

Report on the Deliberation Results

June 9, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name] Livalo Tablets 1 mg
Livalo Tablets 2 mg
Livalo OD Tablets 1 mg
Livalo OD Tablets 2 mg

[Non-proprietary name] Pitavastatin Calcium Hydrate (JAN*)

[Applicant] Kowa Company, Ltd.

[Date of application] August 7, 2014

[Results of deliberation]

In the meeting held on June 5, 2015, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

[Conditions for approval]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since the Japanese clinical study evaluated the product in an extremely limited number of patients, the applicant is required to conduct a use-results survey that should cover all Japanese patients treated with the product after market launch until data from a certain number of patients have been accumulated, to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Report

May 18, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Livalo Tablets 1 mg Livalo Tablets 2 mg (b) Livalo OD Tablets 1 mg Livalo OD Tablets 2 mg
[Non-proprietary name]	Pitavastatin Calcium Hydrate
[Applicant]	Kowa Company, Ltd.
[Date of application]	August 7, 2014
[Dosage form/Strength]	(a) Each 1 mg film-coated tablet contains 1 mg of pitavastatin calcium hydrate as pitavastatin calcium. Each 2 mg film-coated tablet contains 2 mg of pitavastatin calcium hydrate as pitavastatin calcium. (b) Each 1 mg orally disintegrating tablet contains 1 mg of pitavastatin calcium hydrate as pitavastatin calcium. Each 2 mg orally disintegrating tablet contains 2 mg of pitavastatin calcium hydrate as pitavastatin calcium.
[Application classification]	Prescription drug, (6) Drug with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

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Review Results

May 18, 2015

[Brand name] (a) Livalo Tablets 1 mg
Livalo Tablets 2 mg
(b) Livalo OD Tablets 1 mg
Livalo OD Tablets 2 mg
[Non-proprietary name] Pitavastatin Calcium Hydrate
[Applicant] Kowa Company, Ltd.
[Date of application] August 7, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of familial hypercholesterolemia in pediatric patients has been demonstrated and its safety profile is acceptable in view of its observed benefits. The incidences of rhabdomyolysis, hepatic dysfunction and other relevant conditions, the safety in female pediatric patients with familial hypercholesterolemia, and the safety in pediatric patients with homozygous familial hypercholesterolemia, should be evaluated in post-marketing surveillance and other activities.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indications and dosage and administration as shown below, with the following conditions.

[Indications] Hypercholesterolemia, familial hypercholesterolemia
(No change)

[Dosage and administration]

Hypercholesterolemia:

The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day.

Familial hypercholesterolemia:

Adults: The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day.

Pediatric patients: The usual dosage in pediatric patients aged ≥ 10 years is 1 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's condition. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 2 mg/day.

(Underline denotes additions.)

[Conditions for approval]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since the Japanese clinical study evaluated the product in an extremely limited number of patients, the applicant is required to conduct a use-results survey that should cover all Japanese patients treated with the product after market launch until data from a certain number of patients have been accumulated, to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

Review Report (1)

March 13, 2015

I. Product Submitted for Registration

[Brand name]	(a) Livalo Tablets 1 mg Livalo Tablets 2 mg (b) Livalo OD Tablets 1 mg Livalo OD Tablets 2 mg
[Non-proprietary name]	Pitavastatin Calcium Hydrate
[Applicant]	Kowa Company, Ltd.
[Date of application]	August 7, 2014
[Dosage form/Strength]	(a) Each 1 mg film-coated tablet contains 1 mg of pitavastatin calcium hydrate as pitavastatin calcium. Each 2 mg film-coated tablet contains 2 mg of pitavastatin calcium hydrate as pitavastatin calcium. (b) Each 1 mg orally disintegrating tablet contains 1 mg of pitavastatin calcium hydrate as pitavastatin calcium. Each 2 mg orally disintegrating tablet contains 2 mg of pitavastatin calcium hydrate as pitavastatin calcium.
[Proposed indications]	<u>Adults:</u> Hypercholesterolemia, familial hypercholesterolemia <u>Pediatric patients: Familial hypercholesterolemia</u> (Underline denotes additions.)
[Proposed dosage and administration]	<u>Adults:</u> The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day. <u>Pediatric patients: The usual dosage in pediatric patients aged ≥ 10 years is 1 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 2 mg/day.</u> (Underline denotes additions.)

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

Since this application seeks approval of a new dosage, the applicant did not submit “data relating to quality” or “non-clinical study data.”

1. Origin or history of discovery, use in foreign countries, and other information

Pitavastatin calcium hydrate (pitavastatin) is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor originally synthesized by Nissan Chemical Industries, Ltd. Starting in [REDACTED], pitavastatin was jointly developed in Japan by Nissan Chemical Industries, Ltd. and Kowa Company, Ltd. Livalo Tablets 1 mg and 2 mg were approved in Japan for the indications of hypercholesterolemia and familial hypercholesterolemia in July 2003. The product has since been developed by Kowa Company, Ltd. alone. A higher dose formulation, Livalo 4 mg Tablet, was additionally approved in January 2012. Orally disintegrating (OD) tablets were approved in February 2013 (Livalo OD Tablets 1 mg and 2 mg) and in August 2013 (Livalo OD Tablets 4 mg). As of February 2015, pitavastatin has been approved for the treatment of adult patients with hypercholesterolemia or familial hypercholesterolemia (FH) in 43 countries including the US and European countries.

Patients with FH, a hereditary condition with markedly elevated cholesterol levels, tend to experience coronary artery diseases in early life and have a higher risk of dying earlier than healthy adults. In Western countries, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase are approved for the treatment of FH in pediatric patients. In Japan, no hypolipidemic drug is approved for FH in pediatric patients.

The clinical studies of pitavastatin for pediatric FH began in [REDACTED] [REDACTED] in European countries and in [REDACTED] [REDACTED] in Japan. The applicant filed a partial change application of an additional dosage for the treatment of FH in pediatric patients based on Japanese and foreign clinical study results and other data. At present, pitavastatin is not approved for the indication or dosage of pediatric FH in any country or region outside Japan.

2. Clinical data

2.(i) Summary of biopharmaceutical studies and associated analytical methods

Plasma concentrations of pitavastatin and its metabolite (pitavastatin lactone) were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The lower limit of quantification was 1.00 ng/mL for both pitavastatin and pitavastatin lactone.

No new biopharmaceutic study data were submitted.

2.(ii) Summary of clinical pharmacology studies

2.(ii).A Summary of the submitted data

2.(ii).A.(1) Pharmacokinetics in patients

2.(ii).A.(1).1 Japanese phase III clinical study (NK-104-PH-01, 5.3.5.2.1)

In a randomized, double-blind, parallel-group study, the pharmacokinetic profile of pitavastatin was evaluated in 14 Japanese pediatric male patients (aged 10 to 15 years) with FH who received oral

pitavastatin 1 or 2 mg once daily. Table 1 shows plasma concentrations before and 1 hour after pitavastatin administration at Week 8 or 12.

Table 1. Plasma concentrations (ng/mL) following pitavastatin administration in Japanese pediatric patients with FH

		1 mg	2 mg
Pitavastatin	Pre-dose	- ^{a)} (n = 0)	1.06 (n = 2)
	1 hour post-dose	22.79 ± 11.34 (n = 7)	32.17 ± 17.65 (n = 7)
Pitavastatin lactone	Pre-dose	1.57 ± 0.42 (n = 4)	3.85 ± 1.26 (n = 6)
	1 hour post-dose	9.82 ± 3.72 (n = 7)	24.85 ± 15.84 (n = 7)

Mean ± standard deviation (SD)

Only values at or above the quantification limit were used for calculation. (The numbers in parentheses represent the number of patients with a value at or above the quantification limit.)

a) Below the quantification limit in all patients.

2.(ii).A.(1).2 Foreign phase III clinical study (NK-104-4.01EU, 5.3.5.1.1)

In a randomized, placebo-controlled, double-blind, parallel-group study, the pharmacokinetic profile of pitavastatin was evaluated in 106 non-Japanese pediatric patients (aged 6 to 16 years) with dyslipidemia who received pitavastatin 1, 2, or 4 mg or placebo orally once daily. Table 2 shows plasma concentrations before and 1 hour after pitavastatin administration at Week 8 or 12.

Table 2. Plasma concentrations (ng/mL) following pitavastatin administration in non-Japanese pediatric patients

		1 mg	2 mg	4 mg
Pitavastatin	Pre-dose	1.65 (n = 1)	2.81 ± 2.43 (n = 7)	3.73 ± 2.63 (n = 20)
	1 hour post-dose	16.75 ± 9.51 (n = 18)	35.08 ± 39.10 (n = 13)	113.6 ± 81.4 (n = 19)
Pitavastatin lactone	Pre-dose	3.40 ± 1.62 (n = 20)	7.85 ± 9.06 (n = 16)	18.51 ± 12.34 (n = 20)
	1 hour post-dose	12.45 ± 5.32 (n = 18)	25.82 ± 12.63 (n = 13)	73.19 ± 22.93 (n = 19)

Mean ± SD

Only values at or above the quantification limit were used for calculation. (The numbers in parentheses represent the number of patients with a value at or above the quantification limit.)

2.(ii).B Outline of the review by PMDA

2.(ii).B.(1) Differences in plasma drug concentrations between Japanese and non-Japanese patients

The applicant's explanation on differences in plasma drug concentrations between the Japanese and foreign clinical studies:

The foreign phase III clinical study (Study NK-104-4.01EU) enrolled male and female pediatric patients aged 6 to 16 years, whereas the Japanese phase III clinical study (Study NK-104-PH-01) enrolled male pediatric patients aged 10 to 15 years. In order to properly compare the 2 studies, the applicant made a comparison of plasma drug concentrations at 1 hour post-dose at Week 8 or 12 between the entire population of Study NK-104-PH-01 and subgroups of Study NK-104-4.01EU (a subgroup of pediatric patients aged 10 to 15 years and a subgroup of male pediatric patients). Plasma pitavastatin concentrations were slightly higher in the Japanese pediatric patients than in either of the 2 subgroups of non-Japanese pediatric patients. However, in both the Japanese and non-Japanese patients, plasma pitavastatin concentrations tended to increase dose-dependently (Table 3). The

reasons for higher plasma pitavastatin concentrations in the Japanese pediatric patients than in the non-Japanese pediatric patients are unclear, but the difference was less than 2-fold. In addition, the plasma pitavastatin concentrations in patients receiving 1 or 2 mg in Study NK-104-PH-01 were well below those in patients receiving 4 mg in Study NK-104-4.01EU. Thus, the pitavastatin exposure levels in Japanese pediatric patients with FH would not raise safety concerns.

Table 3. Plasma pitavastatin concentrations (ng/mL) at 1 hour post-dose in the Japanese and foreign clinical studies

Study	Analysis population	1 mg	2 mg	4 mg
NK-104-PH-01	Entire population	22.79 ± 11.34 (n = 7)	32.17 ± 17.65 (n = 7)	
NK-104-4.01EU	Entire population	16.75 ± 9.51 (n = 18)	35.08 ± 39.10 (n = 13)	113.64 ± 81.44 (n = 19)
	Aged 10-15 years	13.79 ± 5.52 (n = 14)	21.76 ± 5.95 (n = 7)	102.05 ± 60.38 (n = 11)
	Male pediatric patients	14.32 ± 7.12 (n = 10)	21.34 ± 3.03 (n = 6)	108.10 ± 97.24 (n = 11)

Mean ± SD

PMDA's view:

Based on the explanation of the applicant, PMDA concludes that (1) no clinically significant differences exist in plasma pitavastatin concentrations between Japanese and non-Japanese patients over the studied dose range, and that (2) the foreign clinical study data can be used to evaluate the efficacy and safety of pitavastatin in Japanese patients, although intrinsic and extrinsic ethnic factors other than plasma pitavastatin concentrations should be investigated [see "2.(iii).B.(2) Use of foreign clinical study data"]. However, the safety of pitavastatin 1 and 2 mg should be assessed on the basis of the clinical study results [see "2.(iii).B.(4) Safety"].

2.(ii).B.(2) Pharmacokinetics in pediatric patients

PMDA asked the applicant to explain the differences in the pharmacokinetic profiles of pitavastatin between adult and pediatric patients with FH.

