25 April 2014
EMA/301931/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 29 of Regulation (EC) No 1901/2006

Crestor and associated names

International non-proprietary name: rosuvastatin

Procedure no. EMEA/H/A-29-PAE/1378

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
AUC_{ss}	Area under the plasma concentration time curve at steady-state
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
cIMT	Carotid intima and media wall thickness
CK	Creatine kinase
CL	Clearance
CL/F	Apparent drug clearance
C_{max}	Maximum concentration
CV	Coefficient of variation
CVD	Cardiovascular disease
DAE	Discontinuation of investigational product due to an AE
DM	Diabetes mellitus
FH	Familial hypercholesterolemia (includes HeFH and HoFH)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbA1c	Glycosylated haemoglobin
HDL	High-density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	High sensitivity C-reactive protein
ITT	Intent-to-treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
MA	Market authorisation
OAE	Other significant adverse event (ie, significant AEs, other than SAEs and DAEs, which are of particular clinical importance in this development program)
PK	Pharmacokinetic
PP	Per-protocol
SAE	Serious adverse event
SOC	System organ class
TC	Total cholesterol
TG	Triglycerides
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder (MAH), AstraZeneca submitted to the European Medicines Agency an application for a new paediatric indication of Crestor and associated names, in accordance with Article 29 of Regulation (EC) No 1901/2006.

The MAH applied to extend the following therapeutic indication to include new age subsets in "*adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (mixed type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate'*

to include children aged between 6 - 10 years of age.

The eligibility to the procedure was agreed upon by the EMEA/CHMP in May 2013.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/229/2010 on the agreement of a paediatric investigation plan (PIP) for the following condition:

- Treatment of Primary hypercholesterolaemia (including heterozygous hypercholesterolaemia)

The PIP P/229/2010 is completed and the PDCO had issued an opinion on compliance.

Licensing status

Crestor and associated names have been given marketing authorisations in the following EU Member States: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom in addition to Iceland and Norway.

2. Scientific discussion

2.1. Introduction

Problem Statement

Some diseases of abnormal lipid metabolism that contribute to hyperlipidaemia and elevated serum cholesterol have a genetic basis, including familial hypercholesterolaemia (FH). FH is associated with serious health risks of developing cardiovascular disease (CVD), including premature coronary heart disease (CHD). CVD is the leading cause of mortality worldwide, accounting for more than 30% of all deaths. The prevalence of the homozygous familial hypercholesterolemia (HoFH) is approximately 1 in 1 million, and the prevalence of the heterozygous familial hypercholesterolemia (HeFH) is approximately 1 in 500 individuals (over 10 million cases worldwide).

HeFH is a frequent, inherited disorder of lipoprotein metabolism caused by mutations in the low-density lipoprotein (LDL) receptor or apolipoprotein B (ApoB) genes. Patients with HeFH show symptoms of CHD at a young age. In men with untreated HeFH, this risk of CHD is approximately 50% by the age of 50 years. In children with HeFH, the disease is mostly asymptomatic, however,

autopsy reports of healthy children in the general population have shown atherosclerotic lesions at a young age. The aggressive nature of vascular disease in young adult HeFH patients suggests that these atherosclerotic changes begin in early childhood. It has been observed that (vascular) endothelial dysfunction can occur in hypercholesterolaemic children as young as 8 years. Morphological and functional changes of the arteries can predict future CHD and are present in hypercholesterolaemic children, underscoring the importance of aggressive and early treatment of dyslipidaemia to prevent premature cardiovascular events in HeFH.

Currently, there is only one statin approved for use in children 8 to <10 years (pravastatin), and no statin is approved for use in children <8 years of age. Thus, there is an unmet medical need for an efficacious and safe statin for the youngest patients with HeFH.

About the product

Rosuvastatin is an inhibitor of synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, responsible for de novo synthesis of cholesterol in the body. It is a member of the statin class of lipid-lowering agents and produces its lipid-modifying effects in two ways: it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Crestor (rosuvastatin), 5 mg, 10 mg, 20 and 40 mg film-coated tablets and associated names, is approved in the European Union for the treatment of primary hypercholesterolaemia, mixed dyslipidaemia, and homozygous familial hypercholesterolaemia and for the prevention of cardiovascular events.

