weeks prior to screening or in the 4 weeks prior to the lipid qualifying visit at Week -1;
- Must have been adherent to an appropriate diet for at least 8 weeks;
- Post-menarche females must not have been pregnant or breast feeding and, if they were sexually active, were required to use a reliable form of contraception; and
- Written informed consent and assent were required as per local regulations.

Exclusion Criteria

- Unable or unwilling to take study drug;
- Fasting TG >400 mg/dL;
- Homozygous FH;
- Other secondary causes of hyperlipidemia (e.g., hypothyroidism, human immunodeficiency virus infection, systemic lupus erythematosus, organ transplantation, previous malignancy, nephrotic syndrome, glycogen storage disease);
- Previous history of statin intolerance, adverse effects with other statin use, or hypersensitivity to any components of the study drug;

- Need for non-statin lipid-lowering medications;
- Apheresis therapy;
- Type 1 diabetes mellitus;
- Poorly controlled type 2 diabetes mellitus defined as hemoglobin A1c >9.0% at screening;
- Severe renal impairment defined as serum creatinine >2.0 mg/dL at screening;
- Uncontrolled hypertension;
- Untreated thyroid disease;
- Severe hepatic impairment, active liver disease, or persistent elevation of alanine transaminase (ALT) or aspartate transaminase (AST) >3 × the upper limit of normal (ULN);
- Active muscle disease or creatine kinase (CK) >3 × ULN (unless explained by exercise);
- Screening laboratory values within the following age/gender appropriate reference ranges as assessed by the central laboratory:
- Any other laboratory abnormality that could have compromised patient safety because of study participation
- Malignancy during the past 5 years
- Current smoker or history of drug or alcohol abuse at screening
- Hospitalization for any cause within 30 days prior to the administration of study drug
- History of major surgery in the 3 months prior to screening
- Any medical condition which, in the judgment of the Investigator, would have jeopardized the evaluation of safety and/or constituted a significant safety risk to the patient; or
- Participation in another clinical study involving an investigational drug during the course of this study or within 30 days prior to signing the informed consent/assent form for this study

Removal of Patients from Study

Participation of a patient in this clinical study may have been discontinued for any of the following reasons:

- The patient or the patient's parent or legal guardian withdrew consent or requested discontinuation from the study for any reason;

- Occurrence of any medical condition or circumstance that exposed the patient to substantial risk and/or did not allow the patient to adhere to the requirements of the protocol;

- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicated to the Investigator that continued participation was not in the best interest of the patient;

- Consecutive ALT or AST measurements >3 × ULN at least 1 week apart;

- Consecutive CK measurements >3 × ULN at least 1 week apart with clinical signs of muscular symptoms (such as diffuse myalgia, muscle tenderness, or muscle weakness) in the absence of muscle trauma;

- Consecutive CK measurements >5 × ULN at least 1 week apart with or without muscular symptoms in the absence of muscle trauma;

- Fasting LDL-C >130 mg/dL after at least 4 weeks of treatment with the maximum tolerated dose of study drug at the discretion of the Investigator, if the patient would receive better treatment outside of the trial. If poor compliance was believed to be a factor, the patient was to be counselled and allowed to continue in the study until the next study visit. The patient was to be withdrawn from the study if the LDL-C value at the next study visit was still >130 mg/dL;

- Pregnancy;

- Requirement of prohibited concomitant medication;

- Patient failure to comply with protocol requirements or study-related procedures; or

If a patient withdrew prematurely from the study due to the above criteria or any other reason, study staff were to make every effort to complete the full panel of assessments scheduled for the end of treatment visit (Week 52 [Visit 8]). The reason for patient withdrawal was to be documented in the electronic case report form (eCRF).

If a patient withdrew from the study due to an adverse event, the patient was asked to return to the site for, at a minimum, the evaluations scheduled for the end of treatment visit (Week 52).

If the adverse event still had not resolved, additional follow-up was performed, as appropriate, and documented in the patient's medical records. As a minimum requirement, adverse events, including SAEs, must have been followed for 30 days after the patient's last dose of study drug.

In the case of patients lost to follow-up, attempts to contact the patient were required to be made and documented in the patient's medical records.

Withdrawn patients were not replaced.

Study Treatment

At Week 0, all patients received pitavastatin 1 mg and were instructed to take 1 tablet of study drug each morning with or without food.

At Week 4, patients with a fasting LDL-C below or on target level of ≤110 mg/dL continued taking 1 pitavastatin 1 mg tablet each day. Patients with a fasting LDL-C >110 mg/dL were instructed to stop taking pitavastatin 1 mg and begin taking 1 tablet of pitavastatin 2 mg each morning.

Patients who up-titrated their pitavastatin dose to 2 mg returned to the site for Visit 3 (Week 8). Patients with a fasting LDL-C ≤110 mg/dL continued taking pitavastatin 2 mg tablet each day. Patients with a fasting LDL-C >110 mg/dL were contacted by phone approximately 1 week after the study visit and instructed to stop taking pitavastatin 2 mg and begin taking pitavastatin 4 mg each morning.

Unless they were down-titrated due to dose intolerance or laboratory abnormalities, for the remainder of the study, patients were to take 1 tablet of the highest titrated pitavastatin dose (1 mg, 2 mg, or 4 mg) once daily.

Assignment to Treatment Groups

All patients entering the study received pitavastatin 1 mg once daily and may have had their dose up-titrated to 2 mg once daily or 4 mg once daily based on their LDL-C values at Week 4 and Week 8 and thereafter, if required. Since this was an open label study, no blinding was required.

Prior and Concomitant Medications

In general, any medication not excluded by the protocol was permitted. Additionally, the following frequently prescribed medications were permitted by the protocol, provided that the patient had been on a stable dose for at least 4 weeks prior to the screening visit and dosage changes were not anticipated during the study: digoxin/digitoxin; intra-articular, nasal, and inhaled steroids; and topical steroid creams.

Oral contraceptives and thyroid replacement therapy were permitted by the protocol, provided that the patient had been on a stable dose for at least 3 months prior to the screening visit and dosage changes were not anticipated during the study.

- All hypolipidemic medications affecting lipid measurements;

- Dietary supplements that included plant stanols or sterols;
- Amphetamines, weight loss medications, and amphetamine-derivative agents;
- Anticoagulants;
- Corticosteroids;
- Fusidic acid; and
- Erythromycin, clarithromycin, and cyclosporine

Administrative Structure

The study was sponsored by Kowa Research Europe, Ltd. (Kowa) and conducted at 9 clinical sites in Greece, France, Italy, the Netherlands, and Spain. (b) (4) a contract research organization, performed project management, clinical monitoring, data management, pharmacovigilance, statistical analysis, and study report preparation.

Procedures

During the treatment period, lipid and safety assessments were performed at Week 4, Week 8 (if applicable), Week 12 (if applicable), Week 16, Week 28, Week 40, and Week 52 or ET. Patients were to be in a fasted state for all study visits (i.e., fasted for at least 10 hours). The following table shows the schedule of procedures during this study.

Table 27: Schedule of Procedures, Study NK-104-4.02EU

	Washout Period[a]		52-Week Active Treatment Period							
	Screening Visit[a]	Lipid Qualifying Visit[a]	Visit 1[b]	Visit 2	Visit 3[c]	Visit 4[c]	Visit 5	Visit 6	Visit 7	Visit 8[d]
ASSESSMENTS PERFORMED	Week -5/-1	Week -1	Week 0	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52/ET
Confirmation of consent/assent[e]	X		X							
Review eligibility criteria	X	X	X							
Record/confirm demographic information	X[f]		X[f]							
Record/confirm medical/family history[g]	X[f]		X[f]							
Physical examination	X		X					X		X
Electrocardiogram			X							X
Vital signs (including height and weight)	X		X	X	X	X	X	X	X	X
Genotyping[h]			X							
Serum chemistry[i]	X		X		X	X	X	X	X	X
Haematology[j]	X		X		X	X	X	X	X	X
Hormones[k]	X		X				X	X	X	X
Liver and muscle enzymes[l]	X	X	X	X	X	X	X	X	X	X
Serum creatinine	X		X	X	X	X	X	X	X	X
TSH	X									
Lipoprotein(a)	X									X
Complete lipid profile[m]	X[n]	X	X		X			X	X	X
Partial lipid profile[m]	X[n]			X		X	X			
Urinalysis[o]	X		X				X	X	X	X
Pregnancy test[p]	X	X	X	X	X	X	X	X	X	X
Myoglobin (plasma and urine)[q]		As needed								
Assess menstrual cycle[r]	X	X	X	X	X	X	X	X	X	X
Dietary counselling	X[f]		X[f]							
Dietary assessment	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Assess adverse events[s]		X	X	X	X	X	X	X	X	X
Dispense study drug			X	X[t]	X[u]	X	X	X	X	
Drug accountability by tablet count				X	X	X	X	X	X	X

Source: Study NK-104.4.02EU Suppl Analysis. Table 2, pg. 21/853. a. For patients who were not enrolled in the double-blind study, a screening/washout period occurred before the start of dosing. No screening/washout period was required for patients entering this study upon completion of the double-blind study. The screening visit was at Week -1 for patients who were not taking lipid-lowering medications at screening and at Week -5 for patients who were required to wash out from lipid-lowering medications. Patients who began to wash out from lipid-lowering medications at Week -5 were to return for a separate lipid qualifying visit at Week -1. The lipid qualifying visit was only required for patients who washed out from lipid-lowering medications at the screening visit. b. For patients entering this open-label study upon completion of the double-blind study, Visit 1 was the same visit as the last study visit of the previous study. c. Visit 3 was only required for patients who were instructed to up-titrate their dose of study drug based on their LDL-C level at Visit 2. Visit 4 was only required for patients who were instructed to up-titrate their dose of study drug based on their LDL-C level at Visit 3. d. All Visit 8 procedures were to be completed upon ET. Laboratory samples collected at an ET visit were to be identified with Discontinuation Visit labels, and pages for ET were required to be completed. e. Consent/assent was required to be obtained before any protocol-specific procedures could be performed. f. Demographic and medical history information was obtained and dietary counselling was performed at the screening visit for patients who were not enrolled in the double-blind study and at Visit 1 for patients entering the open-label study upon completion of the 12-week double-blind study. g. A detailed family history was recorded with an emphasis on cardiovascular and lipid status. h. For patients who were not enrolled in the double-blind study, blood samples for genetic testing were collected at Visit 1 (Week 0) to determine the molecular hypercholesterolaemia diagnosis. i. Serum chemistry parameters included sodium, potassium, chloride, bicarbonate, urea, alkaline phosphatase, bilirubin, total protein, albumin, calcium, phosphate, gamma-glutamyl transferase, lactic dehydrogenase, fasting glucose, HbA1c, and cystatin-C. j. Haematology parameters included white blood cell count and differential, red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and platelets. k. Hormone assessments included cortisol, dehydroepiandrosterone sulphate, estradiol (for females only), testosterone (for males only), luteinizing hormone, and follicle-stimulating hormone. I. Liver enzymes included ALT and AST. Muscle enzymes included creatine kinase. m. The complete lipid profile consisted of LDL-C, HDL-C, non-HDL-C, TC, TG, Apo A1, and Apo B. The partial lipid profile consisted of all lipid parameters except Apo A1 and Apo B. n. At the screening visit, a complete lipid profile was assessed for patients who were not currently taking lipid-lowering medications and a partial lipid profile was assessed for patients who were required to wash out from lipid-lowering medications. o. Urinalysis parameters included pH, protein, glucose, ketones, blood, nitrates, and specific gravity. If protein was detected, the urinary albumin/creatinine ratio was assessed. p.