The applicant's response:

Orally administered pitavastatin is absorbed via the gastrointestinal tract and taken up into the liver by hepatic transporters (i.e., several types of organic anion-transporting polypeptides [OATPs]), and inhibits cholesterol synthesis in the liver (Catapano AL. *Atheroscler Suppl.* 2010;11:3-7). OATP expression does not differ significantly between pediatrics aged ≥10 years and adults (Prasad B et al. *Drug Metab Dispos.* 2014;42:78-88). Pitavastatin metabolism is primarily mediated by uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A3, UGT2B7 (Fujino H et al. *Xenobiotica.* 2003;33:27-41), and CYP2C9 (Fujino H et al. *Xenobio Metabol and Dispos.* 1999;14:415-424). No published data on age-related differences in UGT1A3 expression are available, but UGT2B7 expression does not differ by age (Strassburg CP et al. *Gut.* 2002;50:259-265), and the metabolic capacity of CYP2C9 does not differ between pediatric and adult patients (Tanaka E. *J Clin Pharm Ther.* 1998;23:247-255). Pitavastatin taken up into the live is excreted by the bile canalicular transporters (e.g., multidrug resistance protein 1, breast cancer resistance protein, and multidrug resistance-associated protein 2); the expression of these transporters does not differ substantially

between pediatric patients aged ≥ 10 years and adults (Prasad B et al., *Drug Metab Dispos.* 2014;42:78-88; Prasad B et al., *J Pharm Sci.* 2013;102:787-793; Deo AK et al., *Drug Metab Dispos.* 2012;40:852-855). These findings indicate that the pharmacokinetic profile of pitavastatin does not differ significantly between adults and pediatric patients aged ≥ 10 years, the proposed population in this application. Based on the data from a clinical study in healthy Japanese adults, the steady-state plasma concentrations 1 hour after administration of pitavastatin 1 and 2 mg were estimated to be 14.00 ± 2.24 ng/mL and 27.78 ± 10.73 ng/mL (mean \pm standard deviation [SD]), respectively. Thus, plasma pitavastatin concentrations at 1 hour post-dose may be higher in Japanese pediatric patients (22.79 ± 11.34 ng/mL at 1 mg and 32.17 ± 17.65 ng/mL at 2 mg) than in adults. However, this raises no safety concerns because plasma pitavastatin concentrations at 1 hour post-dose in pediatric patients are not expected to exceed those in adults receiving the maximum dose 4 mg (49.8 ± 15.4 ng/mL).

The proposed dosage do not require dose adjustment by age or body weight of pediatric patients. PMDA therefore asked the applicant to explain whether the proposed fixed dose may yield differences in plasma concentrations that may cause any safety concerns.

The applicant's response:

Table 4 shows plasma pitavastatin concentrations at 1 hour post-dose at Week 8 or 12 by age and body weight in Study NK-104-4.01EU. Plasma pitavastatin concentrations tended to be higher in pediatric patients aged < 10 years than in those aged ≥ 10 years, and in pediatric patients weighing < 40 kg than in those weighing ≥ 40 kg. However, these differences are unlikely to cause pharmacokinetic safety problems in the pediatric population proposed in this application, for the following reasons: (1) In Japan, pitavastatin is indicated in patients aged ≥ 10 years. (2) Study NK-104-4.01EU showed no differences in safety between pediatric patients weighing < 40 kg and ≥ 40 kg. (3) Study NK-104-PH-01 showed no correlation between the incidences of adverse events and body weight.

Table 4. Plasma pitavastatin concentrations (ng/mL) by age or body weight in the foreign clinical study

Dose	Age		Body weight	
	< 10 years	≥ 10 years	< 40 kg	≥ 40 kg
1 mg	27.13 ± 14.02 (n = 4)	13.79 ± 5.52 (n = 14)	25.69 ± 12.56 (n = 5)	13.32 ± 5.44 (n = 13)
2 mg	58.01 ± 58.74 (n = 5)	20.75 ± 6.20 (n = 8)	51.79 ± 54.72 (n = 6)	20.77 ± 6.64 (n = 7)

Mean \pm SD

PMDA's view:

On the basis of the study results presented, the proposed dosage is unlikely to cause major safety problems, but the difference in safety according to body weight should continue to be evaluated in the post-marketing investigations because this issue was not fully evaluated in clinical studies.

2.(ii).B.(3) Effects of meal timing on study results

Patients in Study NK-104-PH-01 were instructed to take pitavastatin “before breakfast” while patients in Study NK-104-4.01EU were instructed to take pitavastatin “in the morning” without regard to meals. PMDA asked the applicant to explain the impact of this difference on the study results.

The applicant’s response:

Meal effects were evaluated in the phase I clinical study in healthy Japanese adults. (This study was conducted in order to collect data for a partial change application to eliminate rules on meal timing and administration timing of pitavastatin.) In the study, the maximum plasma concentration (C_{max}) under fasting conditions was 1.6-fold that under fed conditions, but the area under the plasma drug concentration-time curve (AUC) under fed and fasting conditions was almost comparable. The protocol of Study NK-104-4.01EU did not specify the timing of meals for feasibility reasons. However, the results of the phase I study suggested that plasma pitavastatin concentrations at 1 hour post-dose should be determined only under fasting conditions. Therefore, in Study NK-104-EU, pitavastatin was administered before breakfast on the days when plasma pitavastatin concentrations were determined. This means that the pharmacokinetic profile of pitavastatin was evaluated under the identical meal conditions in Studies NK-104-4.01EU and NK-104-PH-01. Meal timing thus did not affect the pharmacokinetic evaluation of pitavastatin. During the review process for the partial change application, it was confirmed that meal and administration timing had no effect on the efficacy and safety of pitavastatin in Japanese adults. Thus, the differences in administration timing between Studies NK-104-PH-01 and NK-104-4.01EU do not affect the efficacy or safety of pitavastatin.

PMDA’s view:

The protocols of Studies NK-104-PH-01 and NK-104-4.01EU specified different meal timings (with regard to pitavastatin administration), but in both studies pitavastatin was administered before breakfast on the days when plasma drug concentrations were determined. This difference in meal timing between the 2 studies are therefore unlikely to have substantially affected the evaluation of plasma pitavastatin concentrations. In Japanese adults, differences in meal and administration timing did not affect the efficacy or safety. This finding also suggests that, despite the difference in meal timing, the results of the 2 studies can be used to evaluate and compare the pharmacokinetics, efficacy, and safety in Japanese and non-Japanese patients.

No instructions on meal timing are provided in the proposed dosage regimen while pitavastatin was “taken before breakfast” in study NK-104-PH-01. However, as stated above, meal and administration timing did not affect the efficacy or safety in Japanese adults. This suggests that meal timing should not substantially affect the pharmacokinetics, efficacy, or safety in Japanese pediatric patients either. Therefore, the omission of instructions on meal timing in the dosage and administration section is acceptable.

2.(iii) Summary of clinical efficacy and safety

2.(iii).A Summary of the submitted data

The applicant submitted evaluation data, in the form of results data from 3 studies: a Japanese phase III clinical study in Japanese pediatric patients, a foreign phase III clinical study in non-Japanese pediatric patients, and a foreign long-term treatment study.

2.(iii).A.(1) Japanese phase III clinical study (NK-104-PH-01, 5.3.5.2.1 [■■■■ to ■■■■])

A randomized, double-blind, parallel-group study was conducted at 16 study centers in Japan to evaluate the efficacy and safety of pitavastatin in male Japanese pediatric patients with FH (target sample size: 7/group, 14 in total).

The patients received oral pitavastatin 1 or 2 mg once daily before breakfast for a 52-week treatment period. In the pitavastatin 2 mg group, the starting dose was 1 mg, which was increased to 2 mg after 4 weeks.

Major inclusion criteria:

- Patients with heterozygous FH
- Patients aged ≥ 10 to ≤ 15 years at the time of informed consent
- Patients who had a low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL or a LDL-C ≥ 160 mg/dL with at least one of the following risk factors:
 - A family history of coronary artery disease, obesity, type 2 diabetes mellitus, hypertension, or hypo-high-density-lipoprotein [HDL] cholesterolemia.
- Patients on physician-directed diet therapy for ≥ 3 months before screening; or Patients who have been on a good and balanced diet for ≥ 3 months before screening and therefore do not require stricter dietary restrictions. In either case, patients were required to receive a fixed regimen of diet therapy or diet/exercise therapy for ≥ 4 weeks before screening.

Fourteen patients (7/group) were randomized and received the study drug. All were included in the safety analysis set and full analysis set (FAS). FAS was used for the primary analysis of efficacy.

The primary efficacy endpoint was percent change in LDL-C (mean \pm SD) from baseline to Week 8 or 12 (see Table 5). The percent changes were evaluated using a repeated-measures analysis of covariance (ANCOVA) with treatment group and evaluation point as fixed effects, patient as a random effect, and baseline LDL-C as a covariate. To adjust multiplicity, the 2 mg group was first evaluated; if the 2 mg group showed a significant percent change in LDL-C, the 1 mg group was then evaluated. The percent change in LDL-C (least-squares mean [95% confidence interval (CI)]) was -34.273% [-41.018%, -27.528%] in the 2 mg group and -27.258% [-34.003%, -20.513%] in the 1 mg group, indicating a significant decrease from baseline in both groups ($P < 0.001$).

Table 5. Percent changes from baseline in LDL-C following pitavastatin administration in Japanese pediatric patients with FH (FAS)

	n	Baseline (mg/dL)	Percent change at Week 8 (%)	Percent change at Week 12 (%)
1 mg	7	245.4 ± 68.1	-24.70 ± 9.93	-27.75 ± 10.34
2 mg	7	269.6 ± 51.2	-33.56 ± 11.94	-37.04 ± 7.34

Mean ± SD

The percent changes (mean ± SD) in LDL-C from baseline to Week 52 (a secondary endpoint) were -24.32% ± 10.25% in the 1 mg group and -32.22% ± 5.94% in the 2 mg group.

The incidences of adverse events were 100% (7 of 7 patients) in the 1 mg group and 71.4% (5 of 7 patients) in the 2 mg group. The adverse events observed in ≥2 patients in either group were nasopharyngitis (2 patients in the 1 mg group; 3 patients in the 2 mg group), gastroenteritis (2 patients in the 1 mg group; 2 patients in the 2 mg group), upper respiratory tract inflammation (1 patient in the 1 mg group; 2 patients in the 2 mg group), seasonal allergy (2 patients in the 1 mg group; none in the 2 mg group), and rhinitis allergic (2 patients in the 1 mg group; none in the 2 mg group). There were no adverse events for which a causal relationship to the study drug could not be ruled out.

No deaths were reported. A serious adverse event (scar) was reported in 1 patient in the 1 mg group, but a causal relationship to the study drug was ruled out.

No patients experienced adverse events leading to discontinuation of the study drug.

2.(iii).A.(2) Foreign phase III clinical study (NK-104-4.01EU, 5.3.5.1.1 [■■■■ to ■■■■])

A randomized, placebo-controlled, double-blind, parallel-group study was conducted at 9 study centers outside Japan to evaluate the efficacy and safety of pitavastatin in non-Japanese pediatric patients with dyslipidemia (target sample size: 24/group, 96 in total).

The patients received placebo or pitavastatin 1, 2, or 4 mg orally once daily in the morning for a 12-week treatment period. In the pitavastatin 4 mg group, the starting dose was 2 mg, which was increased to 4 mg after 4 weeks.

Major inclusion criteria:

- Patients aged ≥6 to <17 years at the time of randomization
- Patients who had a fasting LDL-C ≥160 mg/dL or a fasting LDL-C ≥130 mg/dL with at least one of the following risk factors:
 - Male; a family history of premature heart disease defined as myocardial infarction; hypo-HDL cholesterolemia or hypertriglyceridemia; lipoprotein(a)-hyperlipoproteinemia; type 2 diabetes mellitus; or hypertension.
- Patients who had not taken any lipid-lowering medications for ≥5 weeks before screening or for ≥4 weeks before Visit 2 (1 week before start of treatment)
- Patients who have received appropriate diet therapy for ≥8 weeks

All 106 randomized patients (27, 26, 27, and 26 patients in the placebo, 1 mg, 2 mg, and 4 mg groups, respectively) received the study drug and were included in the safety analysis set. Of the 106 patients, 103 patients (27, 26, 26, and 24 patients in the placebo, 1 mg, 2 mg, and 4 mg groups, respectively) were included in the FAS for the primary analysis of efficacy. (The remaining 3 patients were excluded from the FAS because of the lack of post-baseline lipid measurements). The safety analysis set included 104 patients with FH (27, 26, 26, and 25 patients in the placebo, 1 mg, 2 mg, and 4 mg groups, respectively).

The percent changes in LDL-C from baseline to Week 12 were the primary efficacy endpoint (Table 6). To adjust multiplicity, the percent changes in the 4 mg and placebo groups were first compared, and if a significant difference was identified between the groups, the percent changes in the placebo and 2 mg groups were compared. If a significant difference was identified between the 2 mg and placebo groups, the percent changes in the placebo and 1 mg groups were compared. As a result, all pitavastatin doses showed a significant difference from placebo in the percent changes in LDL-C from baseline to Week 12 (each $P < 0.0001$, by an ANCOVA with baseline LDL-C and age as covariates).

Table 6. Percent changes in LDL-C from baseline to Week 12 in non-Japanese pediatric patients receiving pitavastatin (FAS)

	n	Baseline ^{a)} (mg/dL)	Week 12 ^{a)} (mg/dL)	Percent change ^{b) d)} (%)	Between-group comparison ^{d)}	
					Difference from placebo ^{c)} (%)	<i>P</i> value
Placebo	27	240.5 ± 68.98	239.2 ± 61.13	1.0 ± 2.06		
1 mg	26	231.4 ± 45.45	176.3 ± 34.47	-23.5 ± 2.09	-24.5 [-30.3, -18.6]	<0.0001
2 mg	26	223.1 ± 35.85	156.8 ± 38.63	-30.1 ± 2.11	-31.1 [-37.0, -25.2]	<0.0001
4 mg	24	240.7 ± 54.25	144.4 ± 40.86	-39.3 ± 2.18	-40.3 [-46.2, -34.4]	<0.0001

a) Mean ± SD

b) Least-squares mean ± standard error (SE)

c) Least-squares mean [95% CI]

d) ANCOVA with baseline LDL-C and age as covariates

The final available measurement during the study period was used for patients who discontinued the study before Week 12 (imputation by the last observation carried forward [LOCF]).

