Efficacy and Safety of Pitavastatin in Japanese Male Children with Familial Hypercholesterolemia

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Aim: The purpose of this study was to evaluate the efficacy and safety of LIVALO tablets (pitavastatin) in Japanese male children with heterozygous familial hypercholesterolemia (FH).

Methods: A multicenter, randomized, double-blind, parallel study was conducted in 14 male children 10-15 years of age with heterozygous FH. Pitavastatin (1 mg/day or 2 mg/day) was administered orally for 52 weeks. The primary endpoint was the percent change in the LDL-cholesterol (LDL-C) concentrations from baseline to endpoint (repeated measures ANCOVA at Weeks 8 and 12). Secondary endpoints included the percentage of patients who achieved the target LDL-C concentration and percent changes in the levels of lipoprotein and lipid parameters at the visit performed at 52 weeks.

Results: The percent change in LDL-C from baseline (mean 258 mg/dL for all patients) to the endpoint was -27.3% (95%CI; -34.0, -20.5) and -34.3% (95%CI; -41.0, -27.5) in the patients receiving 1 mg and 2 mg of pitavastatin, respectively. Stable reductions in the total cholesterol (TC), non-HDL cholesterol (non-HDL-C), apolipoprotein B (Apo-B) and LDL-C levels and non-HDL-C/HDL-C and Apo-B/Apo-A1 ratios were observed up to 52 weeks in both groups. One patient in each dose group (14%) reached the treatment target level of 130 mg/dL. Adverse events were observed in seven (100%) patients receiving 1 mg and five (71%) patients receiving 2 mg of pitavastatin, although none were considered related to the study treatment. One patient in the 1 mg group reported a musculoskeletal AE; however, it was attributed to recent excessive exercise.

Conclusions: Pitavastatin significantly reduced the LDL-C levels and was well tolerated when administered at usual adult doses in 14 male children 10-15 years of age with heterozygous FH. Pitavastatin is a promising therapeutic agent for pediatric dyslipidemia with few safety concerns.

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Key words: NK-104, Pitavastatin, Livalo®, Familial hypercholesterolemia, Child, Male, Efficacy, Safety

Introduction

Familial hypercholesterolemia (FH) is an inherited disease caused by genetic abnormalities in the genes encoding the hepatic LDL receptor and its associated molecules. The prevalence of heterozygous FH is commonly reported as 1 in approximately 500 people, with an estimated 250,000 patients in Japan⁷. Since patients with FH often develop coronary artery disease due to premature atherosclerosis and are more
likely to die earlier than unaffected patients, lipid modification is recommended from an early age\(^2\). Statin therapy has been used in pediatric patients with heterozygous FH who cannot achieve lipid control with diet therapy alone in the US and European countries and is recommended in Western guidelines\(^3\). However, in Japan, the use of lipid-lowering therapy in pediatric patients with heterozygous FH is regarded as off-label, to be applied only at the discretion of the physician. The development of therapeutic agents applicable for use in children in Japan is therefore awaited.

Pitavastatin (NK-104, Livalo\(^6\)) is a statin that competitively inhibits HMG-CoA reductase\(^4\), thus suppressing the biosynthesis of cholesterol in the liver\(^4, 5\). Furthermore, this drug enhances the uptake of LDL into the liver via stimulation of the expression of the LDL receptor\(^5, 6\), thereby reducing the LDL-C levels\(^7\). In 2003, pitavastatin was approved for indications of hypercholesterolemia and FH for the first time in Japan. It has also been approved in various Asian countries, the US, EU and several South American countries. In a long-term study\(^8\) conducted in Japan between 1996 and 1999, the efficacy and safety of pitavastatin (2 mg/day to 4 mg/day for 52 to 104 weeks) were assessed in 36 adult patients with heterozygous FH. In that study, pitavastatin produced stable reductions in the LDL-C levels over the long term in the adult patients and was well tolerated among the subjects. Pitavastatin is therefore expected to have therapeutic efficacy in pediatric patients with heterozygous FH, similar to that seen in adult patients.