Urine pregnancy tests were performed for post-menarche females. q. Plasma and urine myoglobin were assessed as needed during the study. r. Monthly menstrual start and stop dates were recorded for post-menarche females. If a female experienced menarche during the study, this was noted. s. Assessment of adverse events included all serious adverse events occurring up to 30 days after the final dose of study drug. t. At Visit 2, patients were dispensed both pitavastatin 1 mg and 2 mg tablets. Patients with a fasting LDL-C >110 mg/dL (2.8 mmol/L) at Visit 2 were contacted by phone approximately 1 week after the study visit and instructed to up-titrate their daily dose to 2 mg. Patients with a fasting LDL-C ≤110 mg/dL (2.8 mmol/L) at Visit 2 continued to take pitavastatin 1 mg. u. At Visit 3, patients were dispensed both pitavastatin 2 mg and 4 mg tablets. Patients with a fasting LDL-C >110 mg/dL (2.8 mmol/L) at Visit 3 were contacted by phone approximately 1 week after the study visit and instructed to up-titrate their daily dose to 4 mg. Patients with a fasting LDL-C ≤110 mg/dL (2.8 mmol/L) at Visit 3 continued to take pitavastatin 2 mg. ALT = alanine aminotransferase; Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; AST = aspartate aminotransferase; ET = Early Termination; HbA1c = haemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.

Study Endpoints

The efficacy endpoints of this study were the following:

• Percent change in LDL-C from baseline over 52 weeks of treatment;

• Percentages of patients who achieved AHA minimal (130 mg/dL) and ideal (110 mg/dL) LDL-C targets over 52 weeks of treatment;

• Percent changes in HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), TG, apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B) from baseline over 52 weeks of treatment; and

• Changes in TC: HDL-C ratio, non-HDL-C: HDL-C ratio, and Apo B:Apo A1 ratio from baseline over 52 weeks of treatment.

Safety:

The safety assessments in this study included adverse events, clinical laboratory evaluations (including assessment of renal function and adrenal, gonadal, and pituitary hormones), vital signs, 12-lead electrocardiograms (ECGs), and physical examinations (including Tanner staging).

Statistical Analysis Plan

An independent (supplemental) statistical analysis plan (SAP) was developed to describe the statistical methods used for the analysis outlined in the Written Request.

No formal statistical hypothesis testing was performed for safety or efficacy endpoints in this open-label extension study. For all analyses, patients were assigned to a treatment group according to the dose they were receiving when they completed the study.

Descriptive statistics of baseline and post-baseline efficacy endpoint measurements and the absolute and percent changes from baseline were presented for each measured lipid level and derived parameter. The evaluation of safety was based on the frequency of adverse events and changes in clinical laboratory values and vital signs. Other safety evaluations, including physical

examinations and Tanner staging, were summarized.

Protocol Amendments

There were three protocol amendments.

Amendment 1 (Protocol v2.0), dated 26 March 2012, was submitted and approved in Greece and the Netherlands. This amendment modified the use of oral contraception to only those patients who had been on the medication for at least 3 months prior to the first study visit, and specified that if oral contraception was started during the course of the study, an additional barrier contraceptive method was required during the first cycle of the oral contraceptive. Additionally, minor corrections were made to clarify inconsistencies between sections of the protocol. This amendment was not submitted in the other participating countries; rather, the changes drafted were included in Amendment 2 (Protocol v3.0, dated 22 May 2012) for the other participating countries.

Amendment 2 (Protocol v3.0), dated 22 May 2012, was written to modify the language about removing patients from the study due to failure to achieve the target LDL-C level of <130 mg/dL. Due to the lack of approved statin treatments available to pediatric patients at the time the study began, the study Investigators requested that they have discretion to maintain children in the trial if it was felt that there was no better therapy available outside the confines of the trial, rather than being required to withdraw them based solely on the LDL-C levels achieved. After the Investigator Meeting, this proposed modification to the study was presented to and supported by the independent DMC for this study. Additionally, in Amendment 2, several typographic errors were corrected.

Amendment 3 (Protocol v4.0), dated 22 January 2014, was written to allow for a potential interim analysis and summarization of both safety and efficacy data once all patients had completed Visit 6 (Week 28) or the ET Visit. Because this was a non-substantial amendment, pre-approval was not required from the Competent Authority or EC, but both were notified of the amendment since it was not expected that a substantial amendment would be drafted before the completion of the study.

8.1.1. Study Results NK-104-4.02EU

Compliance with Good Clinical Practices

According to the Applicant, this study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted. It was also in compliance with Good Clinical Practice Guidelines; Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States

relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use; Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use; amending Regulation (EEC) No 1768/92; Directive 2001/83/EC; and Regulation (EC) No 726/2004.

Financial Disclosure

The Applicant submitted form 3454 with an attachment and certified that they acted with due diligence to obtain from the listed clinical investigators or from the sponsor the information required under 54.4 and no information was received.

Patient Disposition

In total, 85 patients were enrolled in the study and the majority of these patients (78.8%) were enrolled directly from the double-blind study (NK-104-4.01EU). At the completion of the open-label extension study (NK-104-4.02EU), 81 of the 85 patients were receiving pitavastatin 4 mg once daily. In total, 9 patients (10.6%) withdrew early from the open-label extension study, with the primary reason of "withdrew consent or requested discontinuation" being most commonly reported in 7 patients (8.2%). None of the patients withdrew early because of a SAE, clinically significant adverse event, lab abnormality, or other medical condition.

Table 28: Patient Disposition Study NK-104-4.02EU Supplemental Analysis

Status, n (%)	Pitavastatin 1 mg N=1	Pitavastatin 2 mg N=3	Pitavastatin 4 mg N=81	Total N=85
Enrolled	1 (100.0)	3 (100.0)	81 (100.0)	85 (100.0)
New patients	0 (0.0)	1 (33.3)	17 (21.0)	18 (21.2)
Patients enrolled from NK-104-4.01EU	1 (100.0)	2 (66.7)	64 (79.0)	67 (78.8)
NK-104-4.01EU placebo	1 (100.0)	0 (0.0)	12 (14.8)	13 (15.3)
NK-104-4.01EU pitavastatin 1 mg	0 (0.0)	0 (0.0)	15 (18.5)	15 (17.6)
NK-104-4.01EU pitavastatin 2 mg	0 (0.0)	1 (33.3)	19 (23.5)	20 (23.5)
NK-104-4.01EU pitavastatin 4 mg	0 (0.0)	1 (33.3)	18 (22.2)	19 (22.4)
Completed NK-104-4.02EU	0 (0.0)	3 (100.0)	73 (90.1)	76 (89.4)
Early withdrawal from the study	1 (100.0)	0 (0.0)	8 (9.9)	9 (10.6)
Primary reason for study discontinuation				
Withdrew consent or requested discontinuation	1 (100.0)	0 (0.0)	6 (7.4)	7 (8.2)
SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicated to the Investigator that continued participation was not in the patient's best interest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fasting LDL-C > 130 mg/dL (3.4 mmol/L) after ≥ 4 weeks of treatment with MTD of study drug	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)
Other	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)

Source: Study Report NK-104-4.02EU Supp Analysis, Table 3, pg. 29/853.Abbreviations: LDL-C=low-density lipoprotein cholesterol; MTD=maximum tolerated dose

Reviewer Comment: Overall 9/85 or 10% of patients withdrew early from the 52-week trial. Seven patients withdrew consent, 1 patient withdrew for treatment failure, and 1 patient listed "Other" as reason for discontinuation.

Table of Demographic Characteristics

Overall, the mean age of patients at the time of enrollment was 11.4 years, with 28.2% being ≥ 8 to < 10 years old, 61.2% ≥ 10 to < 16 years old, and 10.6% 16 years old; the mean weight was 48.1 (15.8) kg. The majority were female (56.5%), White/Caucasian (95.3%), and Not Hispanic or Latino (95.3%). Most patients were assessed at Tanner stage I or II and had > 1 risk factor for atherosclerotic vascular disease. All 85 patients had a diagnosis of HeFH as determined by the Investigator and genetic testing.