It was first authorised in the Netherlands on 6 November 2002 and was first launched on 19 February 2003, in Canada.

The recommended start dose in children and adolescents 10 to 17 years of age with heterozygous familial hypercholesterolaemia is usually 5 mg daily. The usual dose range is 5-20 mg orally once daily with titration to be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before and during rosuvastatin treatment.

The paediatric investigation plan

In October 2010, the PDCO adopted a positive opinion on the PIP for rosuvastatin followed by subsequent modifications.

The following studies were agreed in the PIP:

1. Non clinical study : Pre- and post-natal developmental toxicity in rats from day 7 of gestation to day 22 of lactation. The results of this study were included in the Crestor marketing authorisation application in 2008.

2. Clinical study: Double-blind, randomised, multi-centre, placebo-controlled trial to evaluate safety and efficacy of rosuvastatin calcium in children from 10 years to less than 18 years of age with heterozygous hypercholesterolemia [Paediatric Lipid-redUction Trial of rOsuvastatin (PLUTO)]. The PLUTO results were implemented in 2010 via either mutual recognition or national procedures and resulted in the approval of a paediatric indication and use of rosuvastatin in children and adolescents with HeFH from 10 years and above.

3. Clinical study: A pharmacokinetic, efficacy and 2-year safety study of open-label rosuvastatin in children from 6 to less than 18 years of age with familial hypercholesterolaemia.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

Environmental risk assessment (ERA)

The ERA submitted in this application is in accordance with the current guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

The CHMP concluded from the ERA that the risk for all compartments was acceptable. The PEC surface water was calculated to be 0.2 µg/l and therefore the risk to surface water, groundwater and STP is negligible.

2.3. Clinical aspects

2.3.1. Introduction

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The total paediatric clinical programme consisted of 4 studies as described in the table below. The current application focuses on the assessment of the CHARON study although throughout this report, reference is also made to the other studies that support a paediatric indication (namely PLUTO).

Table 1 Overview of all paediatric studies with rosuvastatin

Type of Study	Study Identifier	Study design and type of control	No. of subjects enrolled / treated	Duration of treatment	Study status
PK	422IL/0054	Forced-dose titration of 20 mg, 40 mg, and 80 mg with 6-weeks intervals.	8 paediatric patients 8 to <18 years of age with HoFH	18 weeks	Completed
PK	422IL/0086	Open-label, non-randomised PK study with single dose of 10 mg, 40 mg, and 80 mg or multiple doses of 80 mg.	18 paediatric patients 10 to <17 years of age with HeFH	1 or 7 days	Completed
Efficacy and safety	D3561C0087 (PLUTO)	A 12-week, double-blind, multicentre, placebo controlled Phase IIIB study with a 40-week, open-label follow-up period	177 patients 10 to <18 years of age with HeFH	52 weeks	Completed
PK, Efficacy and safety	D3561C00002 (CHARON)	Open-label, multicentre, Phase IIIb, efficacy, safety and PK study of rosuvastatin in paediatric patients	In total 198 patients 6 to <18 years of age with FH Of these, 12 patients 6 years to < Tanner stage II were included in the single-dose PK assessment. 65 healthy siblings were enrolled as control for assessment of cIMT	24 months	Completed

cIMT carotid intima and media wall thickness; FH Familial hypercholesterolemia; HeFH Heterozygous familial hypercholesterolemia; HoFH Homozygous familial hypercholesterolemia; PK Pharmacokinetics

2.3.2. Pharmacokinetics

Introduction

The proposed dosing scheme of rosuvastatin in children and adolescents with HeFH is based on titration (depending on LDL-C response) with a maximal allowed dose of 10 mg in the youngest children (6 years to <10 years of age) and up to 20 mg in older children and adolescents.