The incidences of adverse events were 55.6% (15 of 27 patients) in the placebo group, 69.2% (18 of 26 patients) in the 1 mg group, 59.3% (16 of 27 patients) in the 2 mg group, and 42.3% (11 of 26 patients) in the 4 mg group. The adverse events observed in at least 3 patients in any group were nasopharyngitis (6 in the placebo group, 4 in the 1 mg group, 6 in the 2 mg group, and 2 in the 4 mg group), headache (2 in the placebo group, 6 in the 1 mg group, 5 in the 2 mg group, and 1 in the 4 mg group), abdominal discomfort (3 in the placebo group, 1 in the 1 mg group, 0 in the 2 mg group, and 1 in the 4 mg group), vomiting (3 in the placebo group, 0 in the 1 and 2 mg groups, and 1 in the 4 mg group), and abdominal pain (2 in the placebo group, 3 in the 1 mg group, 2 in the 2 mg group, and 0 in the 4 mg group). The incidences of adverse events for which a causal relationship to the study drug could not be ruled out were 14.8% (4 of 27 patients) in the placebo group, 15.4% (4 of 26 patients) in the 1 mg group, 14.8% (4 of 27 patients) in the 2 mg group, and 15.4% (4 of 26 patients) in the 4 mg group. Adverse events for which a causal relationship to the study drug could not be ruled out that occurred in ≥ 2 patients in any group were abdominal pain (2 in the placebo group, 2 in the 1 mg group,

1 in the 2 mg group, and 0 in the 4 mg group) and vomiting (2 in the placebo group and 0 in the 1, 2 and 4 mg groups).

No deaths were reported. A serious adverse event was reported in 1 patient in the 2 mg group (facial bones fracture), but a causal relationship to the study drug was ruled out.

The serious adverse event (facial bones fracture) led to study drug discontinuation. In addition, 1 patient in the 4 mg group experienced adverse events leading to study drug discontinuation (pyrexia and rash), but a causal relationship to the study drug was ruled out.

2.(iii).A.(3) Foreign long-term treatment study (NK-104-4.02EU, 5.3.5.2.2 [■■■■■ to ■■■■■])

An open-label, uncontrolled study was conducted at 9 foreign study centers to evaluate the safety of long-term pitavastatin therapy in patients completing study NK-104-4.01EU and other non-Japanese pediatric patients with dyslipidemia.

All patients started treatment with oral pitavastatin 1 mg once daily in the morning. Subsequent dose escalation was performed according to fasting LDL-C levels at Weeks 4 and 8 (for details, see below).

Week 4

- Fasting LDL-C >110 mg/dL: pitavastatin dose was increased to 2 mg, and the patient was instructed to visit the study center at Week 8.
- Fasting LDL-C ≤110 mg/dL: pitavastatin dose was maintained at 1 mg, and the patient was instructed to visit the study center at Week 16.

Week 8

- Fasting LDL-C >110 mg/dL: pitavastatin dose was increased to 4 mg, and the patient was instructed to visit the study center at Week 12.
- Fasting LDL-C ≤110 mg/dL: pitavastatin dose was maintained at 2 mg, and the patient was instructed to visit the study center at Week 16.

Patients continued pitavastatin therapy at their respective maximum dose for 52 weeks. They were allowed to reduce the dose as needed and to remain on the reduced dose as long as fasting LDL-C remained <130 mg/dL. Patients discontinued the study when they failed to reach the target LDL-C of <130 mg/dL after ≥4 weeks of pitavastatin therapy at the maximum dose and therefore their investigators determined that they should switch to another therapy.

The major inclusion criteria for the newly enrolled patients were the same as in Study NK-104-4.01EU.

All 112 patients who received the study drug (84 from Study NK-104-4.01EU and 28 newly enrolled patients) were included in the safety analysis set and FAS. FAS was the primary efficacy analysis population.

At the end of the study, 2.7% (3 of 112) of patients received 1 mg, 5.4% (6 of 112) of patients received 2 mg, and 92.0% (103 of 112) of patients received 4 mg.

With regard to efficacy, the percent changes (mean \pm SD) from baseline in LDL-C were $-38.2\% \pm 10.92\%$ at Week 12 and $-37.8\% \pm 12.07\%$ at Week 52 (LOCF).

With regard to safety, the incidence of adverse events was 67.0% (75 of 112 patients). The adverse events reported in ≥ 5 patients were nasopharyngitis (18 patients), influenza (12 patients), gastroenteritis viral (11 patients), influenza like illness (9 patients), headache (9 patients), and abdominal pain (6 patients). The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 8.9% (10 of 112 patients). Adverse events for which a causal relationship to the study drug could not be ruled out that occurred in ≥ 2 patients were asthenia, alanine aminotransferase (ALT) increased, myalgia, and headache (2 patients each).

No deaths were reported. A serious adverse event was reported in 1 patient (tonsillar inflammation), but a causal relationship to the study drug was ruled out.

An adverse event leading to study drug discontinuation occurred in 1 patient (pruritic rash). A causal relationship to the study drug was not ruled out, but the event resolved.

2.(iii).B Outline of the review by PMDA

2.(iii).B.(1) Clinical positioning

PMDA asked the applicant to explain (a) when to use pitavastatin and when to use other treatments (e.g., pharmacotherapy, low-density lipoprotein [LDL] apheresis) for FH in pediatric patients, (b) how to use pitavastatin in combination with these treatments, and (c) the clinical positioning of pitavastatin for the treatment of FH in pediatric patients.

The applicant's response is shown below.

2.(iii).B.(1).1.A Heterozygous FH in pediatric patients

The latest Japanese guidelines (Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. Japan Atherosclerosis Society, 2012, hereinafter called "the Atherosclerotic Disease Guidelines") list bile acid sequestrants (bile acid-binding resins) as first-line pharmacotherapy for heterozygous FH in pediatric patients, out of concern for growth and development and other safety issues. However, as bile acid sequestrants often fail to sufficiently lower cholesterol levels, aggressive lipid reduction therapy is recommended in patients with markedly elevated LDL-C levels. Therefore, the use of an HMG-CoA reductase inhibitor (i.e., statin) should be considered in some situations. In

Western countries, the prevalence of coronary artery disease is higher than in Japan. The Western guidelines therefore recommend aggressive cholesterol lowering therapy, and list statins as the first-line treatment for heterozygous FH in pediatric patients (Watts GF et al., *Int J Cardiol.* 2014;171:309-325; Nordestgaard BG et al., *Eur Heart J.* 2013;34:3478-3490a; and Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, *Pediatrics.* 2011;128 Suppl 5:S213-256). According to these guidelines, a bile acid sequestrant or ezetimibe may be added when the patient does not respond sufficiently to statin therapy.

As shown above, to ensure safety, bile acid sequestrant therapy should be considered first when treating heterozygous FH in pediatric patients. However, the use of a statin including pitavastatin may be appropriate for some patients with markedly high LDL-C levels, and if a greater reduction in LDL-C is necessary, a combination of bile acid sequestrant and pitavastatin would be appropriate. Pitavastatin may also be used in patients who do not respond sufficiently to or are unable to stay on treatment with a bile acid sequestrant. Moreover, some pediatric patients with FH present with atherosclerosis at young age (Harada-Shiba M et al. *J Atheroscler Thromb.* 2012;19:1019-1026); in these patients, the use of pitavastatin as first-line therapy may be considered in the early stages of treatment. Currently in Japan, however, clearly defining when to use pitavastatin is difficult, because there are no guidelines regarding when to start pharmacotherapy or established target LDL-C levels for pediatric patients with FH. An optimal pharmacotherapeutic regimen for a particular patient should thus be selected according to the patient's risk of arteriosclerosis by a physician with adequate knowledge and experience.

2.(iii).B.(1).2.A Homozygous FH in pediatric patients

The Atherosclerotic Disease Guidelines cite the need for strong LDL-C reduction therapy beginning in childhood in patients with homozygous FH who are generally treated by LDL apheresis because of their very poor response to drug therapy compared with patients with heterozygous FH. The Atherosclerotic Disease Guidelines list probucol as an effective drug treatment but do not mention statins. Unlike patients with heterozygous FH, patients with homozygous FH inherit deficiency or abnormality of the LDL receptor gene or of a proprotein convertase subtilisin/kexin type 9 (PCSK9) from both parents and do not achieve sufficient LDL-C reduction with statins, which work by increasing LDL receptor activity. In the package insert for pitavastatin, the Precautions for Indications section states that the use of pitavastatin as adjuvant therapy to LDL apheresis or other comparable therapies should be considered for FH in adults. However, if patients have the slightest residual LDL receptor activity or have inherited an LDL receptor mutation from one parent and a PCSK9 mutation from the other parent, statins may be effective in reducing LDL-C levels. Further, statins are expected to prevent coronary artery disease in several ways other than LDL-C reduction (Wang CY et al. *Trends Mol Med.* 2008;14:37-44). In a Japanese survey on pharmacotherapy in 130 patients with homozygous FH, 88.5% of the patients used a statin, 53.8% used ezetimibe, 28.5% used probucol, 20.8% used a bile acid sequestrant, 34.6% used aspirin, and 8.5% used ticlopidine (Shiba M. Partial Report of Survey and Study of Familial Hypercholesterolemia, 2013, Research Project for Overcoming Intractable Diseases). The figures are considered to be similar in pediatric patients

because patients with homozygous FH require treatment with strong LDL-C reduction therapy beginning in childhood. In Western countries, LDL apheresis (with or without concomitant pharmacotherapy) is the fundamental treatment for FH, and the use of lomitapide or mipomersen is recommended for patients ineligible for LDL apheresis (Watts GF et al. *Int J Cardiol.* 2014;171:309-325). Raal et al. investigated the effectiveness of statins in patients with homozygous FH using Cox proportional hazard model to estimate the risk of death and coronary artery disease among statin-treated patients in comparison with statin-naïve patients. The hazard ratios [95% confidence interval (CI)] were 0.34 [0.14, 0.86] ($P=0.02$) for death and 0.49 [0.22, 1.07] ($P=0.07$) for coronary artery disease, indicating that statins are beneficial in the treatment of homozygous FH (Raal FJ et al. *Circulation.* 2011;124:2202-2207).

In conclusion, LDL apheresis is the fundamental treatment for patients with homozygous FH both in and outside Japan. Patients with homozygous FH are regarded as very poor responders to pharmacotherapy, but they are actually treated with a variety of drugs beginning in childhood, and statins are most commonly used. In light of the above and the urgency of treatment of homozygous FH, pitavastatin can be positioned as a drug for use in pediatric patients with homozygous FH.

PMDA's views on these matters are shown below.

2.(iii).B.(1).1).B Heterozygous FH in pediatric patients

The Atherosclerotic Disease Guidelines, the most recent treatment guideline in Japan, state that bile acid sequestrants are not absorbed from the gastrointestinal tract and therefore have been recommended as the first-line therapy for pediatric patients with heterozygous FH, in order to ensure safety in terms of growth and development. On the other hand, major foreign guidelines state that active statin treatment of heterozygous FH should begin in childhood to prevent coronary artery disease (Watts GF et al., *Int J Cardiol.* 2014;171:309-325; Rodenburg J et al., *Circulation.* 2007;116:664-668), and that the efficacy and safety of statins in children and adolescents aged 8 to 18 years are similar to those in adults (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics.* 2011;128 Suppl 5:S213-256). These guidelines thus state that statins are the first-line therapy for pediatric heterozygous FH, and that a bile acid sequestrant or ezetimibe may be added to a statin in patients with poor response to statin monotherapy. In light of the above and the fact that the efficacy of pitavastatin in pediatric patients with heterozygous FH has been demonstrated by the data from the Japanese and foreign clinical studies submitted in this application [see "2.(iii).B.(3) Efficacy"], pitavastatin, if made available in Japan, will offer a new therapeutic option for pediatric patients with heterozygous FH as monotherapy in those requiring aggressive lipid-lowering therapy and as combination therapy with a bile acid sequestrant in those unable to achieve sufficient cholesterol reduction with a bile acid sequestrant alone.