In the current study, the efficacy and safety of pitavastatin were evaluated in Japanese male children 10 to 15 years of age with heterozygous FH. The primary endpoint was the percent change in the LDL-C levels from baseline to endpoint based on a repeated measures ANCOVA performed at Weeks 8 and 12.

**Methods**

**Patients**

Male patients with heterozygous FH who met the inclusion criteria and did not meet the exclusion criteria were enrolled in the current study.

The inclusion criteria were: (1) patients with an LDL-C level of $\geq 190$ mg/dL or LDL-C level of $\geq 160$ mg/dL with one or more of the following risk factors, a family history of coronary artery disease (relatives in the second degree), obesity (obesity index $\geq 20\%$), type 2 diabetes, hypertension (systolic blood pressure $\geq 125$ mmHg or diastolic blood pressure $\geq 70$ mmHg) and a low HDL cholesterol level ($< 40$ mg/dL); (2) Japanese male children 10 to 15 years of age, inclusive, at the time of informed consent; (3) patients who had received diet therapy for at least three months before screening based on a physician’s instructions or those whose diet for at least three months before screening was judged by the investigator not to require more intensive dietary restrictions (in either case, the patients were required to have received a fixed regimen of diet or diet/exercise therapy for at least four weeks before screening); (4) outpatients; and (5) patients for whom written informed consent was obtained from the patients themselves and their parents or guardians.

The major exclusion criteria were: (1) patients with homozygous familial hypercholesterolemia; (2) patients with secondary hyperlipidemia; (3) patients on apheresis therapy; (4) patients who had recently experienced a cerebrovascular disorder, anginal attack or myocardial infarction; (5) patients with severe hepatic or renal disorders, poor glycemic control, severe hypertension, a history of allergies to drugs or serious adverse drug reactions (ADRs); (6) patients who had participated in other clinical trial(s) and received investigational drug(s) within 12 weeks before screening; and (7) patients judged inappropriate for the study by the investigator.

**Ethics**

This study was conducted based on the spirit of the Declaration of Helsinki, in compliance with GCP guidelines. Since this study was conducted in pediatric patients 10 to 15 years of age, and it was considered that some patients may have difficulty in understanding and consenting to the study protocol adequately and consent was thus obtained from their parents or guardians. An explanation of the study was given to the child based on their level of understanding, with due respect for their human rights, and written consent was obtained in accordance with the procedure for acquiring “informed consent” in the ICH-E11 guidelines. The study protocol was reviewed and approved by the Institutional Review Board prior to the start of the study.

**Study Method**

This multicenter, randomized, double-blind, parallel group study was conducted at 16 hospital sites...
between May 2012 and January 2014. The patients were randomly assigned to two groups (1 mg and 2 mg treatment groups) at a ratio of 1:1 according to the dynamic allocation method using the factor of the baseline LDL-C level. The double-blind protocol was maintained using the double-dummy technique, in which each patient took two tablets once daily before breakfast for 52 weeks. Patients assigned to the 1 mg treatment group received one 1 mg tablet and a matching placebo tablet, while the patients in the 2 mg treatment group received one 1 mg tablet and a matching placebo tablet for the first four weeks, followed by two 1 mg tablets for the subsequent 48 weeks. All patients visited the hospital before administration for informed consent and screening, at the start of treatment (Week 0) and at Weeks 4, 8, 12, 24, 38 and 52. A medical review, assessment of physical measurements, electrocardiogram and blood tests to measure the levels of lipoprotein, lipid and safety parameters were performed at the central lab, and the state of drug compliance was assessed. The patients were instructed not to change their diet or exercise regimen for at least four weeks before screening until at least Week 12. Although it was desirable for the regimen to continue unchanged after Week 12, the need for a change was judged by the investigators. The primary endpoint was the percent change in the LDL-C levels from baseline to Weeks 8 and 12. The secondary endpoints were the percentage of patients who achieved the target LDL-C concentration (≤130 mg/dL), percent change in the levels of lipoprotein and lipid parameters (LDL-C, TC, TG, HDL-C, Apo-A1, Apo-B and non-HDL-C) from baseline to each time point and the changes in the non-HDL-C/HDL-C and Apo-B/Apo-A1 ratios from baseline to each time point. The LDL-C levels were calculated using the Friedewald equation after confirming a TG level of <400 mg/dL. The baseline LDL-C level was defined as the value observed at Week 0.

