Clinical Study Report Synopsis

Drug Substance	Rosuvastatin
Study Code	D3561C00002
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An Efficacy and 2-Year Safety Study of Open-label Rosuvastatin in Children and Adolescents (aged from 6 to less than 18 years) with Familial Hypercholesterolaemia

Study dates: First subject enrolled: 18 February 2010
Last subject last visit: 08 February 2013

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Centre(s)

This study was performed at 14 centres in 5 different countries: 6 in the Netherlands, 5 in Canada and 1 each in Belgium, Norway, and the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy of rosuvastatin in paediatric patients with FH.	*Primary*: Percent change from baseline in LDL-C following 3 months, 12 months and 24 months of treatment with rosuvastatin 5 mg, 10 mg or 20 mg. *Secondary*: Percent change from baseline in HDL-C, TC, TG, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-1, and ApoB/ApoA-1 at 3 months, 12 months and 24 months.
	Safety	To establish long-term safety, tolerability and efficacy of rosuvastatin in paediatric patients with FH.	*Primary*:Assessments of growth by assessment of height (including linear growth [cm and standard deviation score]) and secondary characteristics of sexual maturation by Tanner staging at baseline, 12 months and 24 months. *Secondary*: To assess adverse events (AEs), including: the incidence and severity of AEs, rate of discontinuations due to AEs and abnormal serum laboratory values.
	PK	To characterise the PK profile of rosuvastatin in paediatric patients, aged from 6 to less than Tanner Stage II, with FH.	*Primary*: Single-dose PK of rosuvastatin: C_{max}, t_{max}, and $AUC_{(0-24)}$. Population PK of rosuvastatin: CL/F and $AUC_{(0-24)}$ at steady state. *Secondary*: Single-dose PK of rosuvastatin metabolites: C_{max}, t_{max}, and $AUC_{(0-24)}$. Population PK of rosuvastatin: model dependent
Secondary	Efficacy	To assess cIMT by sonography at baseline and every year in patients and in healthy siblings (of study participants or of other paediatric patients with FH but not participating in the study).	Assessments of intima and media wall thickness of the carotid arteries by sonography at baseline, 12 and 24 months in all enrolled patients in comparison to at least 60 enrolled healthy siblings (of study participants or of other paediatric patients with FH but not participating in the study).
	Safety	To assess growth and maturation in children or adolescents with FH who are receiving long-term rosuvastatin treatment.	Mean change in height, weight and BMI from baseline to 12 months and 24 months.
	Adherence/ Compliance and acceptability	To assess adherence to rosuvastatin during a 2-year period of treatment.	Assessment of rosuvastatin treatment adherence during the 2-year study period, calculated as date of last dose of rosuvastatin – date of first dose of rosuvastatin +1 day.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		To assess the feasibility and acceptability of the current marketed tablet formulation of rosuvastatin for use in children.	As above.

Abbreviations: AE=adverse event, ApoA-1=Apolipoprotein A-1, ApoB=Apolipoprotein B, AUC=area under the curve, BMI=body mass index, cIMT=carotid intima and media wall thickness, CL=clearance, C_{max}=maximum concentration, F=fraction absorbed, FH=familial hypercholesterolaemia, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, PK=pharmacokinetics, TC=total cholesterol, TG=triglycerides, t_{max}=time to maximum concentration.

Study design

This was an open-label study assessing the pharmacokinetics (PK), efficacy and long-term safety of rosuvastatin in children and adolescents with familial hypercholesterolaemia (FH). At least 180 patients were planned to be enrolled in this study. The distribution goal was to enrol at least 60 patients aged 6 to <10 years, at least 60 patients aged 10 to <14 years and at least 60 patients aged 14 to <18 years, eligible for study treatment, at Baseline (Visit 3). Assessment of carotid intima and media wall thickness (cIMT) by sonography was to be assessed in all patients. In addition, assessment of cIMT was to be performed in at least 60 enrolled healthy siblings of study participants or of other paediatric patients, with heterozygous FH (HeFH) not participating in this study; at least 20 healthy siblings aged 6 to <10 years, at least 20 healthy siblings aged 10 to <14 years and at least 20 healthy siblings aged 14 to <18 years.

A total of 12 patients aged from 6 years to <Tanner Stage II, were enrolled in the single-dose PK portion of the study in conjunction with enrolment in the efficacy and 2-year safety phase. The patients were administered a single dose of 10 mg rosuvastatin at baseline (Visit 3) and assessed over a 24-hour period. After patients had received the single dose for PK sampling, they started the efficacy and 2-year safety phase, after the 24-hour PK assessment had been completed. They then followed the remainder of the efficacy and 2-year safety study visits.