2.(iii).B.(1).2.B Homozygous FH in pediatric patients

LDL apheresis is the fundamental treatment of homozygous FH both in and outside Japan because bile acid sequestrants, statins, and other LDL-C-reducing drugs work by increasing LDL receptor activity and because patients with homozygous FH respond more poorly to these drugs than those with heterozygous FH. Patients with receptor-negative homozygous FH, who have no LDL receptor proteins at all, do not respond to LDL-C reducing drugs, but some patients with receptor-defective homozygous FH, who have a slight amount of LDL receptor proteins, responded significantly to combination therapy with bile acid sequestrants, statins, and nicotinate products (Malloy MJ et al. *Ann Intern Med.* 1987;107:616-623). Moreover, pediatric patients with homozygous FH may be unsuitable for highly invasive LDL apheresis because of small body size and the difficulty of vascular access. Such patients probably receive pharmacotherapy first, and subsequently begin LDL apheresis if the pharmacotherapy is not very effective or when vascular access becomes possible. Pitavastatin is expected to be effective in pediatric patients with homozygous FH in light of this situation and the results of the Japanese and foreign clinical studies conducted for this application [see “2.(iii).B.(5) Intended population and indications”]. When made available in clinical practice, pitavastatin would be used as an adjunctive pharmacotherapy to non-pharmacotherapies such as LDL apheresis, offering a new therapeutic option for pediatric patients with homozygous FH.

2.(iii).B.(2) Use of foreign clinical study data

PMDA asked the applicant to present the similarities and differences in intrinsic and extrinsic ethnic factors (including FH pathology and treatments) between the Japanese and non-Japanese populations, and to explain why the applicant considers that the foreign clinical study results can be used to evaluate the efficacy and safety of pitavastatin in Japanese pediatric patients with FH.

First, the applicant explained the development policies in Japan:

The number of male patients with FH aged between 10 and 15 years in Japan, the proposed population for pitavastatin therapy in this application, is estimated to be 7200. However, opportunities to diagnose FH in pediatric patients are few compared with adults because pediatric patients less frequently undergo cholesterol tests in health examinations. At the time of planning the clinical study, the latest edition of the Atherosclerotic Disease Guidelines had not been released and no therapeutic guidelines had been established for pediatric patients with FH in Japan. Thus, the applicant presumed that only a small fraction of pediatric patients with FH were actually treated at a medical institution, and that recruiting enough subjects for a clinical study in Japan was very difficult. The applicant therefore designed the Japanese clinical study with a feasible sample size to demonstrate a statistically and clinically significant LDL-C reducing effect in terms of changes in LDL-C from baseline to post-administration, and decided to use the results of placebo-controlled studies in Europe as well to evaluate efficacy and safety.

The applicant then explained the appropriateness of using the results from foreign clinical studies:

The applicant evaluated differences between Japan and Europe in the following extrinsic ethnic factors: treatment practices, diagnostic criteria, and dietary guidance for pediatric patients with FH. In European countries, the first-line treatment for heterozygous FH in pediatric patients is statin therapy, which may be used in combination with ezetimibe or a bile acid sequestrant, and LDL apheresis is the fundamental treatment for patients with homozygous FH (Nordestgaard BG et al. *Eur Heart J.* 2013;34:3478-3490a). In contrast, the Atherosclerotic Disease Guidelines in Japan list bile acid sequestrants as a first-line therapy for pediatric patients with heterozygous FH, do not mention combination therapy options, and recommend LDL apheresis for patients with homozygous FH. Although the first-line therapy for pediatric patients with heterozygous FH in Japan differs from that in Europe, this difference is unlikely to have affected the results of the clinical studies (Studies NK-104-4.01EU and NK-104-PH-01) because pharmacotherapies other than pitavastatin or concomitant LDL apheresis were not allowed in these studies.

The European guidelines for diagnostic criteria for pediatric FH state that FH should be strongly suspected and genetic testing is recommended in pediatric patients with a LDL-C level >135 mg/dL who have a parent with a diagnosis of FH according to Dutch Lipid Clinic Network criteria (Nordestgaard BG et al. *Eur Heart J.* 2013;34:3478-3490a). In the foreign clinical studies (Studies NK-104-4.01EU and NK-104-4.02EU), clinical diagnosis and genetic testing were both performed, and patients with clinically confirmed FH were enrolled, as in the Japanese clinical study (Study NK-104-PH-01). According to the Atherosclerotic Disease Guidelines in Japan, the diagnostic criteria for heterozygous FH in pediatric patients include (a) an LDL-C level ≥ 140 mg/dL and (b) a family history of FH or premature coronary artery disease (in first- or second-degree blood relative). In both the European and Japanese guidelines, the main diagnostic criteria are (a) a family history of FH and (b) a high LDL-C level, suggesting that Japan and the Europe use almost the same diagnostic criteria. Likewise, difference in dietary guidance appears to be little between Europe and Japan. Thus, extrinsic ethnic factors do not substantially complicate the comparison of the results between the Japanese and foreign studies.

The applicant also evaluated differences between Japan and Europe in the following intrinsic ethnic factors: the pathology of FH and the risk of coronary artery disease. As for FH pathology, the Atherosclerotic Disease Guidelines in Japan define FH as a disease caused by an abnormality of the LDL receptor or a related gene, with 3 major characteristics of hyper-LDL cholesterolemia, premature coronary artery disease, and tendon/skin xanthoma. This definition is similar to that in the European guidelines (Nordestgaard BG et al. *Eur Heart J.* 2013;34:3478-3490a). As for the risk of coronary artery disease, the incidence of coronary artery disease is known to be lower in the Japanese population than in Western populations (Verschuren WM et al., *JAMA.* 1995;274:131-136; Saito I et al., *Int J Epidemiol.* 2000;29:837-844), but the relationship between total cholesterol and coronary artery disease in the Japanese population resembles that observed in a foreign clinical study (Multiple Risk Factor Intervention Trial Research Group, *JAMA.* 1982;248:1465-1477) (Investigating Committee of Guideline for Diagnosis and Treatment of Hyperlipidemias, Japan Atherosclerosis

Society. *J Jpn Atheroscl Soc.* 1997;25:4-12). Thus, there appear to be no ethnic differences in the relationship of cholesterol levels to the risk of coronary artery disease.

The study population of the Japanese phase III study (Study NK-104-PH-01) was limited to male pediatric patients aged 10 to 15 years, while male and female pediatric patients aged 6 to 16 years were enrolled in the foreign phase III study (Study NK-104-4.01EU). Percent changes in LDL from baseline to Week 12 in the studies are shown in Table 7. The percent changes in LDL-C in the subgroups (“male subjects” and “subjects aged 10 to 15 years”) of Study NK-104-4.01EU tended to be smaller than the percent changes in Study NK-104-PH-01, but the percent changes did not differ substantially between the studies.

Table 7. Percent changes in LDL from baseline to Week 12 in Japanese and foreign studies (FAS)

Analysis population		Placebo	1 mg	2 mg	4 mg
Study NK-104-PH-01					
Overall population	Baseline ^{a)} (n)	-	245.4 ± 68.1 (7)	269.6 ± 51.2 (7)	-
	Percent change at Week 12 ^{b)} (n)	-	-27.75 ± 10.34 (7)	-37.04 ± 7.34 (7)	-
Study NK-104-4.01EU					
Overall population	Baseline ^{a)} (n)	240.5 ± 68.98 (27)	231.4 ± 45.45 (26)	223.1 ± 35.85 (26)	240.7 ± 54.25 (24)
	Percent change at Week 12 ^{b)} (n)	1.3 ± 9.77 (22)	-23.3 ± 8.37 (16)	-29.7 ± 14.09 (17)	-40.3 ± 12.05 (19)
Aged 10 - 15 years	Baseline ^{a)} (n)	251.4 ± 81.06 (14)	214.2 ± 37.49 (16)	218.6 ± 36.22 (14)	229.3 ± 41.44 (14)
	Percent change at Week 12 ^{b)} (n)	-2.8 ± 8.75 (11)	-21.2 ± 6.25 (10)	-27.0 ± 18.46 (8)	-41.7 ± 5.10 (12)
Male subjects	Baseline ^{a)} (n)	243.4 ± 90.32 (12)	217.1 ± 50.59 (12)	215.1 ± 47.94 (10)	234.0 ± 42.92 (14)
	Percent change at Week 12 ^{b)} (n)	2.6 ± 8.89 (11)	-21.1 ± 6.57 (9)	-25.5 ± 8.27 (5)	-39.0 ± 15.39 (11)

a) mg/dL (mean ± SD)

b) % (mean ± SD)

Although the incidence of coronary artery disease in Japan is different from that outside Japan, changes in LDL-C levels are an appropriate measure to evaluate the potential for reducing the risk of coronary artery disease both in and outside Japan. LDL-C levels were assessed as an endpoint in both Japanese and foreign clinical studies. In conclusion, differences in intrinsic and extrinsic factors in and outside Japan do not impact the evaluation of the clinical study results.

PMDA’s view:

The first-line therapies for pediatric patients with heterozygous FH differ between Japan and other countries. In both the Japanese and foreign clinical studies, however, patients were prohibited from receiving drugs other than pitavastatin or LDL apheresis; this validates the applicant’s position that differences in extrinsic ethnic factors are unlikely to affect the efficacy evaluation of pitavastatin. With regard to intrinsic ethnic factors, the incidence of coronary artery disease in Japan is different from that outside Japan, but no major differences are found in the pathology of FH. The target disease of Study NK-104-PH-01 (FH) differed from that of Study NK-104-4.01EU (dyslipidemia including FH), but most subjects (104 of 106) in the latter had FH, so the populations of the Japanese and foreign

clinical studies were generally well matched. The baseline LDL-C level (mean \pm SD) was 257.5 ± 59.2 mg/dL in Study NK-104-PH-01, 232.9 ± 52.00 mg/dL in Study NK-104-4.01EU, and 229.7 ± 53.62 mg/dL in the foreign long-term treatment study (Study NK-104-4.02EU). The LDL-C levels in Study NK-104-PH-01 thus tended to be higher than those in the foreign clinical studies (Studies NK-104-4.01EU and NK-104-4.02EU). Moreover, the population of Study NK-104-PH-01 was limited to male pediatric patients aged 10 to 15 years while male and female pediatric patients aged 6 to 16 years were enrolled in Study NK-104-4.01EU, and the percent changes in LDL-C in both subgroups of Study NK-104-4.01EU (“male subjects” and “subjects aged 10 to 15 years”) were smaller than the percent changes in Study NK-104-PH-01. However, these differences in the Japanese and foreign studies are not substantial and are unlikely to greatly affect the evaluation of the efficacy and safety of pitavastatin.

The common goal of treatment for pediatric patients with FH is to reduce LDL-C levels in and outside Japan. The LDL-C-reducing effect of pitavastatin has been demonstrated in the Japanese and foreign studies (Studies NK-104-PH-01 and NK-104-4.01EU), and both studies showed similar dose-response profiles of the LDL-C reducing effect [see “2.(iii).B.(3) Efficacy”]. No clinically significant differences were observed in plasma drug concentrations following pitavastatin administration to pediatric patients between these studies [see “2.(ii).B.(1) Differences in plasma drug concentrations between Japanese and non-Japanese patients”], and the safety profiles in the studies did not differ substantially [see “2.(iii).B.(4) Safety”]. In product development program for adults, pitavastatin demonstrated its LDL-C-reducing effect and an acceptable safety profile in Japanese and non-Japanese patients with hypercholesterolemia or FH; pitavastatin has therefore been approved in and outside Japan as an LDL-C-lowering drug. The difference in incidence of coronary artery disease between Japan and other countries is an important ethnic factor which may impact the evaluation of the efficacy and safety of pitavastatin. Nevertheless, in view of the above findings, PMDA concludes that the efficacy and safety of pitavastatin in Japanese pediatric patients with FH can be evaluated by using the results of foreign clinical studies as well as the Japanese clinical study.

2.(iii).B.(3) Efficacy

The applicant’s explanation on the efficacy of pitavastatin:

Percent changes in LDL-C from baseline to Week 8 or 12 in Study NK-104-PH-01 were evaluated using repeated measures ANCOVA with treatment group and evaluation point as fixed effects, patient as a random effect, and the baseline level as a covariate. Percent changes from baseline in LDL-C (least-squares mean [95% CI]) were -27.258% [-34.003% , -20.513%] in the pitavastatin 1 mg group and -34.273% [-41.018% , -27.528%] in the pitavastatin 2 mg group, indicating a statistically significant reduction in LDL-C levels in both groups ($P < 0.001$). In Study NK-104-4.01EU, percent changes in LDL-C from baseline to Week 12 (least-squares mean \pm standard error) were $-23.5\% \pm 2.09\%$ in the pitavastatin 1 mg group, $-30.1\% \pm 2.11\%$ in the pitavastatin 2 mg group, $-39.3\% \pm 2.18\%$ in the pitavastatin 4 mg group, and $1.0\% \pm 2.06\%$ in the placebo group. The differences from the placebo group (least-squares mean [95% CI]) were -24.5 [-30.3 , -18.6] for the pitavastatin 1 mg group, -31.1 [-37.0 , -25.2] for the pitavastatin 2 mg group, and -40.3 [-46.2 , -34.4] for the pitavastatin 4 mg

group, showing statistically significant differences in all groups ($P < 0.0001$, ANCOVA with baseline LDL-C and age as covariates). Bile acid sequestrants, the first-line treatment for pediatric patients with FH in Japan, reduce LDL-C levels by approximately 21% (package insert for Questran 44.4% Powder); this level of efficacy is often recognized as insufficient. Since pitavastatin is intended to be a therapeutic option for high-risk pediatric patients with FH who do not respond sufficiently to bile acid sequestrants, the LDL-C-reducing effect reported in Study NK-104-PH-01 is necessary for treating high-risk pediatric patients with FH in the treatment environment of Japan. Pitavastatin, moreover, could be beneficial in pediatric patients with FH who require lifetime treatment because the LDL-C-reducing effect was maintained for 52 weeks in Study NK-104-PH-01.