The tolerance of pitavastatin was evaluated based on reports of adverse events (AEs), a physical examination (height, weight, systolic and diastolic blood pressure and heart rate), 12-lead electrocardiogram and changes in laboratory data (hematology, blood biochemistry, including creatinine and cystatin C, and a urinalysis). An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a medicinal product, which did not necessarily have to have a causal relationship with the treatment. An adverse event was therefore any unfavorable and unintended sign, symptom or disease temporally associated with the use of the medicinal product, whether or not it was related to the given medicinal product. An adverse drug reaction (ADR) was defined as an AE with a relationship to the administration of the study drug, as judged by the investigator. Laboratory safety analyses were performed by SRL Medisearch Inc. (Tokyo, Japan). In addition to routine hematology and biochemistry tests, the concentrations of hormones (cortisol, aldosterone, dehydroepiandrosterone sulfate [DHEA-S], testosterone, luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) were determined using methods validated by SRL Medisearch Inc. (Tokyo, Japan).

**Statistical Analysis**

For efficacy, descriptive statistics were calculated for the primary endpoint, the percent change in the LDL-C levels from baseline to Weeks 8 and 12, for each group. The primary analysis, an analysis of covariance with repeated measurements (repeated ANCOVA), was performed with the treatment as a factor and the baseline LDL-C level as a covariate, and two-sided 95% confidence intervals of the percent change from baseline for each treatment group were estimated. Multiplicity was adjusted using the closed testing procedure in which the 1 mg group was tested only when the difference was significant in the 2 mg group. Therefore, the significance level of each test was 0.05. For the secondary endpoints, discrete variables were summarized according to time point in each group, and descriptive statistics were calculated for each time point in each group for continuous variables.

For safety, the number of patients with AEs and ADRs and the number of AEs and ADRs were summarized for each group, in addition to calculating the incidence in each group. Since this study was a multicenter study, AEs were summarized using MedDRA ver.16.1 system organ classes and Preferred Terms.

**Results**

**Patients**

Fourteen patients (7 patients/group) at 12 of the 16 sites were enrolled in the study. All patients completed the study protocol and were included in the efficacy and safety analysis set. The patient characteristics are shown in Table 1. The mean age was 11.8 years, the mean height was 147.6 cm and the mean weight was 41.1 kg. The patient characteristics were generally similar between the 1 mg and 2 mg treatment groups, except for the obesity index, which is commonly used in Japan to evaluate the degree of obesity in children. Although the obesity index was higher in the 1 mg group (7.3%) than in the 2 mg group...
The changes in the mean HDL-C and TG concentrations were more variable between visits and based on the doses of pitavastatin. The non-HDL-C levels were reduced between −22.8% to −25.6% and −26.3% to −34.6% in the 1 mg and 2 mg groups, respectively, and the non-HDL-C/HDL-C ratios were reduced in both groups by −1.1 to −1.3 and −1.4 to −1.7 in the 1 mg and 2 mg groups, respectively. Although the Apo-A1 levels appeared to be unaffected by pitavastatin, the Apo-B levels were decreased at Weeks 12 and 52 by more than 20% and 30% in the 1 mg and 2 mg groups, respectively, and the Apo-B/Apo-A1 ratios were decreased at Weeks 12 and 52 by −0.3 and −0.4 to −0.5 in the 1 mg and 2 mg groups, respectively.