Studies included

Rosuvastatin pharmacokinetics in paediatric patients was based on data from the two paediatric studies CHARON and 4522IL/0086. Non-compartmental PK analysis was performed on the data from both studies including single dose data at 10, 40 and 80 mg and multiple dose data at 80 mg in study 4522IL/0086 and single dose data from CHARON at 10 mg. In addition, a combined population PK analysis was performed across the two studies. This included PK sampling in 18 patients in study 4522IL/0086 and 12 patients in CHARON, as well as multiple trough PK samples in about 200 patients in CHARON. As the population analysis for CHARON was based on a greater number of subjects and a larger data set this is regarded as the more informative analysis.

A modelling plan and report were provided. The PK population model and choices for the base model and covariate model were validated.

CHARON study participants

In this study, 12 patients (aged 6 years to less than Tanner Stage II1) received a single 10 mg dose and had an period of PK sampling prior to start of the 2-year efficacy and safety phase. These data were used to perform non-compartmental pharmacokinetic analyses besides the performed population approach.

The patient age distribution was following: 4 patients were aged 7 years, 4 patients were aged 8 years and 4 patients were aged 9 years. Regarding gender and race, the distribution was following: 5 were males, 7 were females, and all were caucasians. Mean weight was 30.6 kg (SD 5.26 kg). All patients that qualified for the PK study met the inclusion criteria for the efficacy and safety part of the study, and were statin naïve.

For rosuvastatin, the mean C_{max} was 3.57 ng/ml, t_{max} was 2.7h and $AUC_{(0-24)}$ was 27.7 ng.h/ml. This was lower than the exposure seen in study 4522IL/0086 (48.7 ng.h/ml). However no differences in formulation of in the bioanalytical methods offer an explanation for the difference in exposure. The most likely explanation is chance finding due to relatively small numbers and high variability in exposure, as similar cross-study differences in exposure also occurred in healthy adults.

Dose proportionality and time dependencies

Dose proportionality

Proportionality was assessed in the population PK analysis of the combined data from CHARON and Study 4522IL/0086. Dose adjusted exposure in terms of the area under the plasma concentration time curve at steady-state (AUCss)/dose did not appear to increase with increasing dose in either CHARON or 4522IL/0086. Based on the non-compartmental analysis from Study 4522IL/0086 it appeared that exposure was approximately dose proportional across the dose range 10 mg to 80 mg in the age range (10 to <18 years) studied. This proportionality with dose in paediatric patients is consistent with data in adults where dose proportionality was evident across the dose range 10 mg to 80 mg (Study 4522IL/0047).

Accumulation

Accumulation of rosuvastatin in children and adolescents with once daily dosing at 80 mg was estimated to be 1.50 (90% CI 1.31 to 1.71) in Study 4522IL/0086. The population PK model was used to predict the area under the plasma concentration time curve during a dosage interval (AUC0-24) following a single 10 mg dose and at steady-state in the 12 patients enrolled in the single-dose PK portion of CHARON. Accumulation was estimated to be on average 1.8-fold (ranging from 1.39 to 2.17), which is consistent with the accumulation observed in 4522IL/0086. The population PK model predicted steady-state being reached in approximately 6 to 7 days.

In healthy adults, very little accumulation was observed, geometric mean (gmean) values ranged from 1.05 to 1.36 after repeated daily administration of 20-, 40- or 80-mg rosuvastatin in healthy volunteer (studies 4522IL/0002 and 4522IL/0011) and this suggests that the t½ in children and adolescents is somewhat longer than that in adults. However, the time to steady-state does not appear to be significantly longer in children and adolescents (up to 8 days) compared to adults (up to 7 days) and the average steady-state concentrations in children and adolescents following chronic dosing in the CHARON study are similar to dose adjusted concentrations in healthy adults. In addition, dose titration to a maximum dose of 20 mg in children and adolescent 10 to <18 years of age (and 10 mg in children 6 to <10 years of age) results in steady-state exposures (AUCss) lower than those observed in both

[1] The Tanner scale is a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics.

healthy adult volunteers and patients. Therefore the moderate accumulation seen in children is not considered to be clinically meaningful.

