AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Rosuvastatin calcium
Study Code	D3561C00087 (4522IL/0087)
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A phase IIIb, efficacy, and safety study of rosuvastatin in children and adolescents 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH): a 12-week, double-blind, randomized, multi-center, placebo-controlled study with a 40-week, open-label, follow-up period

PLUTO: Pediatric Lipid-redUction Trial of rOsuvastatin

Study dates: First patient enrolled: 28 July 2006
Last patient completed: 04 June 2008

Phase of development: IIIb

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centers

This study was conducted in 20 sites in the following countries: The United States (3 sites), The Netherlands (7 sites), Norway (1 site), Spain (3 sites), and Canada (6 sites).

Publications

None at the time of the writing of this report.

Objectives

The primary objective of this study was to determine the efficacy of once-daily rosuvastatin in reducing low-density lipoprotein cholesterol (LDL-C) in children and adolescents aged 10 to 17 years with heterozygous familial hypercholesterolemia (HeFH) from baseline to the end of the 12-week, double-blind treatment period.

The secondary objectives of this study further characterized the lipid-lowering effects and the safety of rosuvastatin in the same population by determining:

1. The percent change in LDL-C from baseline to Week 6

2. The percent change in high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), non–HDL-C (defined as TC – HDL-C), LDL-C/HDL-C ratio, TC/HDL-C ratio, non–HDL-C/HDL-C ratio, apolipoprotein (Apo) B, ApoA-1, and ApoB/ApoA-1 ratio for each assigned dose level from baseline to Week 6, and to the end of the double-blind treatment period (Week 12) as compared to placebo

3. The efficacy of rosuvastatin in achieving the LDL-C goal of <110 mg/dL (2.8 mmol/L) (percent response rate) after 12 weeks of double-blind treatment and after an additional 40 weeks of titration-to-goal dosing up to a maximum dose of 20 mg once daily

4. The safety of each dose level of once-daily rosuvastatin by assessing the incidence and severity of adverse events (AEs), abnormal serum laboratory values, and rate of discontinuations due to AEs (DAEs) at Week 12 (vs placebo) and during the 40-week, open-label treatment

5. The effects on urinary protein excretion and estimated glomerular filtration rate (GFR)

6. The effect on growth by assessment of height (including linear growth [cm and Standard Deviation Score]) and secondary characteristics of sexual maturation by Tanner staging at baseline and 52 weeks.

This study also measured the change in the level of high-sensitivity C-reactive protein (hsCRP) from baseline to Week 6, and to the end of the double-blind treatment period (Week 12) so that the effects of rosuvastatin on this inflammatory marker could be explored.

Study design

This was a 12-week, double-blind, randomized, multicenter, placebo-controlled, Phase IIIb, efficacy, and safety study of rosuvastatin in pediatric patients (aged 10 to 17 years) with HeFH, which also included a 40-week, open-label, titration-to-goal treatment period. Following a 6-week dietary lead-in/drug washout period, patients were randomly assigned to 12 weeks of double-blind treatment with rosuvastatin 5 mg, 10 mg, or 20 mg, or to matching placebo. At Week 12, all eligible patients entered a 40-week, open-label, titration-to-goal period during which the dose of rosuvastatin could be up-titrated (to the maximum daily dose of 20 mg) to achieve the LDL-C target goal of <110 mg/dL (2.8 mmol/L). Safety assessments were conducted throughout all treatment periods. In addition, the effects on growth and secondary characteristics of sexual maturation were assessed at the end of the study (ie, changes from study entry to Week 52 in height and Tanner staging).