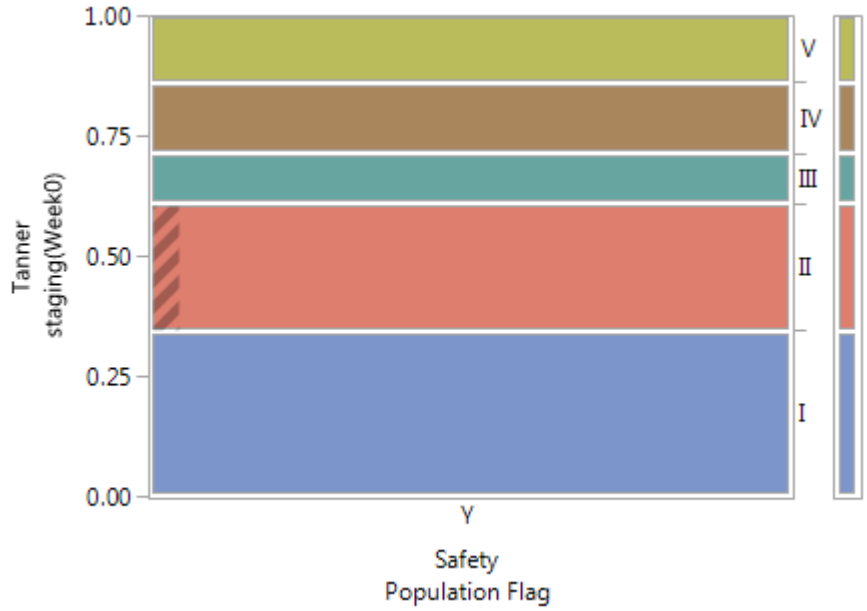
Table 29: Demographics and Baseline Characteristics, Study NK-104-4.02EU

Demographic Parameters	Treatment Group			Total (N=85) n (%)
	Pitavastatin 1 mg (N=1) n (%)	Pitavastatin 2 mg (N=3) n (%)	Pitavastatin 4 mg (N=81)	
Sex				
Male	1 (100.0)	2 (66.7)	34 (42.0)	37 (43.5)
Female	0	1 (33.3)	47 (58.0)	48 (56.5)
Age				
Mean years (SD)	11.0 (NC)	10.7 (3.1)	11.4 (2.6)	11.4 (2.6)
Age Group, n (%)				
≥ 8 to < 10 years	0	1 (33.3)	23 (28.4)	24 (28.2)
≥ 10 to < 16 years	1 (100.0)	2 (66.7)	49 (60.5)	52 (61.2)
16 years	0	0	9 (11.1)	9 (10.6)
≥ 8 to < 12 years	1 (100.0)	2 (66.7)	44 (54.3)	47 (55.3)
≥ 12 to ≤ 16 years	0	1 (33.3)	37 (45.7)	38 (44.7)
White	1(100.0)	3 (100.0)	77 (95.1)	81 (95.3)
Black or African American	0	0	2 (2.5)	2 (2.4)
Other	0	0	2 (2.5)	2 (2.4)
Ethnicity, n (%)				
Hispanic or Latino	0	0	4 (4.9)	4 (4.7)
Not Hispanic or Latino	1 (100.0)	3 (100.0)	77 (95.1)	81 (95.3)
Tanner Staging, n (%)				
I	1 (100.0)	1 (33.3)	27 (33.3)	29 (34.1)
II	0	1 (33.3)	21 (25.9)	22 (25.9)
III	0	0	9 (11.1)	9 (10.6)
IV	0	1 (33.3)	12 (14.8)	13 (15.3)
V	0	0	12 (14.8)	12 (14.1)
Height (cm)				

Demographic Parameters	Treatment Group			Total (N=85) n (%)
	Pitavastatin 1 mg (N=1) n (%)	Pitavastatin 2 mg (N=3) n (%)	Pitavastatin 4 mg (N=81)	
Mean (SD)	144.0 (NC)	147.7 (14.2)	152.7 (14.4)	152.4 (14.3)
Weight (kg)				
Mean (SD)	37.5 (NC)	40.9 (7.1)	48.5 (16.1)	48.1 (15.8)

Source: Study Report NK.104.4.02EU Suppl Analysis, Table 5, pg. 31/853. Abbreviations: NC=not calculated; SD=standard deviation

Figure 9: Baseline Tanner Stage, Study NK-104-4.02EU



Reviewer Comment: Overall, approximately 34% of children were at Tanner 1 stage, which allows better evaluation of growth and developmental effects of study drug.

Other Baseline Characteristics

The following table shows the Baseline lipid parameters of the study population.

Table 30: Baseline Lipid Parameters, Study NK-104-4.02EU

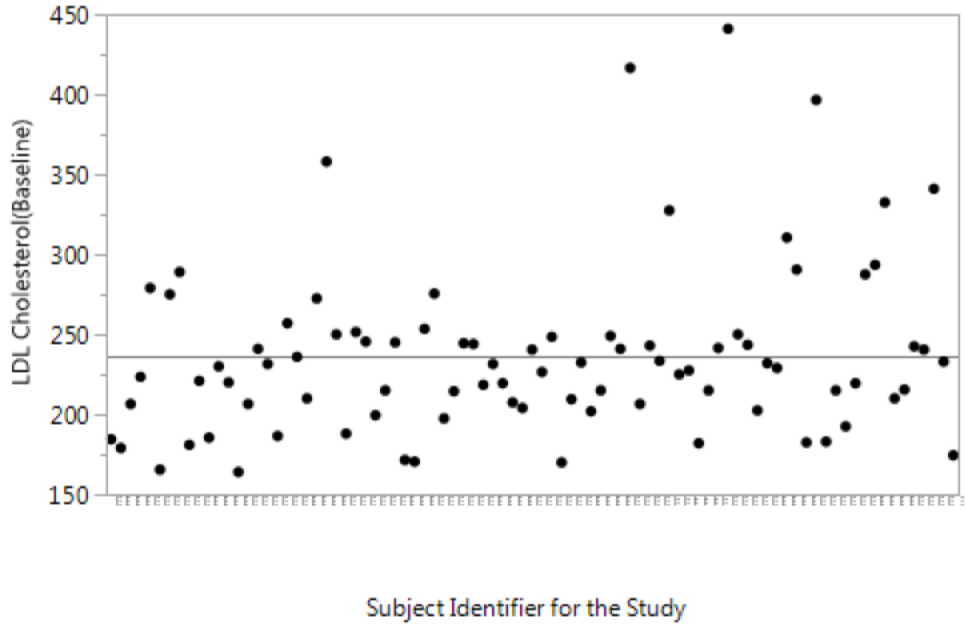
Lipid Parameter	Pitavastatin 1 mg N=1	Pitavastatin 2 mg N=3	Pitavastatin 4 mg N=81	Total N=85
LDL-C, mg/dL				
Mean (SD)	185.5 (NC)	197.8 (18.6)	237.9 (52.0)	235.8 (51.7)
LDL-C Category-n (%)				
≥ 160 to < 190 mg/dL	1 (100)	1 (33.3)	12 (14.8)	14 (16.5)
≥ 190 mg/dL	0 (0.0)	2 (66.7)	69 (85.2)	71 (83.5)
Total	1	3	81	85
HDL-C, mg/dL				
Mean (SD)	59.0 (NC)	50.7 (7.8)	51.8 (11.3)	51.9 (11.1)
TC, mg/dL				
Mean (SD)	266.5 (NC)	265.7 (8.9)	308.0 (55.2)	306.1 (54.7)
Non-HDL-C, mg/dL				
Mean (SD)	207.5 (NC)	215.0 (13.5)	256.2 (54.7)	254.2 (54.2)
TG, mg/dL				
Mean (SD)	112.0 (NC)	85.7 (28.3)	91.7 (39.7)	91.8 (39.1)
Apo B, mg/dL				
Mean (SD)	122.0 (NC)	119.7 (5.0)	146.5 (28.1)	145.2 (28.0)

Source: Study Report NK.104.4.02 Suppl Analysis, Table 6, pg. 33/853.

Reviewer Comment: Overall baseline mean LDL-C was 236 mg/dL, and 84% had LDL-C ≥ 190 mg/dL.

The following figure shows a scatterplot of patients' Baseline LDL-C. The Range of LDL-C is 164 mg/dL to 441 mg/dL.

Figure 10: Scatterplot of Baseline LDL-C, Study NK-104-4.02EU

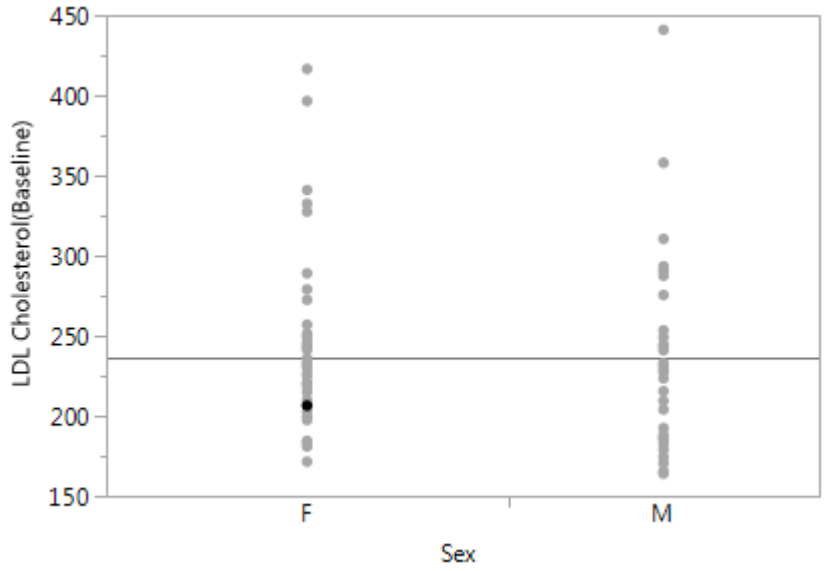


Reviewer Comment: All patients in Study NK-104-4.02 were genetically diagnosed HeFH, but as can be seen from the scatterplot of Baseline LDL-C, the phenotype expression is variable with a LDL-C range that is wide (164 mg/dL to 441 mg/dL) in this study.

The following figure plots Baseline LDL-C by Sex.

APPEARS THIS WAY ON ORIGINAL

Figure 11: Baseline LDL-C by Sex, Study NK-104-4.02EU



Reviewer Comment: The range of Baseline LDL-C is similar in female and male patients with HeFH.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The average treatment compliance was approximately 91% for pitavastatin 1 mg, 90% for pitavastatin 2 mg, and 96% for pitavastatin 4 mg.

Reviewer Comment: In this 52-week study, there was relatively high compliance for all doses of pitavastatin which supports tolerability of pitavastatin.

Efficacy Results – Primary Endpoint

LDL-C

The following table shows the percent change in LDL-C by treatment and visit. Reductions in LDL-C were evident by Week 4, and seemed to reach a plateau by Week 16. At Week 52, LDL-C decreased by 36.62% from Baseline for all patients.