Safety
There were 45 AEs reported in 12 of the 14 patients (85.7%) over the 52 weeks of the trial. All seven patients in the 1 mg group reported an event (a total of 23 events), and five patients reported a total of 22 events in the 2 mg group. AEs observed in two or more patients included seasonal allergies, gastroenteritis, nasopharyngitis, pharyngitis, ligament sprains, epistaxis, allergic rhinitis, upper respiratory tract inflammation and rashes. These AEs were all mild and

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<td>Item</td>
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<td>Age (years)</td>
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<td>Height (cm)</td>
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<td>Weight (kg)</td>
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<td>BMI (kg/m²)</td>
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<td>Obesity index (%)</td>
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<td>LDL-C (mg/dL, at baseline)</td>
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<td>Exercise therapy</td>
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| Abbreviations: BMI, body mass index; LDL-C, LDL-cholesterol |

<table>
<thead>
<tr>
<th>Table 2. Results of repeated ANCOVA with baseline values as covariates (percent change in the LDL-C levels at Weeks 8 and 12)</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>1 mg</td>
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<tr>
<td>2 mg</td>
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Test: Repeated ANCOVA, unit: %

(−0.6%), the difference was small compared to the standard deviation of the obesity index, and the mean values were both within the normal range (±20%).

Efficacy
For the primary endpoint, the results of the repeated measures ANCOVA of the change in the LDL-C levels from baseline to Weeks 8 and 12, with the baseline LDL-C concentrations as the covariate, are shown in Table 2. The percent change in the LDL-C levels from baseline (mean 258 mg/dL for all patients) to the endpoint was −27.3% and −34.3% in the patients receiving 1 mg and 2 mg of pitavastatin, respectively, and the differences from baseline were statistically significant (both p<0.001).

The time course of the changes in the lipoprotein and lipid profiles and ratios from baseline to each time point is shown in Table 3. The mean LDL-C reduction appeared to reach a plateau by Week 4 in the 1 mg group and Week 8 in the 2 mg group; however, the reductions were stable thereafter to Week 52 (Table 3). The differences between the groups were not statistically significant (p=0.1378).

One patient (14.3%) in each treatment group achieved the LDL-C target (<130 mg/dL) during the study period. The same pattern was seen for the mean total cholesterol reductions, which ranged between −17.6% to −20.8% and −22.0% to −29.1% in the 1 mg and 2 mg groups, respectively. The changes in the mean HDL-C and TG concentrations were more variable between visits and based on the doses of pitavastatin. The non-HDL-C levels were reduced between −22.8% to −25.6% and −26.3% to −34.6% in the 1 mg and 2 mg groups, respectively, and the non-HDL-C/HDL-C ratios were reduced in both groups by −1.1 to −1.3 and −1.4 to −1.7 in the 1 mg and 2 mg groups, respectively. Although the Apo-A1 levels appeared to be unaffected by pitavastatin, the Apo-B levels were decreased at Weeks 12 and 52 by more than 20% and 30% in the 1 mg and 2 mg groups, respectively, and the Apo-B/Apo-A1 ratios were decreased at Weeks 12 and 52 by −0.3 and −0.4 to −0.5 in the 1 mg and 2 mg groups, respectively.
resolved during the administration period, and none were considered by the investigators to be related to treatment with pitavastatin.

There were no deaths, and only one serious adverse event was reported in a patient in the 1 mg group. This patient underwent routine admission to the hospital for an operation to revise a scar from a previous operation. This event was not considered to be related to the pitavastatin therapy. There were no AEs leading to discontinuation of the study regimen. Furthermore, there were no AEs judged to be severe, and only two AEs were considered to be moderate in intensity, including sialadenitis and a forearm fracture, reported in two patients in the 1 mg group. All other events were mild.