Target patient population and sample size

The patient population included male or female children and adolescents (Tanner stages II to V, at least 1 year post-menarche) aged 10 to 17 years with HeFH and at least 1 of the following criteria:

- Fasting LDL-C ≥190 mg/dL (4.9 mmol/L) at Visit 2 (prior to the randomization visit)

  or

- Fasting LDL-C >160 mg/dL (4.1 mmol/L) at Visit 2 and either of the following:
  - Family history of premature cardiovascular disease (CVD) defined as onset of clinical atherosclerotic disease before age 55 in males or age 65 in females

    or

  - 2 or more other CVD risk factors (HDL-C <35 mg/dL [0.91 mmol/L], hypertension, cigarette smoking, severe obesity, diabetes mellitus, physical inactivity) present after vigorous attempts were made to control these risk factors during 6 weeks of dietary lead-in

HeFH was defined as a documented genetic defect in LDL receptor or ApoB by DNA analysis, or documented evidence of FH in a first-degree relative (LDL-C >190 mg/dL [4.9 mmol/L] in an adult not receiving a statin, or LDL-C >95 mg/dL [2.5 mmol/L] in an adult receiving statin treatment; LDL-C >160 mg/dL [4.1 mmol/L] in a child <18 years of age not receiving a statin, or LDL-C >80 mg/dL [2.1 mmol/L] in a child <18 years of age receiving statin treatment).

Enrollment in the study was actively managed to achieve a reasonable demographic distribution of patients by age, sex, and Tanner stage. This distribution included a minimum of approximately 10% for each Tanner stage II through V (at least 1 year post-menarche) and a minimum of approximately 30% of patients younger than 14 years of age. Essentially, this involved allowing sites to recruit 10- to 13–year-olds for an additional 2 to 3 weeks once enrollment of 14- to 17-year–olds was completed. Once the target number of patients meeting the age, sex, and Tanner stage criteria were randomized, further enrollment based on these criteria was discontinued.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The study medication was administered orally and consisted of encapsulated tablets of rosuvastatin 5 mg (batch ST76064-001-FA02), 10 mg (batch ST75033-001-FA07), and 20 mg (2 × 10 mg; batch ST75036-001-FA03), and matching placebo (batch ST73074-001-FB02) for the double-blind period and tablets of rosuvastatin 5 mg (batches TS25025, and TX25038) and 10 mg (batches TX15034, TX14049, TX15027, TX16026, and TX26134) for the open-label period. For the 20-mg dose during the double-blind phase, two 10-mg tablets were encapsulated in a single gel capsule. Patients received 2 × 10-mg tablets for the 20-mg dose in the open-label period.

Duration of treatment

Following a 6-week dietary lead-in/drug washout period, patients were randomly assigned to 12 weeks of double-blind treatment with rosuvastatin 5 mg, 10 mg, or 20 mg, or to matching placebo. At Week 12, all eligible patients entered a 40-week, open-label, titration-to-goal period during which the dose of rosuvastatin could be up-titrated (to the maximum daily dose of 20 mg) to achieve the LDL-C target goal of <110 mg/dL (2.8 mmol/L).

Criteria for evaluation - efficacy (main variables)

The primary variable of the study was the percent change in LDL-C from baseline (Week 0) to Week 12 (end of the 12-week, double-blind treatment period). The concentration of fasting LDL-C was determined for all relevant visits by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL (4.52 mmol/L), in which case a β-quantification measurement of LDL-C was used.

The secondary efficacy variables were:

- Percent change in LDL-C from baseline to Week 6
- Percent change in HDL-C, TC, TG, non–HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, non–HDL-C/HDL-C ratio, ApoB, ApoA-1, and ApoB/ApoA-1 ratio from baseline to Week 6, and to Week 12
- Percentage of patients who achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L) (percent response rate) after 12 weeks of double-blind treatment and after an

additional 40 weeks of open-label titration-to-goal dosing up to a maximum rosuvastatin dose of 20 mg once daily.

An additional exploratory efficacy variable was the change in hsCRP from baseline to Week 6, and to Week 12.