Time dependence

The mean temporal change ratio was calculated to be 1.26 following 80 mg once daily dosing (n=6) for 1 week in 4522IL/0086. Although this is slightly greater than unity, the population PK analysis provided a more robust assessment of time dependent changes in the PK over a 2 year period in 196 patients. This analysis provided little evidence to support a change in CL/F as a linear function of time with dose-normalised concentrations appearing to remain relatively constant over time.

The CHMP concluded that there is no indication for time dependence in rosuvastatin pharmacokinetics in children and adults.

Special populations

Weight and gender

Weight and gender were found to be significant covariates for CL/F. CL/F increased with increasing weight. A male child weighing 20 kg had an estimated CL/F of 287 L/h whereas a male child weighing 99 kg had an estimated CL/F of 554 L/h, representing a 2-fold difference (max/min) across the observed weight range in this study.

In addition to weight, gender had an impact on CL/F: CL/F in female children was approximately 30% lower than in male children.

In general, younger children had lower CL/F due to the correlation between age and weight. After differences in weight and gender had been accounted for, age could not significantly explain any additional variability in CL/F.

The dosing scheme of rosuvastatin in children and adolescents with HeFH is based on titration (depending on LDL-C response) with the youngest children (6 to < 10 years of age) allowed a dose up to 10 mg, while a maximum dose of 20 mg was allowed for older children and adolescents. It is therefore unlikely that the impact of gender and weight on CL/F results in any clinical implications.

2.3.3. Discussion on clinical pharmacology

Exposure in paediatric patients appeared to be dose proportional with an increased accumulation observed for the paediatric population (approximately 1.8 fold) compared to the adult population (1.1-1.4 fold). Steady state reached within 1 week. Dose titration to a maximum dose of 20 mg in children and adolescents 10 to <18 years of age (and 10 mg in children 6 to <10 years of age) seems to result in steady-state exposures (AUCs) lower than those observed in both healthy adult volunteers and patients. The relative impact of the increased accumulation factor is therefore small due to the dose titration scheme and dose capping, and is not viewed to be clinically meaningful.

Weight and gender were significant covariates on CL/F with lower weight patients and females having lower clearance. However, the relative impact of these covariates on AUC accomplished is small due to the dose titration scheme and dose capping, and is not viewed to be clinically meaningful. CL/F in paediatric patients appeared similar to adult volunteers but lower than in adult patients. With the lower dose caps used in paediatric patients, exposures were generally lower in paediatric patients than in adult patients.

Independent of dose, weight and gender, exposure was estimated to be 2.7-fold higher in study 4522IL/0086 than in study D3561C00002 (CHARON). This is likely to be a chance finding due to

relatively small numbers and high variability in exposure, as similar cross-study differences in exposure also occurred in healthy adults.

2.3.4. Conclusions on clinical pharmacology

The PK of rosuvastatin in children and adolescents is predictable with respect to both dose and time. The relative impact of the increased accumulation factor is small due to the dose titration scheme and dose capping, and is not viewed to be clinically meaningful. In addition, the demographic variables, weight, age and gender do not appear to provide clinically meaningful changes in steady-state exposure.