PMDA asked the applicant to explain the clinical significance of LDL-C-lowering effect noted in Study NK-104-PH-01.

The applicant's response:

A meta-analysis of large-scale studies (≥ 1000 participants) to evaluate the therapeutic effect of statins in non-Japanese adults revealed that an LDL-C reduction of 1 mmol/L (38.7 mg/dL) by 5 years of statin treatment reduced the incidence of coronary artery disease by 23% (Cholesterol Treatment Trialists' [CTT] Collaborators. *Lancet*. 2005;366:1267-1278). The mean change in LDL-C from baseline to Week 52 in Study NK-104-PH-01 was 61.7 mg/dL in the pitavastatin 1 mg group and 87.9 mg/dL in the pitavastatin 2 mg group. If this effect were maintained for 5 years, the 5-year incidence of coronary artery disease would be reduced by 36.7% (1 mg) and 52.2% (2 mg). Although the meta-analysis was conducted on data from 5-year studies of statin treatment, starting statin treatment earlier in childhood could reduce high LDL-C exposure and could further delay the future onset of coronary artery disease as compared with those starting statin therapy in adulthood. A survey in adult Japanese patients with FH revealed that patients with LDL-C ≥ 260 mg/dL had a 8.29-fold higher odds of experiencing coronary artery disease than patients with LDL-C < 206 mg/dL (Sugisawa T et al. *J Atheroscler Thromb*. 2012;19:369-375). Table 8 shows distributions of LDL-C levels before and after pitavastatin therapy in Study NK-104-PH-01. Pitavastatin therapy resulted in fewer patients with LDL-C ≥ 260 mg/dL and more patients with LDL-C < 206 mg/dL. The results suggest that administration of pitavastatin to Japanese pediatric patients with FH could greatly reduce the risk of coronary artery disease.

Table 8. Distribution of LDL-C in Study NK-104-PH-01 (number of patients)

	Evaluation point	< 206 mg/dL	≥ 206 mg/dL < 260 mg/dL	≥ 260 mg/dL	Total
1 mg	Baseline	2	2	3	7
	Week 52	5	1	1	7
2 mg	Baseline	1	2	4	7
	Week 52	6	1	0	7

PMDA's view:

While an LDL-C target of <3.5 mmol/L (135 mg/dL) for pediatric patients with FH is specified in the foreign guidelines (Nordestgaard BG et al. *Eur Heart J.* 2013;34:3478-3490a), no target has been clearly specified in the Japanese guidelines, and no evidence is available to indicate how much LDL-C should be reduced to prevent future occurrence of coronary artery disease in Japanese pediatric patients with FH. However, the meta-analysis of large-scale studies (≥ 1000 participants), conducted to evaluate the therapeutic effect of statins in non-Japanese adults, revealed that an LDL-C reduction of 1 mmol/L (38.7 mg/dL) by a 5 year-statin treatment reduced the incidence of coronary artery disease by 23% (Cholesterol Treatment Trialists' [CTT] Collaborators. *Lancet.* 2005;366:1267-1278); in view of this finding, reduction in LDL-C levels by pitavastatin therapy is expected to reduce the risk of coronary artery disease also in Japanese pediatric patients with FH. Therefore, assessing the efficacy of pitavastatin by evaluating changes from baseline in LDL-C is acceptable. Percent changes in LDL-C from baseline to Weeks 8 and 12 in Study NK-104-PH-01 were evaluated using repeated measures ANCOVA with treatment group and evaluation point as fixed effects, patient as a random effect, and the baseline LDL-C level as a covariate. The least-squares mean of percent changes from baseline in LDL-C was -27.258% in the pitavastatin 1 mg group and -34.273% in the pitavastatin 2 mg group, indicating a statistically significant reduction from baseline in LDL-C in both groups. In light of these findings and the fact that Studies NK-104-PH-01 and NK-104-4.01EU showed similar dose-response relationships, the results of the 2 studies demonstrate the efficacy of pitavastatin in Japanese pediatric patients with FH. The LDL-C-lowering effect was maintained during the 52 weeks of pitavastatin therapy in Studies NK-104-PH-01 and NK-104-4.02EU; this result indicates that the long-term LDL-C lowering effect of pitavastatin can be expected.

2.(iii).B.(4) Safety

PMDA asked the applicant to discuss whether pediatric patients have a higher risk of adverse events specific to statins than adults.

The applicant's response:

Table 9 presents the incidences of adverse events specifically concerned for statins (e.g., rhabdomyolysis, blood creatine kinase [CK] elevations, liver disorders) reported in the Japanese and foreign clinical studies in pediatric patients with FH (Studies NK-104-PH-01, NK-104-4.01EU, and NK-104-4.02EU) and the Japanese clinical study in adult patients with FH. Laboratory-related events occurred more frequently in adults than in pediatric patients, but the incidences of other adverse events were generally comparable. Time to onset of adverse events was similar in pediatric and adult patients; the events occurred mostly within 90 days of the start of treatment, thereafter showing a decreasing trend in incidence. In both pediatric and adult patients, most events were mild or moderate in severity. Time courses of blood aspartate aminotransferase (AST), ALT, and CK revealed no substantially persistent elevations following treatment in either pediatric or adult patients.

Table 9. Incidences of adverse events in clinical studies in adult and pediatric patients

	Pediatric patients ^{a)}		Adults ^{b)}
	Foreign clinical studies (NK-104-4.01EU, NK-104-4.02EU) (N = 127)	Japanese clinical study (NK-104-PH-01) (N = 14)	Japanese clinical study (N = 155)
Adverse event	70.9 (90)	85.7 (12)	69.0 (107)
Rhabdomyolysis	0	0	0
Hepatobiliary disorders	0	0	19.4 (30)
Investigations	4.7 (6)	0	-
Increased ALT	1.6 (2)	0	9.7 (15)
Increased AST	1.6 (2)	0	8.4 (13)
Increased CK	1.6 (2)	0	12.9 (20)

% (n)

a) Hepatobiliary disorders and investigations are classified according to MedDRA system organ classes. Other events are classified according to preferred terms.

b) Classified according to the system organ classifications of the Japanese Adverse Drug Reaction Terminology (J-ART).

Statins are unlikely to pose greater safety concerns related to adverse events specific to statins (e.g., rhabdomyolysis) in pediatric patients with FH than in adult patients with dyslipidemia. However, musculoskeletal disorders may occur more frequently in pediatric patients because exercise load is a patient-related risk factor for rhabdomyolysis (Manuals for Management of Individual Serious Adverse Drug Reactions: Rhabdomyolysis, Ministry of Health, Labour and Welfare) and pediatric patients tend to engage in daily physical activities more frequently or vigorously than adults. In a 2-year specified use results survey of pitavastatin in adults, the incidence of adverse reactions related to muscle disorders was higher in patients with a high baseline CK level than in patients with a low baseline CK level: 12.7% (126 of 992) of patients with a high baseline CK level and 4.1% (411 of 10,060) of patients with a low baseline CK level. This indicates that a high baseline CK level is a predisposing factor for rhabdomyolysis. Given the above facts, the applicant considers that the risk of rhabdomyolysis can be reduced by including the following precautionary statement in the package insert: “Pitavastatin should be administered with care to pediatric patients with FH after the exercise and CK levels are determined.”

PMDA asked the applicant to explain the potential impacts of pitavastatin in pediatric patients based on its mechanism of action.

The applicant’s response:

Pitavastatin and other statins suppress the synthesis of cholesterol by inhibiting HMG-CoA reductase in the mevalonate pathway. Pharmacologically, they are assumed to affect hormones produced in the body from cholesterol. Testosterone, estrogen, and other sex hormones are particularly important in growing child. Reduction in these hormones by drugs may delay sexual development. Investigation on the effects of statins on sex hormones revealed a slight reduction in testosterone (Schooling CM et al. *BMC Med.* 2013;11:1-9). Various investigations have evaluated the effects of statins on growth and development in pediatric patients with FH, and have revealed no concerns regarding the impact on growth and development (Vuorio A et al. *Cochrane Database Syst Rev.* 2010;7:CD006401). Therefore, attention should be paid to the potential for statin-related decrease in testosterone, but statin is

considered unlikely to affect sexual development. Table 10 shows changes in testosterone and estrogen in Japanese and foreign clinical studies of pitavastatin. Neither hormone decreased substantially in any study. Changes in Tanner stages were evaluated in Study NK-104-4.02EU with a mean treatment period of 342 days. Tanner stage progression was observed in 46.0% (28 of 61) of the patients aged 10 to 15 years during the treatment period. In clinical studies of other statins in pediatric patients with FH (duration of 6 months to 2 years), Tanner stage progression was observed in 14.1% to 63.6% of subjects receiving placebo (Vuorio A et al. *Cochrane Database Syst Rev.* 2010;7:CD006401). Thus, changes in the Tanner stages associated with pitavastatin therapy appear to be comparable to the changes in subjects receiving placebo in these clinical studies.

Table 10. Changes in sex hormones in the Japanese and foreign clinical studies

Measuring point	Testosterone (µg/L)		Estradiol (µg/L)	
	Study NK-104-PH-01		Study NK-104-4.02EU	Study NK-104-4.02EU
	1 mg	2 mg		
Baseline	2.50 ± 2.81 (n = 7)	2.36 ± 2.86 (n = 7)	1.37 ± 1.85 (n = 54)	26.6 ± 36.3 (n = 57)
Week 52	3.23 ± 2.49 (n = 7)	2.83 ± 2.09 (n = 7)	2.04 ± 1.90 (n = 18)	33.4 ± 58.2 (n = 26)

Mean ± SD

Patient height and body weight before and after treatment in Japanese and foreign clinical studies (Studies NK-104-PH-01 and NK-104-4.02EU) were compared with the average heights and weights or growth curves in the respective regions of the studies. No tendency of delayed growth associated with pitavastatin was noted in the Japanese or non-Japanese pediatric patients.

PMDA asked the applicant to explain whether the combination of pitavastatin and another antidiabetic drug may raise greater safety concern in pediatric patients with FH than in adult patients with FH.

The applicant's response:

If approved in pediatric patients with FH, pitavastatin may be used in combination with bile acid sequestrants and ezetimibe. Bile acid sequestrants, which reduce cholesterol by sequestering bile acids in the gastrointestinal tract, are not absorbed into the body and therefore are unlikely to raise any new safety concerns when used with pitavastatin in pediatric patients. Ezetimibe is absorbed into the body and blocks cholesterol absorption in the small intestine. Adults receiving ezetimibe and a statin experience increased ALT, myalgia, etc. more frequently than those taking ezetimibe alone. In a clinical study, pediatric patients receiving ezetimibe and simvastatin experienced increased CK and ALT more frequently than those receiving simvastatin alone (van der Graaf A et al. *J Am Coll Cardiol.* 2008;52:1421-1429). In conclusion, the safety profile of pitavastatin in combination with other antidiabetic drugs in pediatric patients is expected to be similar to that in adults, and therefore should not raise any new safety concerns.

PMDA's view:

Currently, no findings indicate that adverse events specific to statins (e.g., rhabdomyolysis, laboratory test abnormalities) occur more frequently in pediatric patients with FH than in adult patients with FH or dyslipidemia, and there is no evidence suggesting greater safety concerns in pediatric patients with FH than in adults with FH. However, rhabdomyolysis, effects on growth, and other adverse events must be carefully monitored in the post-marketing phase because of the small sample size in the clinical studies. In addition, pitavastatin should be prescribed by physicians with sufficient knowledge and experience on dyslipidemia treatment in pediatric patients and an understanding of pitavastatin's characteristics, because pediatric patients with FH are likely to use pitavastatin longer than adults, and because sufficient data on long-term safety are unavailable. PMDA will make a final decision on the appropriateness of the precautions in the package insert based on comments from the Expert Discussion.

2.(iii).B.(5) Intended population and indications

2.(iii).B.(5).1 Homozygous FH

Only patients with heterozygous FH were included in the Japanese and foreign clinical studies for FH, and the efficacy and safety of pitavastatin have not been demonstrated in pediatric patients with homozygous FH. PMDA therefore asked the applicant to state its position on the appropriateness of indicating pitavastatin for pediatric patients with homozygous FH, and the appropriateness of including precautions for use in pediatric patients with homozygous FH in the draft package insert.