Criteria for evaluation - safety (main variables)

The secondary variables that addressed the safety objective of the study were:

- The incidence and severity of AEs, rate of discontinuation of study treatment due to AEs, and abnormal laboratory values at Week 12 (compared with placebo) and during the 40-week, open-label treatment period
- The effects on urinary protein excretion and estimated GFR at Week 12 and Week 52 (percent change from Week 0)
- The effect on growth by assessment of height (including linear growth) and secondary characteristics of sexual maturation by Tanner staging at 52 weeks (change from Week -6).

Safety assessment included an evaluation of selected AEs of the hepatic, skeletal muscle, and renal systems, based on a list of preferred terms, which were designated as other significant AEs (OAEs).

Statistical methods

The primary efficacy analysis was based on the intention-to-treat (ITT) analysis set (defined as patients who had taken at least 1 dose of study medication and who had both a baseline reading and at least 1 post-baseline reading for LDL-C). The primary analysis of the change in LDL-C from randomization to Week 12 (using the last [valid] observation carried forward [LOCF] principle for missing data) tested the superiority of each rosuvastatin dose group using an analysis of covariance (ANCOVA) model with the baseline LDL-C as the covariate and including treatment as a fixed effect. The contrasts of interest were the treatment differences between each rosuvastatin dose and placebo. The primary analysis of change in LDL-C from randomization to Week 12 was repeated using the per-protocol (PP) analysis set to assess whether the conclusions from the primary analysis were robust. Each of the secondary efficacy lipid and lipoprotein variables was analyzed and summarized for the ITT analysis set in the same manner as the primary LDL-C efficacy variable. For the exploratory variable, hsCRP, the log-transformed change from baseline was analyzed using an ANCOVA model with the baseline LDL-C as the covariate and including treatment as a fixed effect to compare each rosuvastatin dose group to the placebo group.

Descriptive statistics were used to summarize the percentage of patients that achieved the LDL-C target goal at the end of the open-label treatment period (LOCF and observed cases [OC]) as well as at each interim study visit during the open-label period (OC only).

Data from all patients who received at least 1 dose of study drug in the randomized double-blind and/or open-label treatment periods of the study were included in the summaries of safety data.

Patient population

A total of 222 patients entered the dietary lead-in period. Of these, 177 were assigned to randomized treatment (42 patients were randomized to rosuvastatin 5 mg, 44 to rosuvastatin 10 mg, 45 to rosuvastatin 20 mg, and 46 to placebo). One of these 177 patients was randomized in error and did not receive study drug. Of those initiating study medication, 2 patients discontinued from the double-blind period due to AE, 1 with blurred vision (placebo group) and 1 with menorrhagia (rosuvastatin 5-mg group). Of the 176 patients who received at least 1 dose of study medication, 174 (98.9%) completed the 12-week, double-blind treatment period. One of the 174 patients who completed the double-blind period (rosuvastatin 10 mg) chose not to continue study participation thereafter. Therefore, a total of 173 patients entered the 40-week, open-label, titration-to-goal period. Of these, 9 (5.2%) were withdrawn and 164 (94.8%) completed the open-label period. The most common reason for withdrawal during this period was AE (4 of 173, 2.3%).

All 176 treated patients were included in the safety analysis set and in the ITT analysis set. A total of 149 (67.1%) patients were included in the PP population for analysis of efficacy. The frequency of protocol violations and deviations considered serious enough to warrant exclusion of the data ranged from 11% to 14% in the rosuvastatin groups and was 22% for the placebo group.

The majority of patients were Caucasian and male. The proportions of males to females, however, were similar between the treatment groups. The mean ages of randomized males and females were 13.9 and 14.8 years, respectively, and were similar across the treatment groups. Mean height, weight, and body mass index (BMI) were similar across the treatment groups and were within normal ranges based on age and sex, as evidenced by mean z-scores of 0.3, 0.4, and 0.3, respectively. The treatment groups were well balanced with regard to the percentages of patients meeting the alternative LDL-C and HeFH entry criteria. The treatment groups were reasonably balanced with regard to other demographic and baseline characteristics.

Summary of efficacy results

Table S1 summarizes the results of the analysis of the percent change from baseline to Week 12 for LDL-C for all 4 treatment groups during the randomized, double-blind treatment period.