Table 31: Mean Percent Change from Baseline LDL-C by Treatment Arm, Visit, Study NK-104-4.02EU

Visit Statistic	Pitavastatin 1 mg N=1	Pitavastatin 2 mg N=3	Pitavastatin 4 mg N=81	Total N=85
Baseline				
Mean (SD) LDL-C, mg/dL	185.50 (NC)	197.83 (18.58)	237.85 (52.05)	235.82 (51.71)
Week 4				
n[a]	1	3	75	79
Mean (SD) LDL-C, mg/dL	124.00 (NC)	136.00 (23.58)	177.13 (48.35)	174.90 (48.26)
Mean (SD) change from baseline, %	-33.15 (NC)	-31.46 (7.32)	-25.11 (10.05)	**-25.46 (9.97)**
Week 8				
n[a]	1	3	65	69
Mean (SD) LDL-C, mg/dL	140.00	117.67 (17.62)	164.05 (43.41)	161.68 (43.37)
Mean (SD) change from baseline, %	-24.53 (NC)	-40.70 (3.57)	-30.85 (9.23)	**-31.19 (9.24)**
Week 12				
n[a]	0	1	59	60
Mean (SD) LDL-C, mg/dL	NC	168.00 (NC)	146.34 (40.50)	146.70 (40.25)
Mean (SD) change from baseline, %	NC	-23.11	-39.03 (10.57)	**-38.77 (10.68)**
Week 16				
n[a]	1	3	59	63
Mean (SD) LDL-C, mg/dL	134.00 (NC)	156.33 (86.43)	142.02 (36.29)	142.57 (38.51)
Mean (SD) change from baseline, %	-27.76 (NC)	-23.09 (34.88)	-39.45 (10.24)	**-38.49 (12.31)**
Week 28				
n[a]	0	3	59	62
Mean (SD) LDL-C, mg/dL	NC	127.00 (9.64)	145.78 (37.78)	144.87 (37.10)
Mean (SD) change from baseline, %	NC	-35.69 (3.42)	-38.45 (10.58)	**-38.31 (10.35)**
Week 40				
n[a]	0	2	58	60
Mean (SD) LDL-C, mg/dL	NC	119.00 (5.66)	151.31 (46.12)	150.23 (45.71)
Mean (SD) change from baseline, %	NC	-40.35 (4.75)	-37.34(12.56)	**-37.44 (12.38)**
Week 52				
n[a]	0	3	56	59
Mean (SD) LDL-C, mg/dL	NC	131.33 (11.68)	152.27 (41.05)	151.20 (40.30)
Mean (SD) change from baseline, %	NC	-33.28 (7.89)	-36.80 (12.18)	**-36.62 (11.98)**

Source: Study Report NK.104.4.02 Suppl Analysis, Table 9, pg. 36/853.

Reviewer Comment: Most patients were titrated to pitavastatin 4 mg, but the one patient on pitavastatin 1 mg discontinued the trial early. The 3 patients on pitavastatin 2 mg experienced a mean LDL-C change from baseline of -33 % at Week 52, with high variability at interim visits (-23% to -40%). LDL-C reduction on pitavastatin 4 mg seemed to plateau at Week 12 at approximately -39%. This reduction in LDL-C persisted through to the end of trial at Week 52 with a -37% LDL-C reduction.

Efficacy Results – Secondary and other relevant endpoints

The following table shows the mean change and mean percent change from Baseline to Week 52 for HDL-C, non-HDL-C, TC, TG and Apo B.

Table 32: Mean Change and Mean Percent Change From Baseline to Week 52 by Treatment Arm, Study NK-104-4.02EU

Lipid Parameter Statistic at Week 52	**Pitavastatin 1 mg n=1**	**Pitavastatin 2 mg n=3**	**Pitavastatin 4 mg n=81**	**Total n=85**
n[a]	0	3	56	59
HDL-C				
Mean (SD) HDL-C, mg/dL	NC	52.33 (7.64)	50.96 (11.02)	51.03 (10.83)
Mean (SD) change from baseline, %	NC	3.82 (12.33)	0.39 (15.97)	**0.57 (15.74)**
Non-HDL-C				
Mean (SD) non-HDL-C, mg/dL	NC	142.67 (11.72)	168.57 (42.53)	167.25 (41.87)
Mean (SD) change from baseline, %	NC	-33.43 (7.48)	-34.90 (11.94)	**-34.82 (11.72)**
TC				
Mean (SD) TC, mg/dL	NC	195.00 (14.11)	219.54 (45.20)	218.29 (44.42)
Mean (SD) change from baseline, %	NC	-26.52 (6.20)	-29.31 (10.40)	**-29.16 (10.21)**
TG				
Mean (SD) TG, mg/dL	NC	56.67 (8.50)	81.25 (34.10)	80.00 (33.69)
Mean (SD) change from baseline, %	NC	-31.01 (13.02)	-7.62 (31.30)	**-8.81 (31.01)**
Apo B				
Mean (SD) Apo B, mg/dL	NC	86.33 (4.93)	100.41 (23.24)	99.69 (22.87)
Mean (SD) change from baseline, %	NC	-27.79 (4.60)	-32.20 (10.97)	**-31.98 (10.76)**

Source: Study Report NK.104.4.02 Suppl Analysis, Table 10, pg. 39/853. Abbreviations: Apo B = Apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NC = not calculated; SD = standard deviation; TC = total cholesterol; TG = triglycerides. a The number of subjects who had both baseline and post-baseline measurements.

Reviewer Comment: There were clinically meaningful reductions in non-HDL-C (-35%), total

cholesterol (-29%), and Apo B (-32%); Changes in TG (-9%) and HDL-C (+0.57%) were not statistically significant, and the point estimates for these changes from baseline were not clinically meaningful in this population.

Durability of Response/Persistence of Effect

The following line graph shows the mean percent change from Baseline to Week 52; the x-axis represents change over time at 4-week intervals from Baseline, and the y-axis represents percent change in mean LDL-C, with 0% change at Baseline for all dose groups.

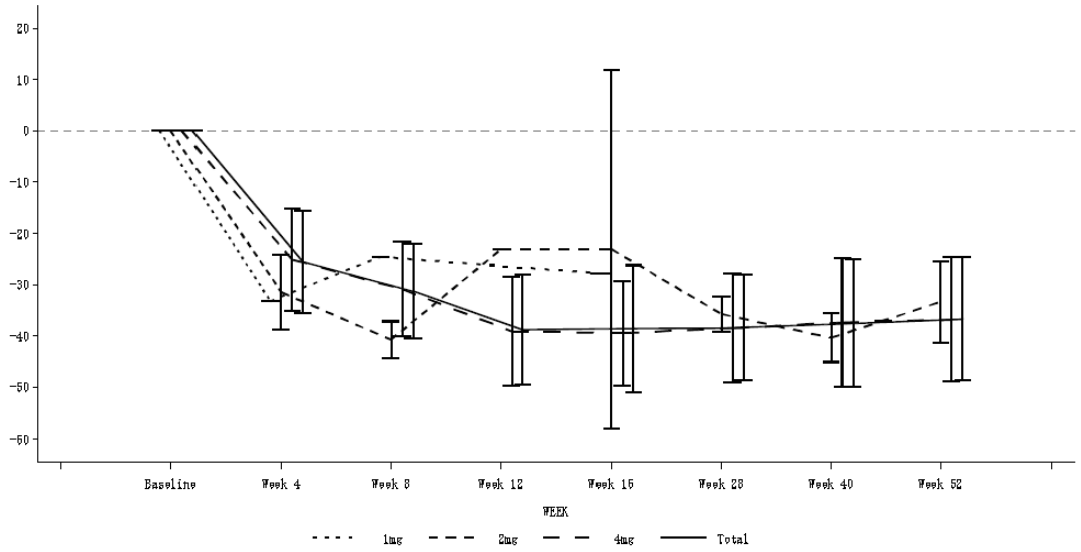


Figure 12: Mean Percent Change From Baseline to Week 52 by Pitavastatin Treatment Arm, Study NK-104-4.02EU

As the figure above shows, LDL-C reductions were sustained over the duration of the study. However, because the pitavastatin dose for most patients was titrated to 4 mg at some point during the study, differences in treatment effect based on dose could not be detected.
The patient on pitavastatin 1 mg withdrew early from the study, and therefore LDL-C could not be evaluated after Week 16 for that treatment arm.

Additional Analyses Conducted on the Individual Trial

Subgroup Analysis for Efficacy by Age Group

Changes in LDL-C were examined by age group ≥ 8 to < 10 years and ≥ 10 and ≤16 years.

Table 33: Summary of LDL-C (mg/dL) and Percent Change form Baseline by Age Category and Treatment Arm, Study NK-104-4.02EU

Visit / Statistic	Pitavastatin 1 mg n=1		Pitavastatin 2 mg n=3		Pitavastatin 4 mg n=81		Total n=85	
	≥ 8 to < 10 years	≥ 10 to ≤ 16 years	≥ 8 to < 10 years	≥ 10 to ≤ 16 years	≥ 8 to < 10 years	≥ 10 to ≤ 16 years	≥ 8 to < 10 years	≥ 10 to ≤ 16 years
Baseline								
n[a]	0	1	1	2	23	58	24	61
Mean (SD)	NC	185.50 (NC)	218.50 (NC)	187.50 (7.07)	241.22 (52.06)	236.52 (52.44)	240.27 (51.12)	234.07 (52.26)
Week 4								
n[a]	0	1	1	2	21	54	22	57
Mean (SD)	NC	124.00 (NC)	162.00 (NC)	123.00 (9.90)	176.19 (51.34)	177.50 (47.64)	175.55 (50.20)	174.65 (47.94)
Mean (SD) change	NC	-33.15 (NC)	-25.86 (NC)	-34.25 (7.76)	-25.84 (10.47)	-24.83 (9.96)	-25.84 (10.22)	-25.31 (9.96)
Week 8								
n[a]	0	1	1	2	16	49	17	52
Mean (SD)	NC	140.00 (NC)	138.00 (NC)	107.50 (0.71)	170.63 (52.75)	161.90 (40.30)	168.71 (51.68)	159.38 (40.59)
Mean (SD) change	NC	-24.53 (NC)	-36.84 (NC)	-42.63 (1.79)	-29.38 (10.77)	-31.33 (8.74)	-29.81 (10.59)	-31.64 (8.82)
Week 12								
n[a]	0	0	1	0	14	45	15	45
Mean (SD)	NC	NC	168.00 (NC)	NC	159.29 (48.23)	142.31(37.49)	159.87 (46.53)	142.31(37.49)
Mean (SD) change	NC	NC	-23.11 (NC)	NC	-36.24 (15.18)	-39.90(8.71)	-35.36 (15.02)	-39.90(8.71)

Source: Study Report NK.104.4.02 Suppl Analysis, Table 11, pg. 41/853. Abbreviations: LDL-C=low-density lipoprotein cholesterol; NC=not calculated; SD = standard deviation. a The number of subjects who had both baseline and post-baseline measurements.