The applicant's response:

As stated in "2.(iii).B.(1) Clinical positioning" and "2.(iii).B.(1).2) Homozygous FH in pediatric patients," although LDL apheresis is the fundamental treatment for pediatric patients with homozygous FH, some patients may benefit from pitavastatin, and pitavastatin may have a certain level of efficacy in patients with homozygous FH even when the LDL-C reduction is not as sufficient as in patients with heterozygous FH. The safety data from clinical studies of other statins in pediatric and adult patients with homozygous FH do not indicate substantial difference in the safety profile between patients with homozygous and heterozygous FH (Raal FJ et al., *Atherosclerosis*. 2000;150:421-428; Yamamoto A et al., *Atherosclerosis*. 2000;153:89-98; Marais AD et al., *Atherosclerosis*. 2008;197:400-406; Raal FJ et al., *Atherosclerosis*. 1997;135:249-256; Gagné C et al., *Circulation*. 2002;105:2469-2475). Although no statin has been extensively used in patients with homozygous FH outside Japan, some are indicated for homozygous FH. The Japanese package inserts for atorvastatin, rosuvastatin, and pitavastatin contain precautions for use in patients with homozygous FH, stating that they should be used as an adjuvant to LDL apheresis and other non-drug therapies. As shown above, (a) pitavastatin has never been used in patients with homozygous FH, but it has been approved as an adjuvant for LDL apheresis and other treatments in adults with homozygous FH, and (b) the start of aggressive treatment in childhood is critical for patients with homozygous FH. Thus, the use of pitavastatin should be allowed in pediatric patients with homozygous FH, as in adult patients. The precautions for indication in the package insert already include a statement to the

following effect: “Pitavastatin has not been used yet in patients with homozygous FH. Therefore in this population, pitavastatin should be used only as an adjuvant to LDL apheresis or other non-drug therapies only when medically necessary.” Moreover, the data submitted for the present application do not include any new findings on the treatment of homozygous FH in pediatric patients. Therefore, no new precautionary statements about pitavastatin therapy in pediatric patients with homozygous FH need to be included in the package insert for pitavastatin.

PMDA’s view:

The efficacy and safety of pitavastatin in pediatric patients with homozygous FH have not been demonstrated because the clinical studies conducted in and outside Japan were limited to patients with heterozygous FH. However, PMDA understands the difficulties in conducting a clinical study in pediatric patients with homozygous FH, an orphan disease, and the data from patients with heterozygous FH in Studies NK-104-PH-01 and NK-401-4.01EU indicate that pitavastatin has LDL-C reducing effect and an acceptable safety profile [see “2.(iii).B.(3) Efficacy” and “2.(iii).B.(4) Safety”]. The following findings suggest that pitavastatin has a certain level of efficacy in patients with homozygous FH, although its LDL-C lowering effect may be weaker for homozygous FH than for heterozygous FH: (a) Although patients with homozygous FH respond poorly to statin therapy, statins may be effective in patients with homozygous FH who have the slightest residual LDL receptor activity, or who inherited an LDL receptor mutation from one parent and a PCSK9 mutation from the other parent (Malloy MJ et al. *Ann Intern Med.* 1987;107:616-623); (b) statins reduced death and coronary artery disease in patients with homozygous FH (Raal FJ et al. *Circulation.* 2011;124:2202-2207); (c) some pediatric patients with a small body size receive pharmacotherapies before the start of an invasive LDL apheresis. According to Japanese and foreign clinical studies of other statins in adult and pediatric patients with homozygous FH, the safety profiles of these statins did not tend to differ substantially between patients with homozygous and heterozygous FH (Raal FJ et al., *Atherosclerosis.* 2000;150:421-428; Yamamoto A et al., *Atherosclerosis.* 2000;153:89-98; Marais AD et al. *Atherosclerosis.* 2008;197:400-406; Raal FJ et al., *Atherosclerosis.* 1997;135:249-256; Gagné C et al., *Circulation.* 2002;105:2469-2475). The safety of pitavastatin is therefore not expected to differ substantially between patients with homozygous and heterozygous FH. Pitavastatin therapy in pediatric patients with homozygous FH is thus unlikely to pose major safety concerns, because the safety and pharmacokinetic profiles of the drug have been confirmed in pediatric patients with heterozygous FH.

On the basis of the above results, PMDA concludes that pitavastatin can be indicated in pediatric patients with homozygous FH as it is for adult patients. However, the first-line therapy for patients with homozygous FH is LDL apheresis, and pitavastatin has never been used in pediatric patients with homozygous FH. As with adults, pediatric patients should receive pitavastatin only as an adjuvant to LDL apheresis only when medically necessary. The applicant decided that no additional precautionary statements were necessary for pediatric patients with homozygous FH, because the current precautionary statement for adult patients with homozygous FH (presented in the package insert)

would also serve as a precaution for pediatric patients with homozygous FH. The applicant's decision is appropriate.

2.(iii).B.(5).2) Use in female pediatric patients

Pitavastatin has never been used in Japanese female pediatric patients because Study NK-104-PH-01 enrolled only male pediatric patients. Most of the other statins indicated in pediatric patients outside Japan are limited to post-menarcheal patients, but not to all female pediatric patients. PMDA therefore asked the applicant to discuss (a) whether pitavastatin therapy is suitable for pre-menarcheal and post-menarcheal female pediatric patients and (b) whether restrictions on pitavastatin use in female pediatric patients are needed in Japan.

The applicant's response:

The applicant decided not to include female pediatric patients with FH in Study NK-104-PH-01, for the following reasons: (a) When Study NK-104-PH-01 was planned, most physicians provided medical care in accordance with the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2007 (Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2007, Japan Atherosclerosis Society, 2007), and had more negative opinions on pharmacotherapy for FH in pediatric patients than they do now; (b) these guidelines state that female patients are at a lower risk for coronary artery disease than male patients, and that the effects of statins on pregnancy should be considered. The latest edition of the guidelines, however, advocate the need to appropriately control LDL-C levels beginning in childhood, recommending as-needed pharmacotherapy for pediatric patients with FH. Pitavastatin therapy may therefore be needed in both female and male pediatric patients with severe FH.

Female pediatric patients with FH were eligible for foreign Study NK-401-4.01EU. Male and female pediatric patients receiving pitavastatin in the study showed similar LDL-C reduction (Table 11) and similar incidences of adverse events, with no major safety problems in female patients. This suggests that pitavastatin has similar efficacy and safety profiles in Japanese male and female pediatric patients with FH. Japanese and foreign clinical studies in adult patients with dyslipidemia have shown no sex differences in the efficacy or safety of pitavastatin.

Table 11. Percent changes in LDL-C from baseline to Week 12 in non-Japanese pediatric patients receiving pitavastatin (FAS)

	n	Baseline ^{a)} (mg/dL)	Week 12 ^{a)} (mg/dL)	Percent change ^{b) d)} (%)	Difference from placebo ^{c) d)} (%)
Male					
Placebo	12	243.4 ± 90.32	241.8 ± 77.99	1.7 ± 3.17	
1 mg	12	217.1 ± 50.59	173.4 ± 43.00	-20.6 ± 3.14	-22.4 [-31.4, -13.3]
2 mg	10	215.1 ± 47.94	156.8 ± 43.08	-27.7 ± 3.50	-29.5 [-39.1, -19.8]
4 mg	14	234.0 ± 42.92	144.1 ± 38.83	-37.8 ± 2.90	-39.6 [-48.2, -31.0]
Female					
Placebo	15	238.1 ± 49.13	237.2 ± 46.38	0.3 ± 2.81	
1 mg	14	243.6 ± 38.20	178.8 ± 26.56	-25.9 ± 2.92	-26.2 [-34.3, -18.0]
2 mg	16	228.1 ± 26.34	156.8 ± 37.06	-31.7 ± 2.75	-32.0 [-39.9, -24.1]
4 mg	10	250.2 ± 68.48	144.9 ± 45.69	-41.3 ± 3.47	-41.6 [-50.6, -32.6]

a) Mean ± SD

b) Least-squares mean ± standard error (SE)

c) Least-squares mean [95% CI]

d) ANCOVA with baseline LDL-C and age as covariates

The final available measurement taken during the study period was used for patients who discontinued the study before Week 12 (i.e., LOCF)

Preventive therapy of coronary artery disease in childhood is intended to prevent the future occurrence of coronary artery disease by inhibiting progression of its risk factors and effectively controlling them. Patients at a high risk of future coronary artery disease should therefore receive aggressive pharmacotherapy during childhood. The Atherosclerotic Disease Guidelines state that coronary artery disease and associated deaths occur 10 years later in women than in men. Thus, Japanese female pediatric usually do not require aggressive pharmacotherapy during childhood because they are generally at a lower risk of coronary artery disease than their Western counterparts; some Japanese female pediatric patients, however, have a high risk comparable to that in male pediatric patients. A study of atherosclerosis in younger Japanese patients autopsied between the ages of 1 month and 39 years revealed that (a) some female patients (although fewer than male patients) developed atherosclerotic lesions before reaching adulthood, and that (b) the size of fatty streaks (i.e., an initial atherosclerotic lesion) was positively correlated with cholesterol levels (Imakita M et al. *Atherosclerosis*. 2001;155:487-497). Although this study was not limited to FH patients, these tendencies would be particularly pronounced in FH patients because of their elevated LDL-C levels. The findings thus support the hypothesis that some female pediatric patients with FH have atherosclerosis. Because of its teratogenic potential, pitavastatin must be used with care in female pediatric patients with FH, but teratogenicity is already mentioned in the current package insert, and new related concerns are unlikely to emerge. In conclusion, the use of pitavastatin is acceptable in female pediatric patients with FH when the risk of future coronary artery disease is very high (e.g., patients with Achilles tendon hypertrophy, thickening of the intima-media complex, or other atherosclerotic lesion).

Many other statins approved in Western countries are limited to post-menarcheal female pediatric patients. This limitation was based on the populations of pediatric clinical studies, which included post-menarcheal female pediatric patients and excluded the pre-menarcheal patients. However, most Western guidelines for the treatment of pediatric FH do not limit statin use to post-menarcheal female

pediatric patients (National Cholesterol Education Program [NCEP], *Pediatrics*. 1992;89:495-501; Daniels SR et al., *Pediatrics*. 2008;122:198-208; Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, *Pediatrics*. 2011;128 Suppl 5:S213-256; Daniels SR et al., *J Clin Lipidol*. 2011;5:S30-37; Watts GF et al., *Int J Cardiol*. 2014;171:309-325; Nordestgaard BG et al., *Eur Heart J*. 2013;34:3478-3490a). Although the reason is unclear, it is presumably because the data gathered from clinical studies of statins in pediatric patients with FH do not suggest the effects of statins on sexual maturation. A systematic Cochrane review of multiple clinical studies in pediatric patients with FH showed no impacts on sexual maturation (Vuorio A et al. *Cochrane Database Syst Rev*. 2010;7:CD006401), and 10-year follow-up data from an investigation of the efficacy and safety of statins in pediatric patients with FH do not show any developmental effects (Kusters DM et al. *JAMA*. 2014;312:1055-1057). A comparison of pre-menarcheal and post-menarcheal pediatric patients enrolled in Studies NK-104-4.01EU and NK-104-4.02EU showed no significant difference in efficacy and safety of pitavastatin, with no difference in the rate of passing through the Tanner stages (although the number of these patients was small).

In conclusion, the use of pitavastatin in female pediatric patients with FH in Japan should not be limited to post-menarcheal patients.

PMDA's view:

The Atherosclerotic Disease Guidelines state that the risk of coronary artery disease (i.e., the onset and mortality of the disease) begin to increase 10 years later in women than in men. In addition, statins are contraindicated in women who are or may be pregnant out of concern for teratogenicity. Therefore, pitavastatin therapy should not be indicated in all female pediatric patients with FH, but should be limited to those in whom the benefits are deemed to outweigh the risks after careful risk-benefit assessment (e.g., patients with an extremely high risk of coronary artery disease). Pitavastatin has never been used in Japanese female pediatric patients, and conducting a clinical study in Japanese female pediatric patients with FH with a high risk of coronary artery disease is not feasible. Thus, there is no other choice but to extrapolate the efficacy and safety data from the foreign studies (Studies NK-104-4.01EU and NK-104-4.02EU) to Japanese female pediatric patients. Study NK-104-PH-01 demonstrated the efficacy and acceptable safety of pitavastatin in male pediatric patients, although it enrolled no female pediatric patients [see “2.(iii).B.(3) Efficacy” and “2.(iii).B.(4) Safety”], and Study NK-401-4.01EU showed that the efficacy and safety did not differ significantly between the male and female pediatric patients. Japanese female pediatric patients may thus be allowed to use pitavastatin.

Although the risks and benefits of pitavastatin must be carefully weighted, the intended population for pitavastatin need not be limited to post-menarcheal patients. This is because (a) the efficacy and safety of pitavastatin did not differ significantly between pre-menarcheal and post-menarcheal pediatric patients in the foreign clinical studies (Studies NK-104-4.01EU and NK-104-4.02EU), and (b) recently issued Western guidelines do not limit the initial treatment with statins to post-menarcheal patients (National Cholesterol Education Program [NCEP], *Pediatrics*. 1992;89:495-501; Daniels SR

et al., *Pediatrics*. 2008;122:198-208; Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, *Pediatrics*. 2011;128 Suppl 5:S213-256; Daniels SR et al, *J Clin Lipidol*. 2011;5:S30-37; Watts GF et al., *Int J Cardiol*. 2014;171:309-325; Nordestgaard BG et al., *Eur Heart J*. 2013;34:3478-3490a).