One patient reported a musculoskeletal event. This patient in the 1 mg group experienced pain in an extremity associated with increased CK (1,919 U/L), AST (83 U/L), ALT (38 U/L) and LDH (328 U/L) levels. These findings were attributed to recent excessive exercise rather than to pitavastatin treatment, and all resolved under continued therapy.

There were no relevant abnormal findings in the assessment of the hematology and biochemistry tests, including the creatinine and cystatin C levels. Particular attention was paid to muscle and liver enzymes; however, there were no marked findings in the mean or individual changes apart from the case described above. The mean values of CK at baseline and Week 52 were 136.6 ± 76.6 and 108.0 ± 39.8 U/L in the 1 mg group and 129.4 ± 42.1 and 151.9 ± 34.4 U/L in the 2 mg group, respectively. The results were similar for AST and ALT.

The effect of pitavastatin on the endocrine func-

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**Table 3.** LDL-C, TC, HDL-C, TG and non-HDL-C levels and rates of change

<table>
<thead>
<tr>
<th>Item</th>
<th>Group</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 38</th>
<th>Week 52</th>
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</thead>
<tbody>
<tr>
<td><strong>LDL-C</strong></td>
<td>1 mg</td>
<td>245.4 ± 68.1</td>
<td>178.4 ± 45.6</td>
<td>181.6 ± 43.1</td>
<td>174.0 ± 39.5</td>
<td>177.7 ± 49.2</td>
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<td>(-26.5 ± 6.5)</td>
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<td>(-27.8 ± 10.3)</td>
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<td>(-24.3 ± 10.3)</td>
<td>(-24.3 ± 5.9)</td>
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<td></td>
<td>2 mg</td>
<td>269.6 ± 51.2</td>
<td>191.0 ± 36.4</td>
<td>175.7 ± 26.9</td>
<td>169.0 ± 34.9</td>
<td>175.4 ± 31.9</td>
<td>181.3 ± 30.2</td>
<td>181.7 ± 32.6</td>
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<td>(-28.9 ± 5.3)</td>
<td>(-33.6 ± 11.9)</td>
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<td>(-33.9 ± 11.3)</td>
<td>(-31.6 ± 11.2)</td>
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<tr>
<td><strong>TC</strong></td>
<td>1 mg</td>
<td>317.9 ± 67.8</td>
<td>253.1 ± 45.4</td>
<td>257.0 ± 49.0</td>
<td>250.3 ± 35.9</td>
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<td></td>
<td>2 mg</td>
<td>344.4 ± 50.5</td>
<td>268.0 ± 41.5</td>
<td>247.7 ± 29.6</td>
<td>242.9 ± 37.3</td>
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<td><strong>HDL-C</strong></td>
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<td>58.6 ± 7.9</td>
<td>61.7 ± 12.6</td>
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<td>(5.8 ± 20.6)</td>
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<td>2 mg</td>
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<td>2 mg</td>
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<td>196.0 ± 48.5</td>
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<td><strong>Non-HDL-C/ HDL-C ratio</strong></td>
<td>1 mg</td>
<td>4.5 ± 1.5</td>
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</table>

*Seven patients/group at all evaluation time points
Abbreviations: LDL-C, LDL-cholesterol; TC, total cholesterol; HDL-C, HDL-cholesterol; TG, triglyceride; non-HDL-C, non-HDL cholesterol
tion was assessed based on measurements of the cortisol, aldosterone, DHEA-S, testosterone, LH and FSH concentrations. The mean testosterone concentration was higher at Week 52 than at baseline. The concentrations of this hormone at baseline and Week 52 were 2.5 ± 2.8 and 3.2 ± 2.5 ng/mL in the 1 mg group and 2.4 ± 2.9 and 2.8 ± 2.1 ng/mL in the 2 mg group, respectively. There were no marked changes in the LH, FSH, cortisol, aldosterone or DHEA-S levels.