Table S1 Analysis of percent change in LDL-C from baseline to Week 12 during the double-blind period (LOCF, ITT analysis set)

Lipid parameter	Rosuvastatin 5 mg (N=42)	Rosuvastatin 10 mg (N=44)	Rosuvastatin 20 mg (N=44)	Placebo (N=46)
LDL-C[a]				
n for % change	42	44	44	46
Baseline[b] Mean (SD) (mg/dL)	237.7 (55.06)	229.1 (44.70)	237.4 (47.84)	229.0 (43.13)
Baseline[b] Mean (SD) (mmol/L)	6.2 (1.42)	5.9 (1.16)	6.1 (1.24)	5.9 (1.12)
Week 12 % change[c] Mean (SD)	-38.5 (11.38)	-44.4 (12.15)	-50.2 (13.30)	-0.5 (13.18)
ANCOVA analysis				
LS mean % change from baseline	-38.3	-44.6	-50.0	-0.7
LS mean difference vs placebo in % change from baseline[d]	-37.5	-43.9	-49.2	NA
LCL to UCL[e]	-42.8 to -32.3	-49.1 to -38.8	-54.4 to -44.1	NA
p-value	<0.001	<0.001	<0.001	NA

[a] The concentration of fasting LDL-C was determined by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL (4.52 mmol/L), in which case a β-quantification measurement of LDL-C would be used. However, there was no case in which TG levels were >400 mg/dL (4.52 mmol/L) during the PLUTO study.
[b] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.
[c] Percent change was calculated as ([Visit value – Baseline value] / Baseline value) × 100.
[d] Analysis of covariance with the baseline LDL-C as the covariate and including treatment as a fixed effect.
[e] Upper and lower bounds of the 95% 2-sided confidence interval of the LS mean difference vs placebo.
ANCOVA Analysis of covariance; ITT Intention-to-treat; LCL Lower confidence interval limit; LDL-C Low-density lipoprotein cholesterol; LOCF Last observation carried forward; LS Least-squares; NA Not applicable; SD Standard deviation; UCL Upper confidence interval limit.

The percent change in LDL-C after 12 weeks of double-blind treatment was significantly greater in the rosuvastatin 5-mg, 10-mg, and 20-mg groups compared with placebo. The least-squares (LS) mean percent reduction in LDL-C at Week 12 was -38.3% in the rosuvastatin 5-mg group, -44.6% in the rosuvastatin 10-mg group, and -50.0% in the rosuvastatin 20-mg group, compared with -0.7% in the placebo group ($p<0.001$ for all 3 rosuvastatin doses compared with placebo, the primary analysis). Results of the primary analysis were confirmed by the results of the PP analysis.

The LS mean percent reductions in LDL-C values after 6 weeks of double-blind treatment were also significantly greater than that with placebo for rosuvastatin 5, 10, and 20 mg (-40.1%, -45.4%, and -49.8%, respectively, compared with -0.8% for placebo; $p<0.001$).

An ad hoc analysis of the percent change from baseline values in LDL-C at Week 12 was performed on a small subgroup of patients with TG levels that were above normal at baseline. This was done to investigate the effects of rosuvastatin treatment in patients with HeFH and elevated TG levels. The cut-off for normal TG levels was based on central laboratory age and sex-specific reference ranges. A significant treatment effect of rosuvastatin on LDL-C levels was observed in this small subgroup (N=27). LS mean percent changes from baseline values were -51.3%, -35.0%, and -52.0% for rosuvastatin 5, 10, and 20 mg, compared with -1.8% for placebo; $p<0.001$.

