Efficacy and Safety of Pitavastatin in Children and Adolescents at High Future Cardiovascular Risk

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Objectives To assess the safety and efficacy of pitavastatin in children and adolescents with hyperlipidemia.
Study design A total of 106 children and adolescents with hyperlipidemia, ages 6 to 17 years, were enrolled in a 12-week randomized, double-blind, placebo-controlled study and randomly assigned to pitavastatin 1 mg, 2 mg, 4 mg, or placebo. During a 52-week extension period, subjects were up-titrated from 1 mg pitavastatin to a maximum dose of 4 mg in an effort to achieve an optimum low-density lipoprotein cholesterol (LDL-C) treatment target of <110 mg/dL (2.8 mmol/L). Adverse events rates, including abnormal clinical laboratory variables, vital signs, and physical examination were assessed.
Results Compared with placebo, pitavastatin 1, 2, and 4 mg significantly reduced LDL-C from baseline by 23.5%, 30.1%, and 39.3%, respectively, and in the open-label study 20.5% of the subjects reached the LDL-C goal <110 mg/dL (2.8 mmol/L). No safety issues were evident.
Conclusions Pitavastatin at doses up to 4 mg is well tolerated and efficacious in children and adolescents aged 6-17 years. *(J Pediatr 2015;167:338-43).*
Trial registration Registered with EudraCT 2011-004964-32 and EudraCT 2011-004983-32.

Elevated serum low-density lipoprotein cholesterol (LDL-C) and its associated apolipoprotein B (apoB) constitute a major risk factor for the development of coronary heart disease (CHD). Although CHD does not generally manifest until adulthood, the underlying atherosclerotic process begins early in life.[1-4] Therefore, lipid assessment in children with conditions that accelerate the rate of atherosclerosis, including hyperlipidemia, diabetes, and increased blood pressure, is recommended at an early age. If LDL-C levels are increased in these high cardiovascular risk subjects, current guidelines advocate statin treatment to be considered from the age of 8 years onwards.[5]

Pitavastatin calcium is a relatively new member of the statin class and approved for the treatment of primary hyperlipidemia and mixed dyslipidemia in adults. On a milligram basis, pitavastatin is the most potent in its class. Pitavastatin has a favorable pharmacologic profile following oral administration, including its long half-life (up to 12 hours), selective uptake into hepatocytes, and minimal metabolism by cytochrome P450 enzymes.[6] This latter property decreases the likelihood of drug-drug interactions with agents that are metabolized by, inhibit, or induce cytochrome P450 enzymes. In the maximum approved dose of 4 mg, pitavastatin improves lipid profiles with an LDL-C reduction of 44%.[7] Efficacy at pitavastatin 4 mg was noninferior to that of equipotent doses of atorvastatin (20 mg) and simvastatin (40 mg).[8-10] Pitavastatin has been shown to be safe and well tolerated in a number of special adult populations, in particular the elderly, those at high cardiovascular risk, and those with diabetes and might, therefore, be a promising treatment for children.[10-12] However, its use has not been studied in a pediatric population.

The aim of this study was to assess the safety, lipid lowering efficacy, and pharmacokinetic (PK) profile of pitavastatin 1 mg, 2 mg, or 4 mg in children and

AHA	American Heart Association	HDL-C	High-density lipoprotein cholesterol
ALT	Alanine aminotransferase		
apoA1	Apolipoprotein A-1	LDL-C	Low-density lipoprotein cholesterol
apoB	Apolipoprotein B	PDCO	Pediatric Committee
AST	Aspartate aminotransferase	PIP	Pediatric Investigation Plan
CHD	Coronary heart disease	PK	Pharmacokinetic
CK	Creatine kinase	QD	Once daily
DHEA-S	Dehydroepiandrosterone sulphate	SAE	Serious adverse event
EC	Ethics Committee	TEAE	Treatment-emergent adverse event
ECG	Electrocardiogram		
FH	Familial hypercholesterolemia	ULN	Upper limit of normal

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adolescents with hyperlipidemia aged 6-17 years in a 12-week randomized controlled trial, followed by an open-label study of 52 weeks.

Methods

The PASCAL study was a multicenter 2-stage trial; a 12-week randomized, double-blind, placebo controlled trial (2011-004964-32), followed by a 52-week open-label safety study (2011-004983-32). After a 5-week dietary run-in period, children were randomly assigned to pitavastatin 1, 2, 4 mg, or matching placebo once daily (QD), stratified based on age (≥6 years and <10 years, ≥10 years and <17 years) and baseline LDL-C (≥130 mg/dL [3.4 mmol/L] and <160 mg/dL [4.1 mmol/L], ≥160 mg/dL [4.1 mmol/L]) for each dose group. Enrollment in the study began in the pitavastatin 1 mg and pitavastatin 2 mg dose groups until sufficient data were collected to reassure the Data Monitoring Committee that the pitavastatin 4 mg dose group should be opened for enrollment. During the placebo-controlled study, lipid and safety assessments were performed every 4 weeks.