Since the patients in this study were growing children, their height and weight were measured to investigate the effects of pitavastatin on growth. During the administration period, the increases in both height and weight were within the range of average increases for healthy male children in the same age group.

There were no clinically significant changes in the other laboratory values or vital signs.

**Discussion**

In this study, pitavastatin at doses of 1 and 2 mg once daily significantly reduced the LDL-C levels at the endpoint (repeated measures ANCOVA at Weeks 8 and 12) by 27.3% and 34.3%, respectively. This reduction was achieved within four weeks of the initiation or uptitration of therapy and was maintained throughout the study period of one year. The differences between the groups were not statistically significant \( p=0.1378 \), possibly due to the small number of patients. However, the LDL-C-lowering effect in the pitavastatin 2 mg group \((-34.3\% \text{ as percent change in LDL-C})\) tended to be stronger than that observed in the 1 mg group \((-27.3\%)\). The magnitude of the difference between the groups \(7\) percentage points) is typical of that seen with a doubling of the statin dose\(^{10}\).

When administered to adult patients with heterozygous FH for 52 to 104 weeks\(^3\), pitavastatin at a dose of 2 mg/day to 4 mg/day showed stable, long-term reductions in the LDL-C levels. We also confirmed that this treatment reduced the LDL-C levels in pediatric patients with heterozygous FH.

Furthermore, stable reductions were observed in the TC, non-HDL-C, Apo-B, non-HDL-C/HDL-C and Apo-B/Apo-A1 values at both doses. There were less consistent changes in the TG and HDL-C values, although these parameters are not usually affected in cases of FH, and the baseline values of TG were low, while those of HDL-C were high. These results suggest that pitavastatin reduces general lipid parameters in pediatric FH patients in the same way as in adult patients and has the potential to help these patients achieve the treatment target.

Adverse events were reported in 12 of the 14 patients \(85.7\%\) over the course of the year, although the vast majority were mild and self-limiting, the rate of events did not increase with the dose and none of the events were considered to have a causal relationship with pitavastatin. Events observed in two or more patients included typical intercurrent conditions in this age-group: seasonal allergy, gastroenteritis, pharyngitis, pharyngitis, ligament sprains, epistaxis, upper respiratory tract inflammation and rashes. There was only one hospital admission in the current study, and this was a routine admission unrelated to pitavastatin therapy. There were no deaths or AEs leading to the discontinuation of treatment.

There were no reports of hepatic dysfunction or renal impairment in the present study and only one case of musculoskeletal symptoms, which was attributed to excessive sporting activities and resolved after continuing the therapy. The investigator judged that there were no causal relationships between this event and pitavastatin.

This study involved male children \(10-15\text{ years old}\), among whom the frequency of premature coronary artery disease is higher than that noted in girls. Since the male children in the study were peripuberal, the levels of cortisol, aldosterone, DHEA-S and testosterone, which are derived from cholesterol, and two peptide hormones, LH and FSH, were measured. Although a transient decrease in the testosterone and aldosterone levels was observed at Week 4, when all of the patients were taking 1 mg of pitavastatin, the levels obtained at Week 52 were higher than the baseline levels. It is possible that the timing of the samples might have affected the testosterone and aldosterone concentrations, since these hormones are subject to diurnal variation\(^{11,12}\).

The effect of the blood sampling time on endocrine hormone measurements was analyzed using a mixed effect model ANOVA with the blood sampling time and dose of pitavastatin as fixed effects and the patient as a random effect. In the analysis, the blood sampling time did affect the measurements of the testosterone, aldosterone, LH or FSH levels; however, there was no evidence of an effect of pitavastatin on the hormone concentrations.