Table 34: Summary of LDL-C (mg/dL) by Age Category and Treatment Arm (Continued)

Visit / Statistic	Pitavastatin 1 mg n=1		Pitavastatin 2 mg n=3		Pitavastatin 4 mg n=81		Total n=85	
	≥ 8 to < 10 years	≥ 10 to ≤ 16 years	≥ 8 to < 10 years	≥ 10 to ≤ 16 years	≥ 8 to < 10 years	≥ 10 to ≤ 16 years	≥ 8 to < 10 years	≥ 10 to ≤ 16 years
Week 16								
n[a]	0	1	1	2	15	44	16	47
Mean (SD)	NC	134.00 (NC)	256.00 (NC)	106.50 (6.36)	144.80 (37.19)	141.07 (36.36)	151.75 (45.43)	139.45 (35.87)
Mean (SD) change	NC	-27.76 (NC)	17.16 (NC)	-43.22 (1.25)	-39.03 (8.34)	-39.60 (10.90)	-35.52 (16.20)	-39.50 (10.71)
Week 28								
n[a]	0	0	1	2	12	47	13	49
Mean (SD)	NC	NC	134.00 (NC)	123.50 (10.61)	150.67 (42.21)	144.53 (36.95)	149.38 (40.68)	143.67 (36.45)
Mean (SD) change	NC	NC	-38.67 (NC)	-34.19 (3.18)	-37.69 (10.49)	-38.64 (10.70)	-37.77 (10.05)	-38.46 (10.52)
Week 40								
n[a]	0	0	1	1	13	45	14	46
Mean (SD)	NC	NC	123.00 (NC)	115.00 (NC)	156.38 (63.70)	149.84 (40.49)	154.00 (61.85)	149.09 (40.36)
Mean (SD) change	NC	NC	-43.71 (NC)	-36.99 (NC)	-38.03 (17.48)	-37.15 (11.00)	-38.44 (16.86)	-37.14 (10.88)
Week 52								
n[a]	0	0	1	2	11	45	12	47
Mean (SD)	NC	NC	129.00 (NC)	132.50 (16.26)	143.18 (47.15)	154.49 (39.69)	142.00 (45.14)	153.55 (39.15)
Mean (SD) change	NC	NC	-40.96 (NC)	-29.45 (6.01)	-40.84 (8.51)	-35.82 (12.80)	-40.85 (8.11)	-35.55 (12.62)

Source: Study Report NK.104.4.02 Suppl Analysis, Table 11, pg. 41/853. Abbreviations: LDL-C=low-density lipoprotein cholesterol; NC=not calculated; SD = standard deviation. a The number of subjects who had both baseline and post-baseline measurements.

Reviewer Comment: There were too few patients in pitavastatin 1 and 2 mg treatment arms to make meaningful comparisons. For Pitavastatin 4 mg, in Weeks 4-52, LDL-C reduction was similar between age subgroups ≥8 years to <10 years and ≥10 years to ≤16 years of age.

9. Review of Safety (NK-104-4.02EU)

9.1. Safety Review Approach

Study NK-104-4.02EU was conducted to assess the long-term safety and tolerability of pitavastatin. This reviewer focused on the known musculoskeletal and liver related adverse events associated with pitavastatin, as well as a general safety review, including routine laboratory assessment. The growth and developmental effects of pitavastatin on children and adolescents with HeFH was reviewed by the Division of Pediatrics and Maternal Health (DPMH).

9.2. Review of the Safety Database

9.2.1. Overall Exposure

Overall, the mean duration of exposure to pitavastatin was 343.6 days. In the 1 mg and 2 mg pitavastatin groups, the highest proportions of patients were exposed to study drug for ≥ 29 to < 57 days, whereas the duration of exposure in the 4 mg group was ≥ 281 to < 365 days in the majority of patients.

Table 35: Study Drug Exposure, Study NK-104-4.02EU

Exposure Parameter	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg	Total N=85
N*	85	84	82	85
Mean (SD) exposure, days	35.2 (11.5)	43.3 (57.1)	275.3 (68.6)	343.6 (63.2)
Exposure category, n/N* (%)				
≤ 28 days	8 (9.4)	37 (44.0)	1 (1.2)	0 (0.0)
≥ 29 to < 57 days	75 (88.2)	40 (47.6)	1 (1.2)	0 (0.0)
≥ 57 to < 85 days	1 (1.2)	3 (3.6)	0 (0.0)	0 (0.0)
≥ 85 to < 113 days	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)
≥ 113 to < 197 days	1 (1.2)	0 (0.0)	7 (8.5)	8 (9.4)
≥ 197 to < 281 days	0 (0.0)	1 (1.2)	6 (7.3)	0 (0.0)
≥ 281 to < 365 days	0 (0.0)	3 (3.6)	66 (80.5)	41 (48.2)
≥ 365 days	0 (0.0)	0 (0.0)	0 (0.0)	35 (41.2)

Source: NK.104.4.02EU Study Report, Table 12 pg. 45/853.
Abbreviations: N*=number of patients who received the specified dose level; SD=standard deviation
Note: Exposure at specified pitavastatin dose level=summation of date of last dose–date of first dose+1 at each dosing period.

9.2.2. Relevant characteristics of the safety population:

Refer to Section 8.1.1 for demographics and other baseline characteristics of the study population.

9.2.3. Adequacy of the safety database:

The size of the safety database was adequate and followed the recommendation in the Written Request of at least 80 patients. The duration of the open label extension was 52 weeks. The patient demographic, HeFH children and adolescents > 8 years of age and ≤ 16 years of age were consistent with the Written Request requirements.

9.3. Adequacy of Applicant's Clinical Safety Assessments

9.3.1. Issues Regarding Data Integrity and Submission Quality

There were no important issues regarding data quality or the quality of the overall submission that had any effect on the safety review. Categorization of Adverse Events
All adverse events presented in Studies NK-104-4.01EU and NK-104-4.02EU were with the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. According to the applicant, adverse events, medical history, and concomitant medications were coded by a coding specialist and reviewed by a medical monitor prior to the study being unblinded.

Reviewer Comment: The categorization of adverse events was adequate.

9.3.2. Routine Clinical Tests

During the treatment period, lipid and safety assessments were obtained at Week 4, Week 8, Week 12, Week 16, Week 28, Week 40 and Week 52 or Early Termination. Patients were to be in a fasted state (at least 10 hours) for all study visits. Refer to the schedule of study procedures in Section 8.1.1.

9.4. Safety Results

9.4.1. Deaths

No deaths were reported in the trial.

9.4.2. Serious Adverse Events

One patient in the supplemental analysis had a SAE during the study: Patient (b) (6)

experienced chronic tonsillar inflammation, which was not related to study drug. The patient was hospitalized, and a tonsillectomy was required. The patient recovered, and the SAE resolved.

9.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no drop outs or discontinuations from the study due to an adverse event.

9.4.4. Significant Adverse Events

Musculoskeletal events

To understand the incidence of all possible muscle-related adverse events and muscle-related laboratory parameters, this reviewer requested that the sponsor summarize in a table all TEAE reported in >1 subject in the SOC of Musculoskeletal and Connective Tissue Disorder and in the SOC of Investigations, all CK related changes. The sponsor submitted the following table.

APPEARS THIS WAY ON ORIGINAL

There were 6 patients who reported 7 different TEAE that were in the Musculoskeletal and Connective Tissue Disorder and 1 patient in the Investigations/ Blood Creatine Phosphokinase Increased.

APPEARS THIS WAY ON ORIGINAL

Table 36: Summary of All Treatment-Emergent Adverse Events Reported in SOC/Musculoskeletal and Connective Tissues Disorders and in SOC/ Investigations CK-Related Laboratory Changes, Study NK-104-4.02EU

Summary of Treatment-Emergent Adverse Events (1≦ Patients) by System Organ Class, Preferred Term, and Dosing Period
Safety Set

MedDRA 【System Organ Class】 Preferred Term	Total (N=85)	<=90 (N=85)	90< <=180 (N=85)	180< <=270 (N=81)	270< <=360 (N=76)	>360 (N=66)
【INVESTIGATIONS】						
BLOOD CREATINE PHOSPHOKINASE INCREASED	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]
【MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS】						
ARTHRALGIA	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(1.3) [1]	0(0.0) [0]
BURSITIS	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(1.3) [1]	0(0.0) [0]
MUSCLE SPASMS	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	1(1.3) [1]	0(0.0) [0]
MYALGIA	1(1.2) [1]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]
PAIN IN EXTREMITY	1(1.2) [1]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]
TENDON DISORDER	1(1.2) [1]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]
MUSCULOSKELETAL STIFFNESS	1(1.2) [1]	0(0.0) [0]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]

Source: Sponsor Submission, dated 06-March-2019.

The following are brief narratives of those patients who met the criteria in the table above:

Patient ID# (b) (6) - 8-year-old male on pitavastatin 4 mg, reported intermittent right leg pain (pain in extremity), mild in severity, lasting 62 days (b) (6) no action taken with study drug, patient recovered.

Reviewer Comment on Patient ID# (b) (6): Adverse event of mild intermittent asymmetric muscle pain is possibly related to study drug.

Patient ID # (b) (6) 15-year-old male on pitavastatin 4 mg, reported bursitis right shoulder (bursitis), mild in severity, lasting 10 days (b) (6) no action taken with study drug, patient given diclofenac for bursitis, patient recovered.

Reviewer Comment on Patient ID# (b) (6) Adverse event of bursitis likely not drug-related.

Patient ID# (b) (6) - 8-year-old female on pitavastatin 1 mg, reported myalgia in upper extremities (myalgia) 4 days after starting study drug, mild in intensity, study drug was not interrupted. When patient titrated to pitavastatin 2 mg in (b) (6), she reported whole body myalgia lasted 25 days (b) (6) Study drug was

interrupted and treatment was required. Patient was re-started on pitavastatin 2 mg in (b) (6) and reported stiffness in legs (musculoskeletal stiffness), mild in intensity, lasting 5 days (b) (6) no action taken with study drug.