Based on the above, PMDA has concluded that pitavastatin may be administered to female pediatric patients with FH who have atherosclerotic lesions with a high risk of coronary artery disease, on the premise that the patients are thoroughly informed that pitavastatin has never been used in Japanese female pediatric patients and that pitavastatin has the risk of teratogenicity (the risk is mentioned in the current package insert).

Based on the information presented in 2.(iii).B.(5).1) and 2.(iii).B.(5).2), PMDA considers that the indication of pitavastatin in pediatric patients should be “familial hypercholesterolemia.” PMDA will make a final decision on the suitability of this conclusion and the specific wording of precautionary statements based on comments raised in the Expert Discussion. Since “familial hypercholesterolemia” is an indication for both pediatric and adult patients, the pediatric dosage regimen should be added to the “dosage and administration” section [see “2.(iii).B.(5).6) Dosage and administration”] and the “indication” section should be left unchanged. The proposed indications should be reworded as follows:

[Indications]

~~Adults:~~ Hypercholesterolemia, familial hypercholesterolemia

~~Pediatric patients:~~ Familial hypercholesterolemia

(Crossed out words were deleted from the proposed indications.)

2.(iii).B.(5).6) Dosage and administration

PMDA asked the applicant to explain the dosage regimen for pitavastatin in pediatric patients.

The applicant’s response:

As mentioned in “2.(iii).B.(3) Efficacy,” the LDL-C reduction effect of pitavastatin has been demonstrated for all doses in Studies NK-104-PH-01 and NK-104-4.01EU. The incidences of adverse events in Study NK-104-PH-01 were 100% (7 of 7 patients) in the 1 mg group and 71.4% (5 of 7 patients) in the 2 mg group, with no tendency toward higher incidence in the 2 mg group than in the 1 mg group. In Study NK-104-4.01EU, the incidences of adverse events were 55.6% (15 of 27 patients) in the placebo group, 69.2% (18 of 26 patients) in the 1 mg group, 59.3% (16 of 27 patients) in the 2 mg group, and 42.3% (11 of 26 patients) in the 4 mg group, with no tendency toward higher incidences in patients receiving higher doses. These findings suggest that Japanese pediatric patients with FH should start pitavastatin therapy at 1 mg and be allowed to increase the dose to 2 mg only when they respond poorly to 1 mg, with careful consideration of safety.

Recently in Western countries, pharmacotherapy for FH in pediatric patients typically starts at 8 to 10 years old, and patients aged approximately ≥ 10 years are allowed to receive other statins indicated for pediatric patients (Nordestgaard BG et al., *Eur Heart J.* 2013;34:3478-3490a; Watts GF et al., *Int J Cardiol.* 2014;171:309-325). Because of this current clinical practice, patients aged 10 to 15 years were enrolled in Study NK-104-PH-01, which demonstrated the efficacy and safety of pitavastatin in this age group. Therefore a dosage regimen for pediatric patients with FH aged ≥ 10 years should be added to the approved dosage. [REDACTED]

PMDA asked the applicant to explain the rationale for selecting 1 mg instead of 2 mg as the standard dose, in spite of the greater LDL-C reduction observed in the higher dose groups than in the lower dose groups without a difference in the incidence of adverse events.

The applicant's response:

Although no safety differences were observed among doses used in Studies NK-104-PH-01 and NK-104-4.01EU, these studies were conducted with carefully controlled populations. In routine clinical settings, a variety of factors such as drug interactions and renal or hepatic impairment could increase pitavastatin exposure than anticipated. Moreover, high-dose statin therapy poses a higher risk of CK elevations and rhabdomyolysis (van Staa TP et al. *Br J Clin Pharmacol.* 2014;78:649-659). The clinical studies of pitavastatin in pediatric patients have shown no specific safety problems, but only limited data are available from Japanese pediatric patients with FH, and the safety profile of pitavastatin has not been established in pediatric patients. Therefore pediatric patients should start treatment at 1 mg and be allowed to increase the dose to 2 mg, as needed, based on their conditions. This position is supported by Western guidelines for FH in pediatric patients, which recommend starting statin therapy at a low dose (Watts GF et al. *Int J Cardiol.* 2014;171:309-325).

PMDA requested that the applicant provide (a) the reason Study NK-104-PH-01 did not use the 4 mg dose, which was used in Study NK-104-4.01EU, and (b) the rationale for the maximum dose used in Study NK-104-PH-01. (PMDA asked the applicant to justify the maximum dose based on [a] the achievement rates of LDL-C targets in the Japanese and foreign studies, and [b] the dose distribution in Study NK-104-4.02EU, which allowed dose escalation depending on the condition of the patient.)

The applicant's response:

The maximum dose in Study NK-104-4.01EU was selected in light of the following background: Pitavastatin 4 mg was non-inferior to atorvastatin 20 mg and to simvastatin 40 mg (both are the maximum pediatric doses approved) in phase III clinical studies of pitavastatin in adults conducted in European countries. Thus, there was little clinical significance in evaluating the efficacy of pitavastatin in pediatric patients only at doses that may have less LDL-C reduction effect compared

with other statins. According to Western guidelines, pharmacotherapy should be started when LDL-C is ≥ 190 mg/dL and an ideal target LDL-C level is 110 mg/dL (McCrindle BW et al. *Circulation*. 2007;115:1948-1967). Taking account of the effect size of pitavastatin 2 mg in adults, pitavastatin 2 mg is unlikely to reduce LDL-C ≥ 190 mg/dL (baseline) to 110 mg/dL (the target level) in pediatric patients with FH; a higher dose was needed to control and maintain LDL-C levels in pediatric patients with FH. Pitavastatin 4 mg was thus selected as the maximum dose in Study NK-104-4.01EU. Meanwhile, the incidence of coronary artery disease is lower in the Japanese population than in Westerners (Saito I et al., *Int J Epidemiol*. 2000;29:837-844; Verschuren WM et al., *JAMA*. 1995;274:131-136), and the approved dosage of many statin products in Japan is lower than that in Western countries. This suggested that pitavastatin may be effective at lower doses in Japanese pediatric patients than in Western pediatric patients. In addition, no clinical studies of statins had been conducted in Japanese pediatric patients with FH, and the applicant considered that increased pitavastatin exposure may cause adverse drug reactions in pediatric patients, who are smaller in body size than adults. Accordingly, Study NK-104-PH-01 included pitavastatin 1 and 2 mg doses, but excluded the 4 mg dose.

While no target LDL-C level for FH in pediatric patients is established in Japan, the U.S. guidelines recommend a target of <130 mg/dL (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics*. 2011;128 Suppl 5:S213-256) or <110 mg/dL (McCrindle BW et al. *Circulation*. 2007;115:1948-1967). Because of the LDL-C targets recommended by the U.S. guidelines, the achievement rate of target LDL-C levels was evaluated as a secondary endpoint in the clinical studies (Studies NK-104-PH-01, NK-104-4.01EU, and NK-104-4.02EU) (See Table 12). The achievement rate was lower in the pitavastatin 2 mg group in Study NK-104-PH-01 than in the 2 mg group of Study NK-104-4.01EU; this is probably due to the higher baseline levels in the 2 mg group in Study NK-104-PH-01. Recent foreign guidelines recommend that the LDL-C target be <135 mg/dL (Nordestgaard BG et al. *Eur Heart J*. 2013;34:3478-3490a), and that LDL-C be decreased to <135 mg/dL using a statin and, as necessary, a bile acid sequestrant or ezetimibe in combination (Watts GF et al. *Int J Cardiol*. 2014;171:309-325); the guidelines thus do not recommend reducing LDL-C to the target level with a statin alone.

Table 12. Achievement rates of target LDL-C levels in Japanese and foreign clinical studies (FAS)

	Study NK-104-PH-01		Study NK-104-4.01EU				Study NK-104-4.02EU
	1 mg	2 mg	Placebo	1 mg	2 mg	4 mg	
n	7	7	27	26	26	24	112
Baseline ^{a)} (mg/dL)	245.4 ± 68.1	269.6 ± 51.2	240.5 ± 68.98	231.4 ± 45.45	223.1 ± 35.85	240.7 ± 54.25	229.7 ± 53.62
Achievement rate of LDL-C < 130 mg/dL ^{b)}	14.3 (1)	0 (0)	0 (0)	3.8 (1)	30.8 (8)	37.5 (9)	42.0 (47)
Achievement rate of LDL-C < 110 mg/dL ^{b)}	0 (0)	0 (0)	0 (0)	0 (0)	7.7 (2)	16.7 (4)	20.5(23)

a) Mean ± SD

b) % (number of patients achieving the level)

At the end of Study NK-104-4.02EU, 2.7% (3 of 112) of the patients were receiving pitavastatin 1 mg, 5.4% (6 of 112) were receiving 2 mg, and 92.0% (103 of 112) were receiving 4 mg. Most of the patients were using 4 mg because the design of Study NK-104-4.02EU required dose increase in patients not achieving LDL-C of 110 mg/dL. (This study design is based on the-then available guidelines recommending a target LDL-C <110 mg/dL.) In Japan, no consensus has been reached regarding the optimal level of reduction in LDL-C (i.e., target LDL-C) in pediatric patients with FH. As described above, the current Western guidelines recommend the combination therapy with a statin and other drugs to achieve LDL-C targets; this suggests that the maximum dose of pitavastatin in Japanese pediatric patients with FH should not be determined based solely on the fact that most patients in Study NK-104-4.02EU received pitavastatin 4 mg.

Differences in body size could mean that pitavastatin 4 mg may lead to higher pitavastatin exposure in pediatric patients than in adults, and the safety of >4 mg doses has not been established in adults either. LDL-C reductions observed in the pitavastatin 1 and 2 mg groups in Study NK-104-PH-01 were clinically significant [see “2.(iii).B.(3) Efficacy”], and the benefits of aggressive therapy with pitavastatin 4 mg may not outweigh the risks in Japanese pediatric patients with FH, who are expected to have a lower incidence of coronary artery disease than their Western counterparts.

In conclusion, not using 4 mg as the maximum dose in Study NK-104-PH-01 was justified, and currently, pitavastatin 2 mg is the appropriate maximum dose for Japanese pediatric patients with FH.

PMDA’s view:

CK elevations and rhabdomyolysis may occur in a dose-proportional manner in patients receiving pitavastatin. This justifies the proposed dosage regimen out of safety concerns: the starting dose is 1 mg (a low dose), and the dose is escalated to 2 mg in patients with poor response to 1 mg. This is in line with the regimen used in the clinical practice in Japan. Pitavastatin doses should be adjusted according to changes in the patient’s condition, because pitavastatin is intended for long-term use, and because pediatric patients can be at risk for increased pitavastatin exposure caused by various factors (e.g., drug interactions with antimicrobials used to treat infections, renal disorders associated with dehydration).

In Japan, no consensus has been reached regarding the optimal level of reduction in LDL-C in pediatric patients with FH, with no established target LDL-C levels. Meanwhile, the maximum doses of statins are lower in Japanese adults than in Western adults. As was previously stated, increased pitavastatin exposure may cause CK elevations and rhabdomyolysis, and therefore the risk-benefit balance (between safety and aggressive reduction in LDL-C) differs between Western countries and Japan, where the prevalence of coronary artery disease is lower than in Western countries. Accordingly, the Japanese clinical study should not use the same maximum dose used in the foreign clinical studies. PMDA has thus concluded that the doses used in Study NK-104-PH-01 were appropriate.

Statin therapy is the first-line treatment for pediatric patients with heterozygous FH in European countries, where there is a need to aggressively reduce LDL-C levels. On the other hand, the Japanese Atherosclerotic Disease Guidelines list bile acid sequestrants as the first-line therapy for Japanese pediatric patients with FH, placing a greater emphasis on safety. Japanese pediatric patients with poor response to bile acid sequestrants may use concomitant pitavastatin, but they are unlikely to require LDL-C reduction therapy as aggressive as that administered to high-risk patients in Western countries. The maximum dose of 2 mg is thus appropriate for Japanese patients.

The lower age limit of 10 years in Study NK-104-PH-01 was appropriate taking account of (a) the typical age to start pharmacotherapy in pediatric patients with FH in Western countries and (b) the eligible age range for statin therapy in pediatric patients outside Japan. The proposed age range for pitavastatin therapy in Japan (≥ 10 years old) is appropriate, based on the age range in Study NK-104-PH-01.

Based on the above, PMDA has concluded that the dosage and administration for pitavastatin should be as follows:

[Dosage and administration]

Hypercholesterolemia:

The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day.

Familial hypercholesterolemia:

The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day.

The usual dosage in pediatric patients aged ≥ 10 years is 1 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's condition. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 2 mg/day.

2.(iii).B.(5).7) Pediatric formulations

PMDA asked the applicant to state how pitavastatin may be used by pediatric patients who are unable to swallow tablets and then explain whether pediatric formulations should be developed.