The subsequent 52-week open-label study included patients who completed the 12-week, double-blind study, but was also open for eligible children and adolescents who had not participated in the first study. At baseline, all patients in the open-label study were assigned to treatment with pitavastatin 1 mg QD, that could be been up-titrated to a maximum dose of 4 mg QD in an effort to achieve an optimum LDL-C treatment target of <110 mg/dL (2.8 mmol/L). During the treatment period, lipid and safety assessments were performed at week 4, week 8 (if applicable), week 12 (if applicable), week 16, week 28, week 40, and week 52 or early termination. The study was approved by the Independent Central/National Ethics Committee (EC) and Local EC, if applicable, and written informed consent was obtained from participants and/or their parents.

Patients were enrolled at 10 centers in 6 European countries (The Netherlands, Greece, Norway, Italy, Spain, and France). Children, age 6-17 years were eligible if they had diet-controlled fasting LDL-C ≥160 (4.1 mmol/L) mg/dL, or LDL-C ≥130 mg/dL (3.4 mmol/L) with one of the following risk factors: male; family history of premature cardiovascular disease; presence of low high-density lipoprotein cholesterol (HDL-C) <45 mg/dL or high triglycerides >150 mg/dL; increased lipoprotein(a) >75 nmol/L; type 2 diabetes mellitus diagnosed by treating physician according to current guidance; or systolic and diastolic blood pressures above the 95th percentile for age and height.

The study was conducted under a Pediatric Investigation Plan (PIP) approved by the Pediatric Committee (PDCO). The PDCO is the committee at the European Medicines Agency that is responsible for assessing the content of PIPs and adopting opinions on them. For the present study, the PDCO encouraged the recruitment of a range of patients at high risk (beyond familial hypercholesterolemia [FH]) as well as the inclusion of children as young as 6 years old. The current European Medicines Agency decision number for pitavastatin (Livazo and associated names) is P/0230/2012, dated October 5, 2012.

The agreed PIP was modified twice. The initial modification was done in 2011 prior to initial protocol finalization. The major modifications were dividing 2 studies instead of 1 study with an extension period, which allowed recruiting patients for the 52-week study who had not completed 12-week study. Second, patient enrollment originally was started for the 1 mg cohort only, and once sufficient data were available, the Data Monitoring Committee could decide to open the 2 mg cohort. Then, the same procedure was continued to open the 4 mg cohort. This was changed to starting enrollment for both the 1 and 2 mg cohorts, then, opening the 4 mg cohort after confirmation by the Data Monitoring Committee. Third, in an effort to enroll participants without FH in the studies, the LDL-C levels for inclusion were decreased. Originally, children with an LDL-C >190 mg/dL without a risk factor and >160 mg/dL with a risk factor could be enrolled. These levels were changed to >160 mg/dL without a risk factor and >130 mg/dL with a risk factor.

Further modification of the 52-week study protocol was done in 2012, prior to study enrollment. The initial protocol for the 52-week study had the following withdrawal criteria: patients whose LDL-C concentration cannot be reduced below 130 mg/dL will be withdrawn from the study. This was modified to patients whose LDL-C concentrations cannot be reduced below 130 mg/dL should be withdrawn from the study, at the discretion of the investigator, if they will receive better treatment outside of the trial.

The primary outcome measure of the double-blind study was the percentage change in LDL-C from baseline for each treatment group compared with placebo. Secondary outcome measures were changes in other lipoproteins and achieving American Heart Association (AHA) minimal (130 mg/dL [3.4 mmol/L]) and ideal (110 mg/dL [2.8 mmol/L]) LDL-C targets target in all active treatment groups.[5] The PK endpoints of this study included pitavastatin and pitavastatin lactone concentrations at trough and 1-hour postdose at each dose level.

Safety assessments included incidence and severity of adverse events, clinical laboratory measures (including assessment of renal function, and adrenal, gonadal, and pituitary hormones), vital signs, electrocardiogram (ECG) measures, and physical examinations (including Tanner staging). Compliance was assessed by pill count.

Based on data from previous clinical studies of pitavastatin in adults, the treatment difference between pitavastatin doses and placebo was expected to be at least 25% in the pediatric population, with common SD of 15%. With a 2-sided *t* test significance level of 0.05, 9 patients per treatment group should have provided 90% power. With the consideration of dropouts and safety follow-up for the pediatric population, a sample size of 24 patients per treatment group (96 patients in total) was planned for this study.