All rosuvastatin doses (5, 10, and 20 mg) achieved significantly greater mean changes from baseline values at Weeks 6 and 12 compared with placebo for the following secondary lipid and lipoprotein variables: non–HDL-C, TC, ApoB, ApoB/ApoA-1, LDL-C/HDL-C ratio, TC/HDL-C, non–HDL-C/HDL-C ($p<0.001$ for all rosuvastatin doses vs placebo for each of these variables). These changes were all in the direction of improved lipid and lipoprotein responses. No significant differences were observed at Weeks 6 or 12 between placebo and any dose of rosuvastatin for the following secondary lipid measurements: HDL-C and ApoA-1.

Treatment with rosuvastatin 10 mg achieved a significant mean change from baseline values in TG levels compared with placebo at Week 12 ($p=0.048$). No significant differences were observed at Week 12 between placebo and the 5- and 20-mg doses of rosuvastatin for TG.

Mean baseline values of the inflammatory marker, hsCRP, were low and similar across the 4 treatment groups. Changes from baseline values to Week 6 and to Week 12 in hsCRP levels were small and did not differ significantly between the rosuvastatin and placebo treatment groups.

At Week 12, 5 of 42 (11.9%), 18 of 44 (40.9%) and 18 of 44 (40.9%) patients treated with rosuvastatin 5, 10, and 20 mg, respectively, achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L), compared with none of the placebo patients. Patients who did not achieve the LDL-C target goal during the 40-week, open-label period were up-titrated with rosuvastatin to a maximum dose of 20 mg, according to the treatment plan. As of Week 52, the distribution of patients by rosuvastatin dose was 26 patients at 5 mg, 25 patients at 10 mg, and 122 patients at 20 mg. At Week 52, 70 of 173 patients (40.5%) had achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L).

An ad hoc analysis was conducted to evaluate the percentage of patients achieving the LDL-C goal of <130 mg/dL (3.4 mmol/L), since most historical data available for comparison used this less stringent target. At Week 12, 33.3%, 63.6%, and 68.2% of patients receiving rosuvastatin 5, 10, and 20 mg, respectively, achieved this goal, compared with 1 (2.2%)

patient treated with placebo). At Week 52, 68.2% of all rosuvastatin-treated patients were at a level of <130 mg/dL (3.4 mmol/L).

Summary of safety results

Based on an evaluation of AEs, clinical laboratory evaluations, and vital signs assessment (including growth), rosuvastatin treatment at 5, 10, and 20 mg was generally well tolerated during both the 12-week, double-blind treatment period and the 40-week, open-label treatment period in this pediatric population with HeFH. The overall frequencies of AEs during the double-blind period were 50.0%, 63.6%, 54.5%, and 54.3% in the rosuvastatin 5-mg, rosuvastatin 10-mg, rosuvastatin 20-mg, and placebo groups, respectively. The most common AEs in the rosuvastatin treatment groups were headache and nasopharyngitis; the most common AEs in the placebo group were headache, nasopharyngitis, and influenza. The majority of patients experienced AEs that were mild to moderate in severity. One patient (placebo) had a serious AE (SAE) during the double-blind period (blurred vision). Two patients had SAEs during the open-label period. These included appendicitis (counted at both 10 and 20 mg rosuvastatin because this patient was up-titrated from 10 to 20 mg while the SAE was ongoing) and vesicular rash (rosuvastatin 20 mg). Two patients had DAEs during the double-blind period (rosuvastatin 5 mg, menorrhagia and placebo, blurred vision [also reported as an SAE]). Four patients had DAEs during the open-label period (rosuvastatin 5 mg, nausea; rosuvastatin 5 mg, nausea; rosuvastatin 10 mg, fatigue; and rosuvastatin 20 mg, vesicular rash [also reported as an SAE]). One of these DAEs (fatigue) was not considered to be treatment-emergent, because the patient had experienced a previous AE of fatigue while receiving rosuvastatin. The frequency of SAEs and DAEs was low and there was no evidence of an increased frequency with rosuvastatin treatment compared with placebo.