2.4. Clinical efficacy

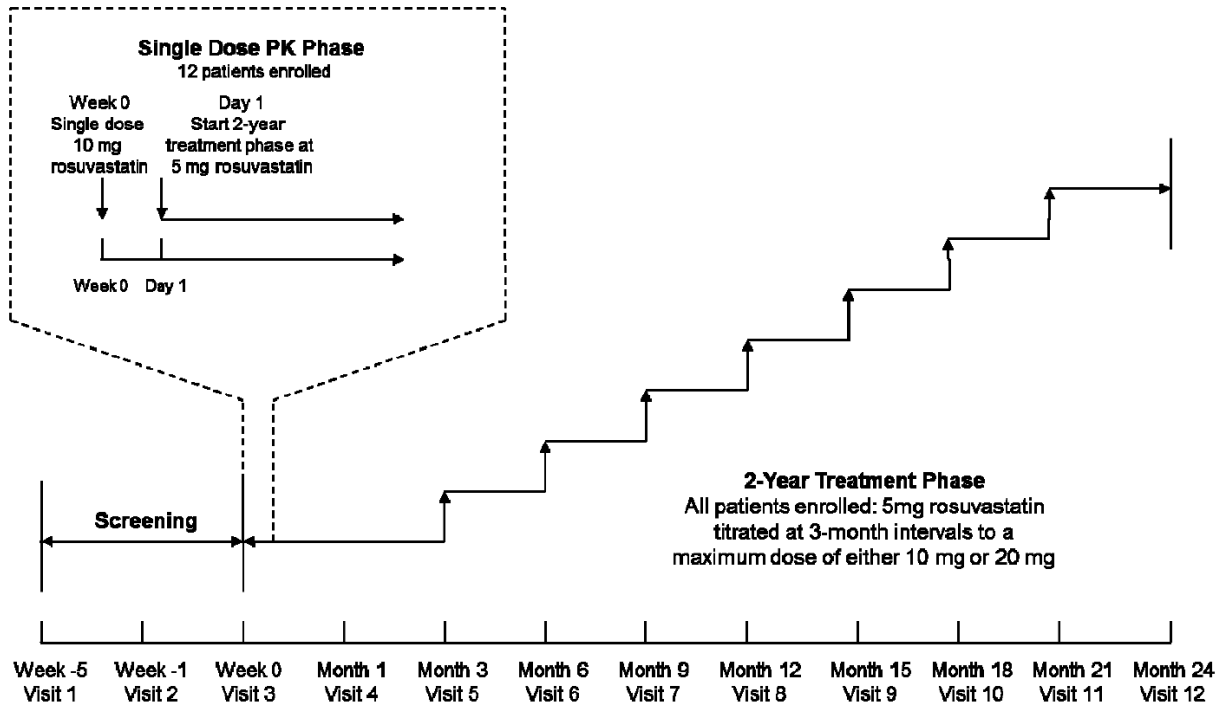
2.4.1. Main study (CHARON)

The CHARON single arm open label study was designed to assess the PK, efficacy, tolerability and long-term safety, including growth and sexual development, of rosuvastatin, as compared to baseline, in children between the ages of 6 and <18 years with HeFH.

Methods

The general study design is outlined in the figure below.

Figure 1 CHARON study design



Run-in period

A run-in period of minimum 4 weeks was applied for patients being withdrawn from previous lipid therapy. Inclusion and exclusion criteria were screened at Visits 1 and/or 2. Potentially eligible patients had current lipid therapy withdrawn after Visit 1. A minimum of 4 weeks later, LDL-C was assessed at Visit 2. Patients aged from 6 to less than 10 years of age were not required to attend screening Visit 2, as they were required to be statin-naïve. Visit 3 (baseline) dosing took place approximately 1 week after Visit 2, when LDL-C results were available.

Study visits

Patient visits were at month 1 and every 3 months until 24 months of treatment. For the study visits in the open-label treatment period, a visit window of ± 7 days was allowed. The visit schedule had to be adhered to as closely as possible. If it was determined that the patient should be withdrawn from the study, the patient was asked to return for the final visit procedure (Visit 12). Patients started treatment with the 5 mg dose and could be up-titrated in 3 month intervals to 10 or 20 mg (see also section on treatment).

Lipid profiles were generally measured at every visit (with primary and secondary efficacy assessed for Month 3, 12 and 24), while cIMT measurements were performed at baseline, Month 12 and Month 24.

Safety assessment

Safety assessments were conducted at every visit throughout the treatment period of 2 years. Effects on growth by measurement of height, weight and BMI with the assessment of sexual maturation using Tanner staging were assessed after 12 months of treatment and at the end of the study.