All patients started the efficacy and 2-year safety phase of the study on 5 mg rosuvastatin once daily. The younger children in the efficacy and 2-year safety study (aged 6 to <10 years of age) were eligible to titrate to treatment goal (low-density lipoprotein cholesterol [LDL-C] target of <2.85 mmol/L [110 mg/dL]) up to a maximum rosuvastatin dose of 10 mg once daily. However, if the single-dose PK assessment results indicated that 5 mg rosuvastatin was the maximum tolerated dose, this lower dose was the maximum daily dose administered to patients within this age group. If a patient reached age 10 during the trial (ie, they were aged 9 when they were enrolled but then turned 10), a dose of up to a maximum of 20 mg rosuvastatin was allowed. Patients aged 10 to <18 years were eligible to titrate to treatment goal (LDL-C target of <2.85 mmol/L [110 mg/dL]) up to a maximum rosuvastatin dose of 20 mg daily. Up-titration, to achieve the LDL-C target was performed in 3-month intervals from baseline (ie, the first up-titration visit would be Visit 5). If higher doses were not well tolerated, the patients could be down-titrated at the investigator's discretion. Patients could be up-titrated, if the LDL-C target had not been met, at the investigator's discretion.

Target subject population and sample size

A total of 12 paediatric patients aged from 6 years to <Tanner Stage II with FH were included in the single-dose PK assessment. At least 180 enrolled paediatric patients aged from 6 to <18 years (at baseline) with FH were included in the efficacy and safety assessment. In addition, assessment of cIMT was performed in at least 60 enrolled healthy siblings of study participants or of other paediatric patients, with HeFH not participating in this study. No formal sample size calculation was performed for this study since it was an exploratory study.

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

Rosuvastatin 5 mg, 10 mg and 20 mg tablets were manufactured by AstraZeneca. A total of 7 batches of rosuvastatin 5 mg, 6 batches of rosuvastatin 10 mg and 6 batches of rosuvastatin 20 mg were used in this study. Individual batch numbers and further information are included in the clinical study report.

Doses and treatment

Rosuvastatin 5 mg, 10 mg and 20 mg tablets were to be taken orally, once daily, either in the morning or in the evening. Daily dosing had to be consistent throughout the study (ie, always in the morning or always in the evening).

Duration of treatment

This study consisted of an enrolment/run-in period (minimum 4 weeks for patients being withdrawn from previous lipid therapy), a 24-hour, single-dose open-label PK phase (at 3 centres) and an efficacy and 2-year safety, open-label, multiple dose phase.

Statistical methods

Descriptive statistics were used to characterise the PK, efficacy, and safety variables.

Descriptive statistics were used to summarise all efficacy variables by age group and overall. The percentage of patients achieving the LDL-C target of <2.85 mmol/L (110 mg/dL) during titration-to-goal (maximum rosuvastatin dose 10 mg daily for aged 6 to <10 years and 20 mg daily for 10 to <18 years) were also summarised. Percent change from baseline was analysed using t-tests to estimate rosuvastatin efficacy in reducing LDL-C at 3, 12 and 24 months. Similar analyses were performed for the secondary efficacy variables. An analysis of variance was also used to compare LDL-C reduction among age groups.

An analysis of between-group and within-group comparisons of the change in maximum cIMT from baseline to the end of the 12 month and 24 month open-label treatment phase in the far walls of the right and left common carotid artery was presented in a paired (age across families) and cohort fashion. Similar analyses were performed for the mean cIMT from baseline to the end of the 12 month and 24 month open-label treatment phase in both the right and left segments of the common carotid artery, carotid bulb and internal carotid artery.

All tests were 2-sided, and a p-value of ≤0.05 was considered statistically significant.

Incident rates of adverse events (AEs) were summarised by system organ class and preferred term for the following categories: all AEs, AEs by intensity, and AEs by causality. Treatment discontinuations due to any AE were summarised. Relative days from randomisation date to AE onset date were computed. Serious AEs or deaths were listed and summarised, when appropriate.

Descriptive statistics were used to summarise all reported laboratory values, vital signs, and electrocardiograms (ECG) for the changes from baseline to each subsequent visit. Additionally, individuals with abnormal serum laboratory values, vital signs, ECG and physical examinations were also summarised and listed.

Descriptive statistics were used for growth and sexual maturation (Tanner Staging) at baseline, 12 and 24 months. Growth assessments (height, weight, and body mass index) were summarised in the context of population means using z-scoring in addition to presenting means (standard deviation). The shift in the Tanner stage for individual patients from baseline to 12 and 24 months were summarised.

Maximum dose, mean dose, median dose and total duration of exposure to rosuvastatin and compliance rate during the 2-year period of treatment were summarised and listed for standard review.