Overall, there were a total of 3 rosuvastatin-treated patients with hepatic OAEs (1 during the double-blind period and 2 in the open-label period) and 2 rosuvastatin-treated patients with renal OAEs (both during the open-label period). The frequency of skeletal muscle-related OAEs was <3% for any given OAE, with the exception of myalgia, which occurred in 4 (3.1%) rosuvastatin-treated patients during the double-blind period and 5 (2.9%) rosuvastatin-treated patients during the open-label period. There was evidence for an influence of exercise on the occurrence of skeletal muscle OAEs in rosuvastatin-treated patients in each of the 5 patients for whom muscle narrative information was available. Each of these renal, hepatic, and skeletal muscle OAEs resolved on treatment or with treatment interruption and resumption of rosuvastatin. None of these hepatic, renal, or skeletal muscle OAEs led to permanent treatment discontinuation.

Mean changes in clinical laboratory results were generally small and showed no clinically important treatment-related trends. No individual patient in any treatment group experienced clinically important alanine aminotransferase (ALT) elevations (>3 × the upper limit of normal [ULN]) at any visit during the double-blind period. One patient receiving rosuvastatin 5 mg experienced a clinically important ALT elevation during the open-label period. Treatment was temporarily stopped, then resumed, and the ALT values were normal thereafter. No patients experienced clinically important ALT elevations on 2 consecutive

visits at any time during the study. A total of 3 rosuvastatin-treated patients (10 mg, 20 mg, and 20 mg) experienced clinically important aspartate aminotransferase (AST) elevations (>3 × the ULN) during the double-blind period, each of which was associated with marked concurrent creatine kinase (CK) elevations. None of these AST elevations led to treatment discontinuation. Overall, a total of 4 patients receiving rosuvastatin had clinically important CK elevations during the double-blind period (2 at 10 mg, 2 at 20 mg) and 4 patients had CK elevations during the open-label period. Details of these events suggest that they were influenced by exercise. In each instance of CK elevation, patients either had temporary treatment interruption and resumption of rosuvastatin treatment (N=4) or continued treatment (N=4), and levels returned to within normal limits. None of these events led to permanent treatment discontinuation. No patients in the study had a clinically important (>50%) increase in serum creatinine from baseline values during the double-blind period, and 1 rosuvastatin-treated patient (20 mg) had a clinically important increase during the open-label period. There were no individual clinically important abnormalities in estimated GFR during the randomized treatment period. During the open-label period, there were 2 patients with a ≥25% decrease from baseline in estimated GFR (both at 20 mg rosuvastatin). One of these was also a ≥50% decrease from baseline. In both cases, serum creatinine values remained within the normal range, and there were no abnormal changes in urinalysis findings. No patient had proteinuria during the double-blind period. Two patients (receiving rosuvastatin 10 mg and rosuvastatin 20 mg) had hematuria during the double-blind period, neither of whom had concurrent abnormal serum creatinine values. There was no apparent pattern of mean changes in urinary protein/creatinine ratio, a marker for proteinuria, in any treatment groups. A total of 4 patients (rosuvastatin 5 mg, 5 mg, 10 mg, and 20 mg) exhibited a shift in urinary protein/creatinine ratio from ≤0.2 mg/mg to >0.2 mg/mg during the study. In each of these patients, serum creatinine values remained within normal ranges, and there were no abnormal urinalysis findings.

There was no notable impact of treatment on changes from baseline to the end of the open-label period (Week 52) in height, weight, BMI, or systolic and diastolic blood pressure (BP) as assessed by mean values and by z-scores. Z-scores express these parameters as normalized data relative to the mean for children of the same age and sex according to the National Health and Nutrition Examination Survey (NHANES) growth data. A normal progression of sexual maturation, as assessed by Tanner stage, was noted. No clinically important patterns for physical findings were identified, and no new safety concerns were raised for physical evaluations.

Although the adult tablet formulation of rosuvastatin was used in this study, compliance was approximately 90% among rosuvastatin-treated patients, indicating that pediatric patients aged 10 to 17 years were consistently willing to take this medication daily, thereby demonstrating their tolerance for the formulation and dosing regimen.