Reviewer Comment on Patient ID (b) (6) This patient's myalgia was probably related to pitavastatin. She reported myalgia in upper extremities on pitavastatin 1 mg, which then increased to whole body myalgia on pitavastatin 2 mg. On treatment interruption, patient recovered. Then on restarting pitavastatin 2 mg she was able to tolerate drug better on second attempt with a limited duration (5 days) AE of leg stiffness which resolved without action on study drug.

Patient ID# (b) (6) 11-year-old male on pitavastatin 4 mg, reported muscle spasms (muscle spasms), mild in intensity, lasting 23 days (b) (6) no action taken with study drug, patient recovered.

Reviewer Comment on Patient ID# (b) (6): This patient's mild muscle spasms lasted 23 days and is possibly related to pitavastatin 4 mg. Although patient continued to take study drug, the patient was able to tolerate and recover from the muscle spasms.

Patient ID# (b) (6) - 14-year-old male on pitavastatin 2 mg, reported thickening of Achilles tendon (tendon disorder), mild in intensity, lasting unknown days (b) (6) no action taken with study drug, patient did not recover.

Reviewer Comment on Patient ID# (b) (6): Relationship to study drug and thickening of Achilles tendon unlikely.

Patient ID# (b) (6) – 11-year-old male on pitavastatin 4 mg, reported knee pain (arthralgia), mild in intensity, lasting 1 day (b) (6) no action taken with study drug, patient recovered.

Reviewer Comment on Patient ID# (b) (6) This patient seemed to have a limited duration (1 day) of knee pain more likely due to injury than related to study drug.

Patient ID # (b) (6) - 13-year-old male on pitavastatin 4 mg, noted to have elevated creatinine kinase (blood creatinine phosphokinase elevated) of 1067 U/L, lasting 4 days (b) (6) No action was taken with study drug and patient improved. Patient's Week 52 labs showed a creatine kinase of 491 U/L (normal range 25-300 U/L).

Reviewer Comment: Patient's CK increased to 3.5XULN, but reportedly asymptomatic. On retesting 4 days later, the CK was 300 U/L, at the upper end of normal. During the course of the

study the patient had increased CK at Week 40 (876 U/L) and Week 52 (491 U/L). It is possible that in active children and adolescents, CK is elevated but related more to exercise/activity.

Reviewer Comment: There were 6 out of 85 patients who reported AEs that mapped to Musculoskeletal and Connective Tissue SOC. On review of the patient cases, 3 of the 6 patients may not have had an AE related to the study drug. Overall the musculoskeletal event rate was low and consistent with the profile in adults. No patients experienced an event suggestive of myopathy or rhabdomyolysis, and no events resulted in permanent discontinuation of study drug.

Liver-related events

The following table shows all TEAEs in SOC/Investigations and related to liver enzyme changes. There were two patients with three occurrences of aminotransferase elevations.

Table 37: Treatment Emergent Adverse Events, Reported in ≥1 Subject by SOC Investigations/ ALT or AST Related Changes, Study NK-104-4.02EU

Summary of Treatment-Emergent Adverse Events (1≦ Patients) by System Organ Class, Preferred Term, and Dosing Period
Safety Set

MedDRA 【System Organ Class】 Preferred Term	Total (N=85)	<=90 (N=85)	90< <=180 (N=85)	180< <=270 (N=81)	270< <=360 (N=76)	>360 (N=66)
【INVESTIGATIONS】						
ALANINE AMINOTRANSFERASE INCREASED	2(2.4) [2]	1(1.2) [1]	0(0.0) [0]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]
ASPARTATE AMINOTRANSFERASE INCREASED	1(1.2) [1]	1(1.2) [1]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]	0(0.0) [0]

Source: Sponsor Submission, dated 06-March-2019.

Patient ID# (b) (6) – 11-year-old white male on pitavastatin 1 mg (had been on Placebo in double-blind study), noted to have an ALT increase (ALT=112U/L), lasting 22 days (b) (6) This patient also had AST increase (AST=72 U/L), lasting 108 days (b) (6) Patient's laboratory values improved, but patient withdrew study early. The patient withdrew from the study due to parental request. On Early Termination, patient's ALT=43 U/L (normal range 5-35 U/L) and AST=36 U/L (normal range 0-40 U/L).

Patient ID # (b) (6) - 1 event- 11-year-old white male on pitavastatin 4 mg (had been on pitavastatin 2 mg in double-blind study), noted to have ALT increase (ALT = 101 U/L), lasting 43 days (b) (6) No action was taken with study drug and patient recovered. At Week 52, ALT=35 U/L, which was within normal limits.

Investigation of Hy's Law

There were no cases of Hy's Law in the 52-week study NK-10404.02EU. However, there were two patients with elevations of ALT approximately 3XULN (see circle in figure below). These two patients are the same patients (b) (6) identified with ALT/AST increases in the AE dataset and their narratives are related above.

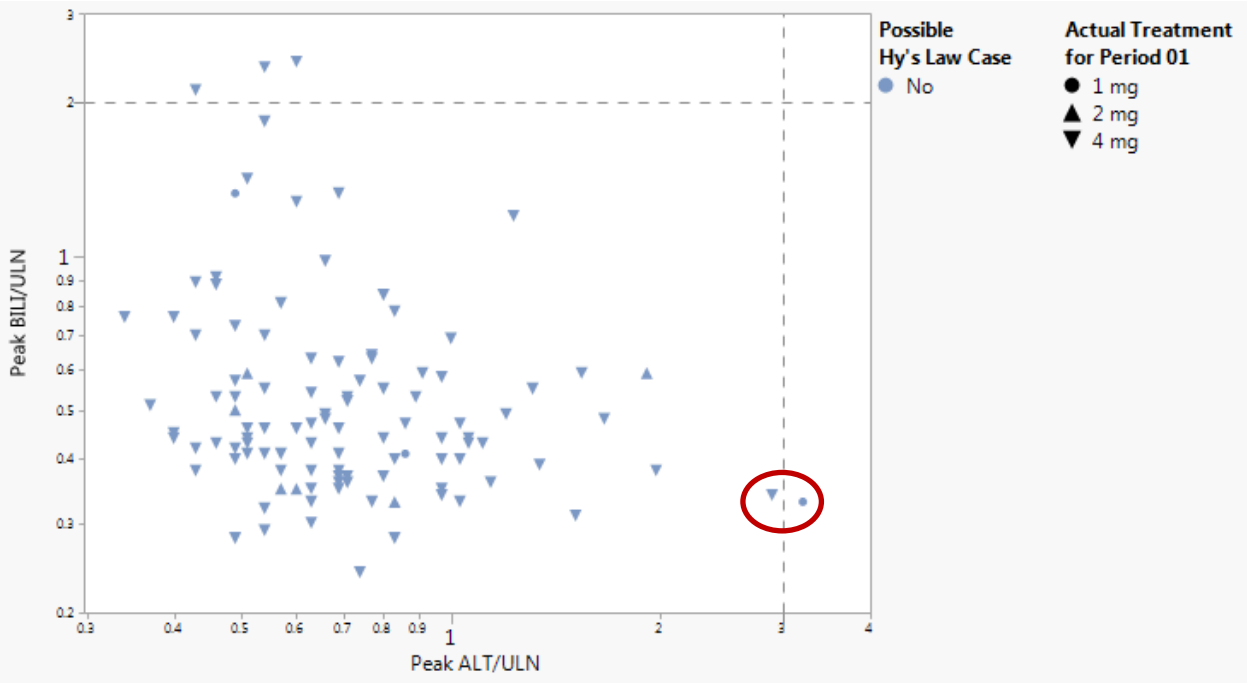


Figure 13: Peak ALT vs Peak Total Bilirubin, Study NK-104.402EU

Patient ID# (b) (6)- 11-year-old male, was on Placebo in Study NK-104-4.01EU, then started pitavastatin 1 mg in Study NK-104-4.02EU. On Day 34, patient was noted to have elevated ALT (3.2XULN) and AST (1.8XULN), with Total Bili (0.33XULN)- Not Hy's Law. Pt was discontinued study, due to parental request.

Patient ID# (b) (6)- 11-year-old male, was on pitavastatin 2 mg in Study NK-104-4.01EU, then started on pitavastatin 4 mg in Study NK-104-4.02EU. Patient noted to have ALT (2.89XULN) and AST (1.23XULN) with Total Bilirubin (0.34XULN)- Not Hy's Law.

Reviewer Comment:
In summary, one patient experienced ALT elevation ≥ 3x ULN once during the study which was noted to decrease to near normal limits on repeat laboratory testing. Pitavastatin treatment was not interrupted. However, the patient ultimately discontinued study due to parental request. Another patient experienced ALT elevation nearly 3x ULN but recovered spontaneously

without discontinuation or dose adjustment.

The following figure shows an overview of peak ALT, AST, total bilirubin, and alkaline phosphatase over the course of the study.