The mean height of the patients increased by 7.1 and 5.3 cm and the mean weight increased by 5.5 and 6.0 kg in the two dose groups over the course of the year. In the comparison of the individual height and weight data with the data for age-stratified standard height and weight of Japanese children, the SD changes

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\(53\)

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from before to after treatment were $-0.2\text{SD}$ to $+0.7\text{SD}$ (in height) and $-0.3\text{SD}$ to $+0.4\text{SD}$ (in weight) in the patients receiving pitavastatin at 1 mg ($n=7$) and $-0.3\text{SD}$ to $+0.1\text{SD}$ (in height) and $-0.2\text{SD}$ to $+0.5\text{SD}$ (in weight) in the patients taking pitavastatin at 2 mg ($n=7$), respectively. No significant impact was observed on the height or weight pre- and post-treatment in either group. Additionally, there were no apparent differences between the changes in the height and weight (mean ± SD) in the two dose groups. These results suggest that the administration of pitavastatin at 1 and 2 mg did not have a deleterious effect on the growth or maturation of the pediatric patients in this trial. Although pitavastatin was administered for 52 weeks in this study, other 10-year follow-up studies of statins have also not reported any safety concerns or deleterious effects on the growth and development of children\(^{[3]}\).

According to the U.S. guidelines\(^{[3]}\) for the treatment of coronary artery disease in children, medical treatment is recommended in children with heterozygous FH and other risk factors for coronary artery disease exhibiting an LDL-C concentration of $\geq 190 \text{mg/dL}$ or $\geq 160 \text{mg/dL}$ after adequate diet therapy. The guidelines recommend medical therapy with statins in these cases due to the strong effectiveness of these drugs in reducing the LDL-C concentration and highlight the aggressive reduction of LDL-C in children with heterozygous FH. The results of clinical studies of other statins in pediatric patients with heterozygous FH in other countries were systematically evaluated in a Cochrane review. In this review, a pooled analysis of randomized, placebo-controlled studies using atorvastatin, simvastatin, pravastatin and lovastatin (5 studies, 566 patients) indicated a difference from placebo in the percent change in LDL-C of $-32.15\%$ with high efficacy. In addition, there were no significant safety concerns\(^{[4]}\). The efficacy and safety results for pitavastatin obtained in this study were generally similar to those of the Cochrane review and support the existing evidence for the use of pharmacotherapy in pediatric FH cases. Based on the above results, pitavastatin is considered to be a potentially useful therapeutic agent for pediatric patients with FH, similar to other statins that have already been used for pediatric FH in the US and European countries.

**Conclusion**

In male pediatric patients 10-15 years of age with heterozygous FH, pitavastatin at doses of 1 and 2 mg daily produced stable reductions in the LDL-C levels during a 1-year study period. Pitavastatin was well tolerated and did not have any deleterious effects on the endocrine function or growth. Since pitavastatin has already been established to have a role in the treatment of dyslipidemia, including heterozygous FH, in adults, it has the potential to be an effective treatment for heterozygous FH in pediatric patients as well.

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**Conflicts of Interest**

Dr. Mariko Harada-Shiba
Kowa Co. Ltd. – Medical Expert
Dr. Osamu Arisaka
Kowa Co. Ltd. – Advisory Board
Dr. Akira Ohtake
Kowa Co. Ltd. – Advisory Board
Dr. Tomoo Okada
Kowa Co. Ltd. – Advisory Board
Dr. Hideki Suganami
Kowa Co. Ltd. – Employment

**Appendix**

NK-104-PH 01 study registration group:
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Abbreviations

ADR, adverse drug reaction; AE, adverse event; ALT, alanine aminotransferase; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; AST, aspartate aminotransferase; CK, creatine kinase, DHEA-S, dehydroepiandrosterone sulfate; FH, familial hypercholesterolemia; FSH, follicle stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; ICH, International Conference on Harmonization; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; non-HDL-C, non-high-density lipoprotein cholesterol; SAE, serious adverse event; TC, total cholesterol; TG, triglycerides.

References

2) Japan Atherosclerosis Society eds., Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012; Japan Atherosclerosis Society; 2012