Subject population

The age distribution goal was achieved. In total, 250 patients with FH were screened and 198 patients were enrolled into the study. Of these patients, 12 patients aged 6 years to <Tanner Stage II were included in the single-dose open-label PK phase of the study. All 198 patients enrolled were included in the efficacy and 2-year safety open-label, multiple dose phase of the study. Of these, 16 patients withdrew from the study and 182 patients completed the study.

A total of 65 healthy siblings were enrolled into the study and included in the assessment of cIMT (62 were healthy siblings of the study participants and 3 were healthy siblings of other paediatric patients with HeFH that were not participating in the study). Of these 65 healthy siblings, 6 healthy siblings withdrew from the study and 59 healthy siblings completed the study.

Summary of efficacy results

After 3 months of treatment with rosuvastatin, the mean percent reduction from the baseline value in LDL-C was -37.86% ($p<0.001$). After 12 months of treatment with rosuvastatin, the mean percent reduction from the baseline value in LDL-C was -43.67% ($p<0.001$). After 24 months of treatment with rosuvastatin, the mean percent reduction from the baseline value in LDL-C was -42.88% ($p<0.001$).

In the current study, the efficacy of rosuvastatin in reducing LDL-C in paediatric patients with FH was demonstrated by the significant reductions in LDL-C after 3 months, 12 months, and 24 months of treatment. All age groups showed statistically significant reductions in LDL-C from baseline values.

After 3 months of treatment with rosuvastatin, 34 of 196 (17.3%) patients achieved the LDL-C goal <2.85 mmol/L (<110 mg/dL). After 12 months, the number of patients achieving the LDL-C goal increased to 66 of 196 (33.7%). After 24 months, the number of patients achieving the LDL-C goal increased further to 74 of 197 (37.6%).

Rosuvastatin 5 mg, 10 mg, and 20 mg as titrated according to protocol achieved statistically significant mean changes from baseline values at 3 months, 12 months, and 24 months for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes from baseline were each in the direction of improved lipid responses and were sustained over 2 years. Statistically significant mean changes from baseline in TG levels were observed following treatment with rosuvastatin at 3 months and 12 months. Statistically significant mean changes from baseline in ApoA-1 levels were observed following treatment with rosuvastatin at 3 months and 24 months. No consistent changes were observed in hs CRP.

Although there were no statistically significant differences in maximum or mean cIMT between the treated patients and the siblings at the 12- and 24-month time points, graphic representation of the findings suggest a trend for slowing of intima media thickening in the treated patients compared with the siblings for each age group and for the age groups combined.

Summary of pharmacokinetic results

The PK of rosuvastatin in children and adolescents with FH are predictable with respect to both dose and time. In addition, the demographic variables, weight, age and gender do not appear to provide clinically meaningful changes in steady-state exposure. CL/F (and hence dose normalised steady-state exposure) in these children and adolescents appears to be visually similar to healthy adults.

The exposure to metabolites, N-desmethyl, and lactone, was lower than that to rosuvastatin, consistent with rosuvastatin being the main circulating moiety responsible for activity.

Summary of safety results

Of the 198 patients enrolled into the study, 197 (99.5%) received at least 1 dose of study medication and were included in the safety analysis set. The mean total duration of rosuvastatin treatment was 704 days. The mean duration of rosuvastatin treatment at 5, 10 and 20 mg treatment was 175, 268, and 439 days, respectively.

The incidence of treatment-emergent AEs during the treatment phase was 87.3% and was similar across each age group. There were no deaths during the study. Overall, 3 patients

discontinued study treatment due to a treatment-emergent AE: migraine in 1 patient aged 12 years, nausea in 1 patient aged 15 years, and paraesthesia in 1 patient aged 17 years. These treatment-emergent AEs were of mild intensity and were nonserious. The treatment-emergent AEs were considered by the investigator to be related to study treatment. Overall, 10 SAEs were reported in 9 patients (2 patients aged 6 to <10 years, 4 patients aged 10 to <14 years and 3 patients aged 14 to <18 years). All SAEs were considered by the investigator to be unrelated to study treatment and none resulted in discontinuation from the study. The most common treatment-emergent AEs by PT were nasopharyngitis (44.2%), headache (23.4%), and influenza (10.2%). The most common treatment-emergent AEs of specific interest (skeletal muscle events) by PT were arthralgia (6.1%) and myalgia (5.6%). The majority of treatment-emergent AEs were of mild intensity. The frequency of skeletal muscle OAEs was 3.6%, hepatic OAEs was 1.0%, and renal OAEs was 0.5%. All OAEs were of mild intensity, except for hepatic pain, which was of moderate intensity. None of the OAEs were serious nor did they result in the patient being discontinued from the study.

Evaluation of z-scores and Tanner staging indicated that growth and sexual maturation remained within normal ranges for age and sex during the 2-year study on rosuvastatin.