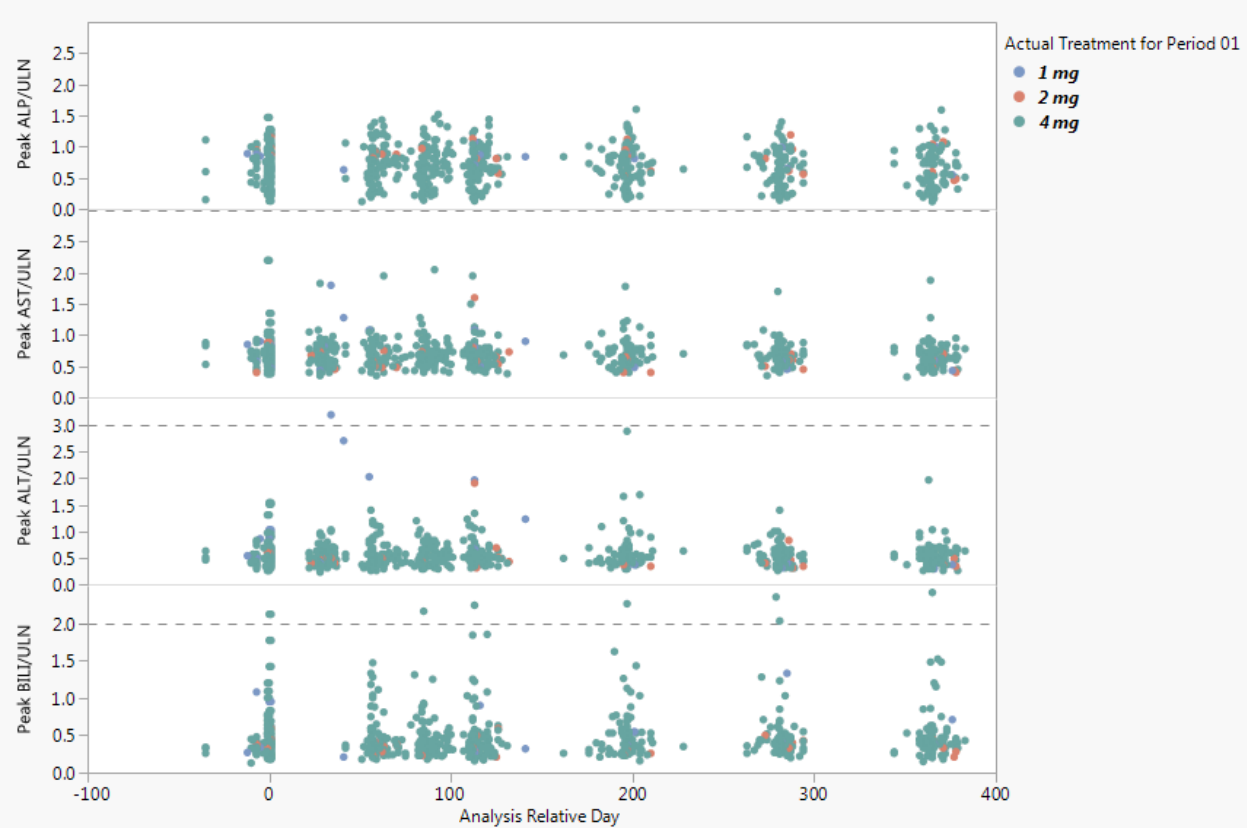


Figure 14: Peak Liver-Related Laboratory Test Per Subject and By Study Day

Reviewer Comments: As can be seen in the figure above, most patients ALT/AST levels were within normal limits during the course of pitavastatin treatment, and only one patient had ALT >3XULN once in the study. This is reassuring data for liver function for this pediatric population.

Pituitary/ Gonadal hormones

This reviewer requested that the sponsor summarize dehydroepiandrosterone sulphate, estradiol (for females), testosterone (for males), luteinizing hormone, and follicle-stimulating hormone values by visit and by Tanner stage for individual patients. Although there were a few values higher/ lower than the normal range at various visits, no consistent signal was detected during the course of the 52-week study.

9.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following table is an overview of adverse events reported during the open-label extension study.

Table 38: Study NK.104.4.02EU, Overview of Adverse Events

Event Type	Pitavastatin 1 mg N=1	Pitavastatin 2 mg N=3	Pitavastatin 4 mg N=81	Total N=85
Adverse event	1 (100.0)	2 (66.7)	54 (66.7)	57 (67.1)
Treatment Emergent AE	1 (100.0)	2 (66.7)	54 (66.7)	57 (67.1)
SAE	0	0	1(1.2)	1 (1.2)
Treatment-emergent SAE	0	0	1(1.2)	1(1.2)
TEAE leading to discontinuation	0	0	0	0
Death	0	0		

Source: NK.104.4.02EU Study Report, Table 46/853.

There were no deaths, serious adverse events, or adverse events leading to discontinuations in any of the pitavastatin treatment arms.

The following table summarizes the treatment emergent adverse events over the 52-week open label study. Because of the open-label design, it is difficult to assign causality, or to associate adverse events with certain timing.

Table 39: Summary of Treatment Emergent Adverse Events in ≥3 Patients by SOC/ PT and Dosing Period, Study NK-104-4.02EU

SOC/ Preferred Term	Total N=85	≤ 90 days N=85	>90 to **≤180** days N=85	>180 to **≤270** days N=81	>270 to ≤ 360 days N=76	> 360 days N=66
Gastrointestinal Disorders						
Abdominal Pain	4 (4.7%) [4]	4 (4.7%) [4]	0	0	0	0
General Disorders and Administration Site Conditions						
Influenza-like illness	8 (9.4%) [8]	4 (4.7%) [4]	1 (1.2%) [1]	3 (3.7%) [3]	0	0
Infections and Infestations						
Gastroenteritis, Viral	7(8.2) [7]	4 (4.7) [4]	3 (3.5) [3]	0	0	0

SOC/ Preferred Term	Total N=85	≤ 90 days N=85	>90 to **≤180** days N=85	>180 to **≤270** days N=81	>270 to ≤ 360 days N=76	> 360 days N=66
Influenza	11(12.9) [11]	4 (4.7) [4]	5 (5.9) [5]	0	0	0
Nasopharyngitis	18 (21.2) [18]	9 (10.6) [9]	5 (5.9) [5]	3 (3.7) [3]	1 (1.3) [1]	0
Nervous System Disorders						
Headache	7 (8.2) [7]	4 (4.7) [4]	1 (1.2) [1]	2 (2.5) [2]	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Oropharyngeal Pain	3 (3.5) [3]	1 (1.2) [1]	0	1 (1.2) [1]	1 (1.3) [1]	0

Source: NK.104.4.02EU Study Report, Table 12 pg. 598/853.

Reviewer Comment: Because of the open-label design, it is difficult to assign causality, or to associate adverse events with certain timing.

9.4.6. Laboratory Findings

The following table shows descriptive statistics for hemoglobin A1C from Baseline to Week 52/Early Termination

Table 40: Changes in Hemoglobin A1C from Baseline to Week 52/Early Termination, Study NK-104-4.02EU

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Visit Variable	Statistic	1mg	2mg	4mg	Total
Week 52/Early Termination	n[1]	1	3	81	85
Baseline	Mean(SD)	5.30(.)	5.37(0.12)	5.31(0.27)	5.32(0.26)
	Median	5.30	5.30	5.30	5.30
	Q1,Q3	5.30,5.30	5.30,5.50	5.10,5.50	5.10,5.50
	Min,Max	5.3,5.3	5.3,5.5	4.7,6.0	4.7,6.0
	95%CI		5.08,5.65	5.26,5.37	5.26,5.37
Value	Mean(SD)	5.20(.)	5.47(0.21)	5.38(0.26)	5.38(0.26)
	Median	5.20	5.40	5.30	5.30
	Q1,Q3	5.20,5.20	5.30,5.70	5.20,5.50	5.20,5.50
	Min,Max	5.2,5.2	5.3,5.7	4.7,6.1	4.7,6.1
	95%CI		4.95,5.98	5.32,5.43	5.32,5.43
Change	Mean(SD)	-0.10(.)	0.10(0.30)	0.06(0.16)	0.06(0.16)
	Median	-0.10	0.10	0.10	0.10
	Q1,Q3	-0.10,-0.10	-0.20,0.40	0.00,0.10	0.00,0.10
	Min,Max	-0.1,-0.1	-0.2,0.4	-0.3,0.9	-0.3,0.9
	95%CI		-0.65,0.85	0.03,0.10	0.02,0.10

Reviewer Comment: The mean change of 0.06 (SD of 0.16) in hemoglobin A1C from Baseline to Week 52/Early Terminiation is not clinically meaningful.

Evalution of selected chemistry and hematology parameters did not identify any safety signal. The following table summarizes the percent change from Baseline to Week 52/Early Termination for some laboratory parameters.

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Table 41: Percent Change from Baseline to Week 52/Early termination in Selected Chemistry, Urinalysis, and Hematology Parameters, Study NK-104-4.02EU

Parameter Statistic	Pitavastatin 1 mg N=1	Pitavastatin 2 mg N=3	Pitavastatin 4 mg N=81	Total N=85
Creatine kinase, U/L				
Baseline mean (SD)	152.0 (NC)	201.7 (136.9)	120.7 (74.5)	124.0 (77.2)
Week 52/ET mean (SD)	132.0 (NC)	110.3 (23.1)	120.7 (70.8)	120.4 (69.3)
Mean (SD) change	-20.0 (NC)	-91.3 (148.0)	-0.1 (74.4)	-3.5 (78.0)
Creatinine, mg/dL				
Baseline mean (SD)	0.540 (NC)	0.610(0.174)	0.566 (0.113)	0.567 (0.114)
Week 52/ET mean (SD)	0.510 (NC)	0.647 (0.183)	0.582 (0.122)	0.583 (0.124)
Mean (SD) change	-0.030 (NC)	0.037 (0.021)	0.016 (0.055)	0.016 (0.054)
Cystatin C, mg/L				
Baseline mean (SD)	0.770 (NC)	0.707 (0.049)	0.699 (0.107)	0.700 (0.105)
Week 52/ET mean (SD)	0.790 (NC)	0.700 (0.075)	0.678 (0.088)	0.680 (0.088)
Mean (SD) change	0.020 (NC)	-0.007 (0.051)	-0.021 (0.077)	-0.020 (0.076)
Hemoglobin, g/dL				
Baseline mean (SD)	13.70 (NC)	13.63 (1.27)	13.35 (0.86)	13.36 (0.87)
Week 52/ET mean (SD)	13.00 (NC)	13.40 (1.15)	13.27 (0.91)	13.27 (0.91)
Mean (SD) change	-0.70 (NC)	-0.23 (0.29)	-0.07 (0.58)	-0.09 (0.57)
eGFR, mL/min[a]				
Baseline mean (SD)	109.0 (NC)	104.3 (26.7)	113.4 (16.8)	113.0 (17.0)
Week 52/ET mean (SD)	117.0 (NC)	102.0 (24.3)	114.3 (18.8)	113.9 (18.8)
Mean (SD) change	8.0 (NC)	-2.3 (4.6)	0.8 (11.0)	0.8 (10.8)

Source: NK.104.4.02EU Study Report, Table 17/853.
Abbreviations: eGFR=estimated glomerular filtration rate; SD=standard deviation; TEAE=treatment-emergent adverse event
a Calculated from creatinine adjusted for body surface area.

9.4.7. Vital Signs

The table below summarizes the mean changes in vital signs (including systolic blood pressure, diastolic blood pressure, and heart rate) from baseline to Week 52/ET for the Safety Set in the supplemental analysis. No clinically important differences in mean changes in systolic blood pressure, diastolic blood pressure, or heart rate from baseline to Week 52/ET were noted among patients in the supplemental analysis.