PK substudy

For 12 patients, a 24-hour, single-dose, open-label PK study has been performed (see section 2.3.2 pharmacokinetics). These patients were directly included in the main study at day 1 with a starting dose of 5 mg rosuvastatin similar to the rest of the participants.

Measuring lipids

Analyses of all laboratory samples were performed by a central laboratory. The concentration of fasting LDL-C was determined for all relevant visits by the Friedewald Equation2.

Measuring cIMT

Carotid ultrasonography was performed. All examinations for a given patient were performed by a certified sonographer (physician, registered sonographer or research nurse) trained in performing the procedures required for this study. The cIMT was defined as the distance between the leading edges of the lumen-intima and media-adventitia interfaces. The maximum cIMT was calculated as the average of the 2 measurements and the mean cIMT was calculated as the average of the 6 measurements.

Readings of the cIMT were randomly assigned to image analysts for qualitative and quantitative evaluation according to the study specific image analysis protocol. Image analysts were blinded to subject and visit identifiers.

The cIMT was measured at baseline (Visit 3), Month 12 (Visit 8) and Month 24 (Visit 12) in all patients and in healthy siblings.

[2] LDL-C= Total cholesterol - {HDL-C + TG/2.2}

Study participants

Relevant inclusion criteria

The patient population included were male and female children and adolescents aged 6 to less than 18 years with HeFH (defined by a documented genetic defect in LDL-R or ApoB by DNA analysis or documented evidence of FH in a first-degree relative (LDL-C >4.90 mmol/L [189 mg/dL] in an adult; >4.10 mmol/L [158 mg/dL] in a child <18 years of age)) and at least 1 of the following criteria:

- Fasting LDL-C >4.92 mmol/L (190 mg/dL) prior to Visit 3, per Visit 1 laboratory results (statin-naïve only) or Visit 2 laboratory results (previously treated) or
- Fasting LDL-C >4.10 mmol/L (158 mg/dL) prior to Visit 3, per Visit 1 laboratory results (statin-naïve only) or Visit 2 laboratory results (previously treated) in combination with evidence of other risk factors, such as family history in first or second degree relatives of premature CVD, defined as onset of clinical atherosclerotic disease before age 55 in males or age 65 in females at Visit 1.

In addition, patients aged between 6 and less than 10 years of age must have been statin treatment naïve.

For the cIMT measurements, patients were compared to a group of healthy siblings. For inclusion of healthy siblings in the study, they must fulfil the following criteria:

- Documented absence of the genetic defect in LDL receptor or Apo B (by DNA analysis) or
- Historical documented LDL-C of <3.00 mmol/L (116 mg/dL), without lipid lowering medication.

Healthy siblings of non-participating patients must have a sibling with FH.

Relevant exclusion criteria

Patients were excluded from the study if they had a history of statin-induced myopathy or serious hypersensitivity reaction to statins; a fasting TG ≥2.87 mmol/L (254 mg/dL); a fasting serum glucose of >9.99 mmol/L (180 mg/dL) or glycosylated haemoglobin (HbA1c) >9% or patients with a history of diabetic ketoacidosis within the past year; uncontrolled hypothyroidism; current active liver disease or hepatic dysfunction as defined as elevations of 1.5 times the ULN for any age; serum creatine kinase (CK) ≥3 × the ULN; eGFR <50 mL; ≥2+ proteinuria on urine dipstick; stage 2 hypertension; history of organ transplantation; or weight <20 kg.

Healthy siblings were excluded from the study if they participate in a study requiring ingestion of a lipid lowering therapy.

Treatments

General dosing

Patients started treatment with the 5 mg dose and could be up-titrated in 3 month intervals to 10 or 20 mg. 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 (i.e. always in the morning or always in the evening).

Single-dose PK substudy

In the single-dose PK phase, a total of 12 patients aged from 6 years to less than Tanner Stage II were administered a single dose of 10 mg rosuvastatin at baseline (Visit 3). After patients had received the

single 10 mg dose (at Visit 3), they were directly enrolled into the efficacy and 2-year safety phase, receiving the starting dose of 5 mg rosuvastatin after the 24-hour assessment on Day 1 after Visit 3.