The applicant's response:

The 1 mg and 2 mg tablet formulations are relatively small, measuring 6.2 mm and 7.1 mm in diameter, respectively. These sizes make the tablets suitable for use in pediatric patients aged ≥ 10 years. Patients who are unable to take the tablets for some reason may use pitavastatin orally disintegrating (OD) tablets. The size of OD tablets does not matter because they disintegrate in the mouth.

In conclusion, pediatric formulations need not be developed since pediatric patients with FH will be able to take the existing formulations.

PMDA's view:

At present, there is little need to develop pediatric formulations because most patients aged ≥ 10 years are able to take tablets, and those unable take the tablets can use pitavastatin OD tablets. This reduces the likelihood of confusion in clinical practice. However, the applicant must be prepared so that it can immediately begin the development of pediatric formulations upon the request from healthcare professionals.

2.(iii).B.(5).8) Post-marketing investigations

The applicant's initial plan for post-marketing investigations for pitavastatin was as follows: (a) A use-results survey with a 1-year observation period will be conducted to evaluate the safety and efficacy of pitavastatin in pediatric patients with FH treated in clinical settings. (b) No target sample size will be determined for the survey because pitavastatin is rarely used in pediatric patients with FH.

PMDA asked the applicant to reconsider the plan for the following reasons: (a) The use-results survey should be conducted in all patients receiving pitavastatin because of limited information available on the efficacy and safety of pitavastatin due to the small number of Japanese pediatric patients with FH enrolled in the clinical study. (b) The observation period should be as long as possible since the effects of pitavastatin on development should be evaluated in growing pediatric patients.

The applicant's response:

Pitavastatin is expected to be used for a long period in pediatric patients with FH, and the sample size of the clinical studies of pitavastatin was small. Therefore, the applicant plans to conduct a use-results survey to evaluate long-term safety and efficacy in clinical settings (observation period, from the first

day of treatment to the day of treatment discontinuation or 3 years after approval, whichever is shorter; target sample size, 120). The survey will register every pediatric patient with FH who started pitavastatin therapy within 2 years after approval, including the patients who started taking pitavastatin before the start of survey. Data will be collected from these patients, specifically data on adverse events (e.g., developmental abnormalities), effects on lipid parameters, test values related to rhabdomyolysis, hepatic and renal function tests, and growth and development.

The rationale for the proposed target sample size:

FH is a genetic disease with an incidence of 1/500 people (Austin MA et al. *Am J Epidemiol.* 2004;160:407-420), which, multiplied by 6,987,000 pediatric patients aged 10 to 15 years (Population Statistics in Statistical Data of Statistics Bureau, Ministry of Internal Affairs and Communications [as of October 1, 2013]), produces an estimate of 14,000 pediatric patients with FH aged ≥ 10 to 15 years. The findings of a nationwide survey in pediatric patients with FH in 2004, however, indicate that only approximately 1% of the affected population (i.e., approximately 140 patients) receives treatment for FH (Ota T. Partial Report on Establishment of Diagnostic Criteria for Familial Hypercholesterolemia in Children and Characteristics of Type IIb Hyperlipidemia in Children, 2004, Refractory Disease Research Project). If male and high-risk female pediatric patients with FH in this population were to be treated with pitavastatin, 120 patients can be registered in the survey. The Atherosclerotic Disease Guidelines state that pharmacotherapy for FH in pediatric patients should be administered under the guidance of a specialist. This means that the survey will cover all patients treated with pitavastatin if it is conducted at the institutions participating in the Japanese clinical study and other medical institutions with a physician of the Japanese Society for Lipid Research in Children and Adolescents, a specialist certified in atherosclerosis by the Japan Atherosclerosis Society, or a specialist certified in endocrine metabolism by the Japanese Society for Pediatric Endocrinology. If the applicant finds that a pediatric patient with FH has been prescribed pitavastatin at a medical institution other than listed above, the institution will be covered by early post-marketing phase vigilance and post-marketing surveillance, to collect safety data.

PMDA's view:

The clinical study enrolled the very limited number of patients. The post-marketing surveillance should therefore include all patients receiving pitavastatin to actively and expeditiously collect data on (a) the long-term safety and efficacy in clinical settings and (b) the safety in populations with limited data from the clinical studies (e.g., patients with homozygous FH, female pediatric patients, patients with hepatic impairment, patients with renal impairment). PMDA will make a final decision on the details of post-marketing surveillance, including the suitability of Safety Specification, risk categories, pharmacovigilance activities, and risk minimization activities according to the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1 by the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW; PFSB/ELD Notification No. 0411-2 by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 11, 2012) and based on comments from the Expert Discussion.

III. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

1. PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and data integrity assessment in accordance with the provisions of the Pharmaceutical Affairs Act. PMDA concluded that there should be no problem with conducting a regulatory review based on the application documents submitted.

2. PMDA's conclusion concerning the results of on-site GCP inspection

The new drug application data (CTD 5.3.5.2.1) were subjected to a GCP on-site inspection in accordance with the provisions of the Pharmaceutical Affairs Act. PMDA concluded that there should be no problem with conducting a regulatory review based on the application documents submitted.

IV. Overall Evaluation

Based on the submitted data, the efficacy of pitavastatin in pediatric patients with FH has been demonstrated and its safety profile is acceptable in view of its observed benefits. Pitavastatin is clinically meaningful because it offers a new pharmacotherapeutic option for pediatric patients with FH. Further discussion is required to review the intended population of the product, the wording of precautionary statements in the package insert, and post-marketing investigations.

PMDA considers that the present application may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 18, 2015

I. Product Submitted for Registration

[Brand name]	(a) Livalo Tablets 1 mg Livalo Tablets 2 mg (b) Livalo OD Tablets 1 mg Livalo OD Tablets 2 mg
[Non-proprietary name]	Pitavastatin Calcium Hydrate
[Applicant]	Kowa Company, Ltd.
[Date of application]	August 7, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the “Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Safety

PMDA’s conclusion:

The Japanese and foreign clinical studies of pitavastatin in pediatric patients with familial hypercholesterolemia (FH) do not suggest that pitavastatin may pose greater safety concerns in pediatric patients with FH than in adults with FH. In the post-marketing setting, however, adverse events (e.g., rhabdomyolysis and effects on growth) in patients receiving pitavastatin (Livalo Tablets and Livalo OD Tablets) should be carefully monitored, because only a limited number of Japanese pediatric patients with FH were evaluated in the Japanese clinical study. In addition, pediatric patients with FH are likely to use pitavastatin longer than adults, but long-term safety data are lacking. Pitavastatin for pediatric use should therefore be prescribed by a physician with sufficient knowledge and experience on the treatment of pediatric dyslipidemia who understands the characteristics of pitavastatin.

This conclusion was supported by the expert advisors

Based on the comments from the Expert Discussion, PMDA has concluded that the precautionary statements on prescribing pitavastatin to pediatric patients in the draft package insert submitted by the applicant are appropriate.

(2) Intended population and indication

1) Homozygous FH

PMDA' conclusion:

As with adults with homozygous FH, pediatric patients with homozygous FH should be included in the intended population for pitavastatin therapy, in light of the data available to date from the Japanese and foreign clinical studies. The first-line therapy for patients with homozygous FH is LDL apheresis, and pitavastatin has never been used in pediatric patients with homozygous FH. Physicians should therefore consider pitavastatin therapy only as an adjuvant to low-density lipoprotein (LDL) apheresis only in pediatric patients (as well as adults) who require the drug for therapeutic purposes. This should be indicated in the package insert in the same way as in the adult indication.

This conclusion was supported by the expert advisors.

2) Treatment in female pediatric patients

PMDA's conclusion:

Although pitavastatin has never been used in Japanese female pediatric patients with FH, the data from the Japanese and foreign clinical studies indicate that the efficacy and safety of pitavastatin do not differ substantially between sexes, and that Japanese female pediatric patients with FH may be included in the intended population of pitavastatin therapy. However, pitavastatin should be administered to female pediatric patients only when the benefit outweighs the risk (e.g., when the risk of coronary artery disease is very high).

The expert adviser discussed this conclusion at the Expert Discussion.

The expert advisors agreed that female pediatric patients with FH should not be excluded from the intended population of pitavastatin because some such patients need statin therapy such as pitavastatin. The expert advisors also expressed the following views: (a) Physicians should consider pitavastatin therapy in a female pediatric patient with FH only when she is at high risk of coronary artery disease; this therapeutic approach should be adopted for male pediatric patients as well. (b) Physicians should be advised to carefully consider whether pitavastatin is necessary to treat female pediatric patients, because pitavastatin has teratogenic potential, and because coronary artery disease occurs later in females than in males.

In light of this discussion and the discussion described in item (1) above, PMDA has concluded that the precautions for the indications should be worded as in (3) and (4) below:

[Precautions for indications]

(3) For pediatric use, pitavastatin should be used only in pediatric patients deemed eligible for pitavastatin therapy by a physician with sufficient knowledge and experience on the treatment of familial hypercholesterolemia in pediatric patients. (See "Pediatric use.")

(4) For use in female pediatric patients, the risks and benefits of pitavastatin should be carefully weighed to determine the necessity of pitavastatin therapy, because coronary artery disease has been reported to occur later in females than in males [see “Adverse reactions” and “Use in Pregnant, Parturient and Nursing Women”]. Pitavastatin was not administered to female pediatric patients in the Japanese clinical study.

(3) Measures for proper use

The expert advisors commented that the following information should be provided to healthcare professionals:

- (a) The pediatric dosage regimen of pitavastatin has been shown to be effective and safe only in pediatric patients with FH.
- (b) Pitavastatin should be used only in pediatric patients deemed eligible for pitavastatin therapy by a physician with sufficient knowledge and experience on the treatment of FH in pediatric patients.
- (c) Information on how to use pitavastatin and on the treatment of FH in pediatric patients (The expert advisors commented that this information should be provided to physicians prescribing pitavastatin without fail.)

In light of the views from the expert advisors, PMDA asked the applicant to formulate measures to provide appropriate information.

The applicant responded that it would take the following measures:

- (a) Prepare materials to inform healthcare professionals how to properly use pitavastatin.
- (b) Provide information on how to use pitavastatin for medical institutions and pharmacies that will use pitavastatin.
- (c) Publish clinical study data available at the time of approval application and disclose the progress and results of special drug use-results surveillance (in relevant medical conferences and journals).

PMDA has concluded that these information provision measures to promote proper use, are generally acceptable.

(4) Risk management plan (draft)

In view of the discussions in “II.2.(iii).B.(8) Post-marketing considerations” of Review Report (1) and the comments from the expert advisors, PMDA considers that the current risk management plan for pitavastatin should include the safety and efficacy specifications presented in Table 13, and that the applicant should conduct pharmacovigilance activities and risk minimization activities presented in Table 14. The applicant prepared a risk management plan (draft) and post-marketing surveillance plan (draft), based on Tables 13 and 14, and submitted the plans. (The outline is shown in Table 15).

Table 13. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
<ul style="list-style-type: none"> • Rhabdomyolysis • Liver disorders and jaundice • Platelets decreased • Interstitial pneumonia 	Not applicable.	<ul style="list-style-type: none"> • Long-term safety in pediatric patients with FH • Safety in female pediatric patients with FH • Safety in pediatric patients with homozygous FH
Efficacy specification		
<ul style="list-style-type: none"> • Long-term efficacy for pediatric FH in clinical settings 		

Table 14. Outline of additional pharmacovigilance activities and risk minimization activities included in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
<ul style="list-style-type: none"> • Early post-marketing phase vigilance (pediatric patients with FH) • Special drug use-results survey covering all pediatric patients with FH (all-case surveillance) 	<ul style="list-style-type: none"> • Provide information obtained in the early post-marketing phase vigilance (pediatric patients with FH) • Prepare and distribute materials for healthcare professionals (pediatric patients with FH)

Table 15. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate long-term safety and efficacy in clinical settings.
Method	All-case surveillance
Population	Pediatric patients with FH (aged ≥ 10 and < 15 years)
Observation period	From the first day of treatment to the day of treatment discontinuation or 3 years after approval, whichever is shorter, in each patient
Planned sample size	100 ^{a)}
Main survey items	Lipid parameters, test values related to rhabdomyolysis, hepatic and renal function tests, data on growth and development

a) The sample size was originally chosen based on the number of FH patients aged ≥ 10 and ≤ 15 years but was later selected based on the number of the intended population, i.e., patients aged ≥ 10 and < 15 years.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration statements as shown below, with the following conditions. Since this application is for the approval of a drug with new dosage, the re-examination period for the proposed dosage and administration should be 4 years.

[Indications] Hypercholesterolemia, familial hypercholesterolemia

(No change)

[Dosage and administration]

Hypercholesterolemia:

The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day.

Familial hypercholesterolemia:

Adults: The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day.

Pediatric patients: The usual dosage in pediatric patients aged >10 years is 1 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's condition. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 2 mg/day.

(Underline denotes additions.)

[Conditions for approval]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since the Japanese clinical study evaluated the product in an extremely limited number of patients, the applicant is required to conduct a use-results survey that should cover all Japanese patients treated with the product after market launch until data from a certain number of patients have been accumulated, to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.