Table 42: Change from Baseline to Week 52/ Early Termination in Vital Signs, Safety Set, Study NK-104-4.02EU

Parameter Statistic	Pitavastatin 1 mg N=1	Pitavastatin 2 mg N=3	Pitavastatin 4 mg N=81	Total N=85
Systolic BP, mmHg				
Baseline mean (SD)	90.0 (NC)	102.0 (9.8)	107.7 (9.1)	107.3 (9.2)
Week 52/ET mean (SD)	89.0 (NC)	106.3 (3.2)	108.4 (9.7)	108.1 (9.8)
Mean (SD) change	-1.0 (NC)	4.3 (7.5)	0.7 (10.1)	0.8 (9.9)
Diastolic BP, mmHg				
Baseline mean (SD)	68.0 (NC)	68.3 (12.6)	65.5 (7.2)	65.7 (7.3)
Week 52/ET mean (SD)	69.0 (NC)	60.3 (5.5)	65.6 (8.4)	65.4 (8.3)
Mean (SD) change	1.0 (NC)	-8.0 (16.6)	0.0 (8.6)	-0.2 (8.9)
Heart rate, bpm				
Baseline mean (SD)	75.0 (NC)	70.3 (9.1)	74.9 (10.9)	74.8 (10.8)
Week 52/ET mean (SD)	75.0 (NC)	69.3 (12.1)	72.8 (10.6)	72.7 (10.6)
Mean (SD) change	0.0 (NC)	-1.0 (7.5)	-2.1 (12.1)	-2.0 (11.8)

Source: NK.104.4.02EU Supplemental Study Report, Table 25, pg. 61/853.
Abbreviations: BP=blood pressure; bpm=beats per minute; ET=Early Termination; SD=standard deviation

9.4.8. Electrocardiograms (ECGs)

Not applicable.

9.4.9. QT

Not applicable.

9.4.10. Immunogenicity

Not applicable.

9.5. Additional Safety Explorations

9.5.1. Human Carcinogenicity or Tumor Development

Not Applicable

9.5.2. Human Reproduction and Pregnancy

Not Applicable

9.5.3. Pediatrics and Assessment of Effects on Growth

DPMH reviewed the available growth and pubertal development data in Study NK-104-4.02EU. The team concluded that although these data were collected in accordance with the Written Request, the measurements and analyses of the data conducted by the applicant (which were not specified in the WR) were not able to provide meaningful and interpretable information, specifically information adequate for DPMH to determine whether pitavastatin use impacts growth and developement.

An Information Request by DPMH and the Clinical team was sent to the Applicant on April 15, 2019 to obtain information on how height measurements were obtained, to submit standard operating procedures related to stadiometry, and to specify whether persons taking measurement were the same persons each time and if they were blinded to the patients' status in the study. Additional analyses on height velocity and weight gain in patients who were Tanner Stage I at Baseline were also requested.

The Applicant responded with the following: "No additional instruction or training was provided to clinical trial investigators regarding the precision of measurements for height and weight other than the instructions included in the protocol. Based on the Case Report Form used for the study and database specifications, height was collected to the nearest centimeter (cm) without any decimals. The Sponsor relied on the sites to use standard clinical practice in the collection of height and weight, including calibration of equipment and procedures for taking measurements/collecting data. The protocol instructed that height and body weight should be measured, whenever possible, under the same conditions (e.g., no shoes, clothing of similar weight, using the same scale, etc.) that were employed for the first measurement in the study. It was also noted that, whenever possible, the same person should perform all of the vital sign assessments for a given subject. There was no requirement specified that the individual taking these measurements was to be blinded to the status of a patient in the study (e.g., off treatment but still in follow-up versus receiving open-label treatment). The sites selected and utilized for the study were experienced in the care of children and had participated in pediatric clinical trials previously."

The Information Request to the Applicant also asked whether Tanner staging was based on assessments of breast development, genital development, pubic hair development, or a composite. The Applicant was asked to specify whether an orchidometer was used in male Tanner staging.

The Applicant responded: "Tanner staging was based on testicular size (males) and breast size (females) in conjunction with each physical examination to assess pubertal development as described in the protocol. In addition, Original NK-104-4.02EU Protocol Appendix C provides the Tanner staging criteria that was to be referenced by investigators in the study. An orchidometer

was not used in male Tanner staging. No additional instruction or training was provided to clinical trial investigators to assess Tanner staging."

The Applicant provided summary tables for height velocity and height velocity z-score over the 52 week period for patients who were Tanner Stage I at Baseline and on pitavastatin 4 mg.

Table 43: Study NK-104-4.02EU, Height velocity compared to height velocity z-score (CDC data)

Variable	Factor	Level	N	n (Tanner stage I at baseline)	Annual velocity(unit/yr) (Tanner stage I at baseline)	n (Tanner stage >I at baseline)	Annual velocity(unit/yr) (Tanner stage >I at baseline)
HEIGHT(cm)	Overall		103	44	5.04	59	4.68
HEIGHT(cm)	Sex	Female	55	19	5.60	36	4.45
HEIGHT(cm)	Sex	Male	48	25	4.63	23	5.16
HEIGHT(z-score)	Overall		103	44	-0.12	59	0.17
HEIGHT(z-score)	Sex	Female	55	19	-0.14	36	0.21
HEIGHT(z-score)	Sex	Male	48	25	-0.12	23	0.10

Reviewer Comment: There were 44 patients who were Tanner Stage 1 at Baseline. The annual height velocity compared to the Center for Disease Controls' z-score is reassuring, suggesting that children were growing along their respective growth curves. No differences were seen by sex.

The Applicant provided summary tables for weight velocity and weight velocity z-score over the 52 week period for patients who were Tanner Stage I at Baseline and on pitavastatin 4 mg.

Table 44: Study NK-104-4.02 EU, Weight gain velocity compared to weight gain velocity z-score (CDC data)

Variable	Factor	Level	N	n (Tanner stage I at baseline)	Annual velocity(unit/yr) (Tanner stage I at baseline)	n (Tanner stage >I at baseline)	Annual velocity(unit/yr) (Tanner stage >I at baseline)
WEIGHT(kg)	Overall		103	44	3.96	59	4.95
WEIGHT(kg)	Sex	Female	55	19	3.99	36	4.36
WEIGHT(kg)	Sex	Male	48	25	3.95	23	6.05
WEIGHT(z-score)	Overall		103	44	0.01	59	0.02
WEIGHT(z-score)	Sex	Female	55	19	-0.01	36	0.02
WEIGHT(z-score)	Sex	Male	48	25	0.01	23	0.02

Reviewer Comment: The annual weight gain velocity of the 44 patients was 4.95 units/year and compared to the Center for Disease Controls' z-score of 0.02 suggests that children on pitavastatin 4 mg did not vary from CDC normative data. No differences were seen by sex. Please see DPMH consult for more detailed analyses.

9.5.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

10. Advisory Committee Meeting and Other External Consultations

Pediatric Executive Board Recommendations- Unanimous vote to grant exclusivity on 3/27/2019

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The following is the current wording proposed by the Division for the pitavastatin labeling as it relates to this NDA efficacy supplement.

Indication: Pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated TC, LDL-C, and Apo B.

Recommended Dosage for Pediatric Patients Aged 8 Years and Older: The recommended starting Livalo dosage is 2 mg once daily.

Section 6.1: Adverse Reactions in Pediatric Patients Aged 8 Years and Older with HeFH
In a 12-week, double-blind, placebo-controlled trial of LIVALO 1 mg, 2 mg, and 4 mg once daily in 82 pediatric patients 8 years to 16 years of age with HeFH and a 52-week open-label trial in 85 pediatric patients with HeFH, the safety profile was similar to that observed in the adult population.

Section 8.4: Pediatric Use The safety and effectiveness of LIVALO as an adjunctive therapy to diet to reduce elevated TC, LDL-C, and Apo B in pediatric patients aged 8 years and older with HeFH have been established. Use of LIVALO for this indication is supported by a 12-week, double-blind, placebo-controlled trial in 82 pediatric patients 8 to 16 years of age with HeFH [see Clinical Studies (14.2)] and a 52-week open-label trial in 85 pediatric patients with HeFH.

The safety and effectiveness of LIVALO have not been established in pediatric patients younger than 8 years of age with HeFH or in pediatric patients with other types of hyperlipidemia (other than HeFH).

Section 14.2 HeFH in Pediatric Patients In a double-blind, placebo-controlled, 12-week trial, 82 pediatric patients (36 boys and 46 girls), 8 to 16 years of age with genetically confirmed HeFH, fasting low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL or LDL-C ≥160 mg/dL with an additional cardiovascular risk factor (male gender, a family history of premature CV disease, presence of low HDL (<45 mg/dL) or high TG (>150 mg/dL), presence of high lipoprotein (a) (>75 nmol/L), presence of type 2 diabetes mellitus or presence of hypertension) were randomized to LIVALO 1 mg, 2 mg, and 4 mg. Mean LDL-C at baseline was 235 mg/dL (range 160.5 mg/dL to 441mg/dL). Approximately 39% of patients were Tanner Stage 1 at baseline.

LIVALO significantly reduced plasma LDL-C, non-HDL-C, TC, and Apo-B compared to placebo. The reductions in LDL-C, Apo-B, TC, and non-HDL-C were dose dependent. No dose-dependent improvement in HDL-C or fasting TG was observed for any LIVALO dose. See the lipid results in Table 9.

Table 9. Lipid Response in Pediatric Patients with HeFH (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG*#	HDL-C*	non-HDL-C
Placebo	19	-1	-3	-1	-3	-1	-1
LIVALO 1 mg daily	20	-21	-20	-16	-14	7	-21
LIVALO 2 mg daily	24	-30	-25	-25	-15	-3	-29
LIVALO 4 mg daily	19	-38	-28	-30	5	-2	-36

*Difference from placebo not statistically significant
Median Percent Change from Baseline at Week 12

The long-term efficacy of LIVALO initiated in childhood to reduce morbidity and mortality in adulthood has not been established.

12. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13. Post-marketing Requirements and Commitments

Not applicable.

14. Appendices

14.1. References

Goldberg, A. (2011). Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric adn adult patients. Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology* , 5: S1-S8.

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Nordestgaard, B. (2013). Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J*, 34(45):3478-90a.

Sniderman, A. (2014). The severe hypercholesterolemia phenotype: clincial diagnosis, management, and emerging therapies. *J Am Coll Cardiol*, 63(19) 1935-47.

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NK-104-4.01EU and NK-104-4.02EU

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 10		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): N/A		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): N/A		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) all investigators		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

IFFAT N CHOWDHURY
05/15/2019 01:20:06 PM

JOHN M SHARRETTS
05/15/2019 05:09:03 PM