Main study

In the efficacy and 2-year safety phase of the study, all patients started on 5 mg rosuvastatin once daily. Up-titration to achieve an LDL-C target of <2.85 mmol/L (110 mg/dL) was performed in 3-month intervals starting at Month 3 to a maximum rosuvastatin dose of 10 mg once daily for patients aged from 6 to <10 years and 20 mg once daily for patients aged 10 to <18 years. If higher doses were not well tolerated, the patients may have been down-titrated to the previous dose, at the discretion of the investigator.

Objectives and outcomes/endpoints

The primary objective of this study was to determine the efficacy of once-daily rosuvastatin in reducing LDL-C in paediatric patients 6 to <18 years of age with FH. An overview of all the objectives and variables of the CHARON study are summarized in Table 2.

Table 2 CHARON - study objectives and variables

Objective			Variable
Priority	Type	Description	Title and 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.

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

Sample size

At least 180 patients aged from 6 to <18 years were planned to be enrolled in this study. The distribution goal was to enroll 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).

A total of 12 paediatric patients aged from 6 years to less than Tanner Stage II with FH were planned to be included in the single-dose PK assessment.

In addition, at least 60 healthy siblings were planned to be enrolled in the study for cIMT analysis (at least 20 siblings aged 6 to<10 years, 20 siblings aged 10 to <14 years and 20 siblings aged 14 to< 18 years).

Randomisation

This was an open label single-arm trial, therefore, no randomisation across treatment groups have been performed. However, enrolment was actively managed to achieve a reasonable demographic distribution of patients by age, gender, and Tanner stage.

Statistical methods

All objectives in this study were exploratory. Descriptive statistics were mainly used to summarise single-dose PK, efficacy and safety variables. Formal statistical analysis was performed on efficacy variables only. All tests were 2-sided, and a p-value of ≤0.050 was considered statistically significant. No adjustments for multiple comparisons were made. Inference statistics on ITT analysis set mainly utilised LOCF data.

Percent change from baseline in LDL-C, 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 was analysed using t-tests to estimate rosuvastatin efficacy at Month 3, 12 and 24. ANCOVA was used to compare the reduction among age groups, using centre and the baseline value as covariates. Least-squares mean (LS) and its 95% confidence interval (CI) were calculated for each age group and overall.

Change from baseline in both maximum cIMT and mean cIMT were analysed using mixed-effects models between all enrolled patients and healthy siblings at 12 and 24 months. Both within-group and between-group comparisons in a paired and cohort fashion were conducted. In the mixed-effects model, subject group, age group, interaction of subject group by age group, centre and the baseline value were fixed effects, and family was the random effect. LS and its 95% CI were calculated for each age group and overall, both for patients and healthy siblings. Between-group comparisons also calculated LS mean difference (patient - healthy sibling).

Results

Participant flow

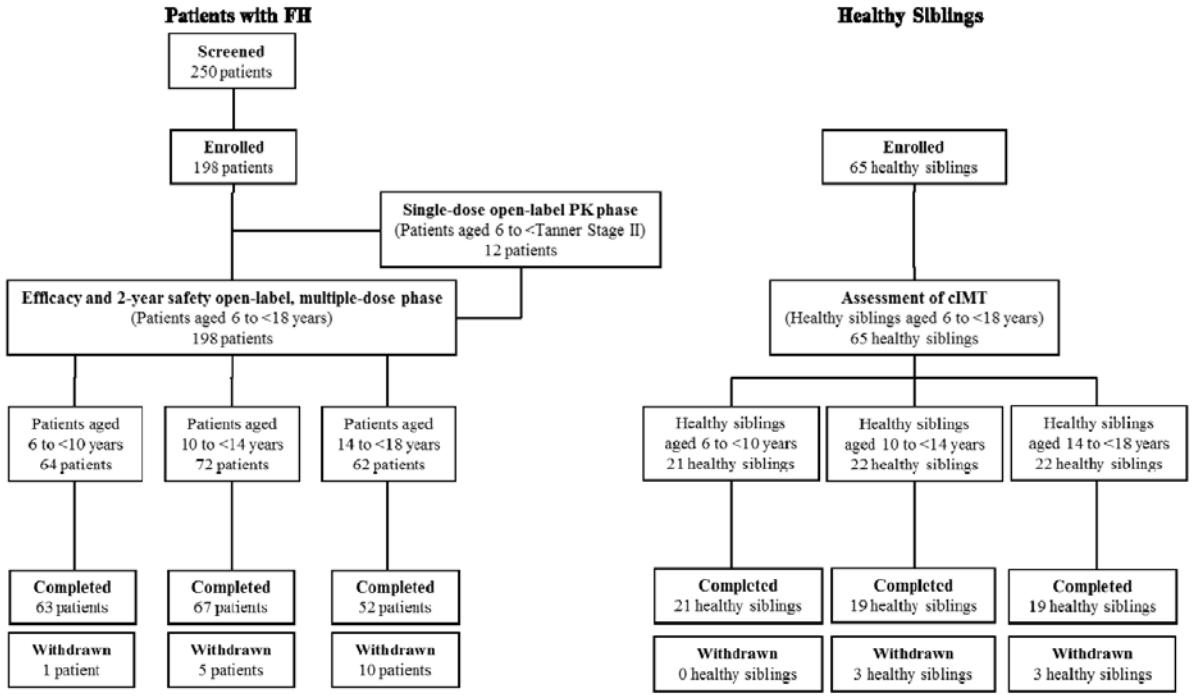
A total of 250 patients with FH were screened and 198 of these patients were enrolled into the study (64 patients aged 6 to <10 years, 72 patients aged 10 to <14 years and 62 patients aged 14 to <18 years). Of these patients, 12 patients aged 6 years to <Tanner Stage II were included in the single-dose open-label PK phase of the study (4 patients aged 7 years, 4 patients aged 8, and 4 patients aged 9 years).

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 (91.9%) patients completed the study. The number of withdrawals increased by age group:

- In the 6 to <10 age group, 1 (1.6%) patient withdrew (as a result of the patient's decision).
- In the 10 to <14 age group, 5 (6.9%) patients withdrew (as a result of the patient's decision [n=2], an AE [n=1], other reasons [n=1; the subject moved out of the country], and severe non-compliance to the protocol [n=1]).
- In the 14 to <18 age group, 10 (16.1%) patients withdrew (as a result of the patient's decision [n=4], severe non-compliance to the protocol [n=3], AEs [n=2] and other reasons [n=1; the patient was not able to attend the last visit due to being abroad]).

In addition, 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.

Figure 2 CHARON - Disposition of patients and healthy siblings



Recruitment

Of the 250 patients screened, 52 patients withdrew during the screening phase. No reason for withdrawal of these patients during the screening phase has been described. The primary reasons for patients not being included were eligibility criteria not fulfilled (n=47) and subject decision (n=4).

Conduct of the study

This study was performed at 14 centers in 5 different countries: 6 in the Netherlands (72 subjects), 5 in Canada (68 subjects) and 1 each in Belgium (6 subjects), Norway (35 subjects), and the United States (17 subjects).

Baseline data

In the CHARON study, enrolment was actively managed to achieve an appropriate demographic distribution of patients by age, gender, and Tanner stage (tables 3 and 4). There were similar numbers of treated patients in each age group, and the mean ages of randomised females and males were 11.5 and 11.7 years, respectively. More females than males were randomised to study treatment (55.6% and 44.4%, respectively).

The majority of patients were Caucasian (89.9%).

A total of 152 (77.2%) patients had a family history of premature CVD. A total of 182 (92.4%) patients had a first degree adult relative with FH defined as LDL-C >4.92 mmol/L (190 mg/dL) and 105 (53.3%) patients had a first degree relative <18 years with FH defined as LDL-C >4.10 mmol/L (160 mg/dL).

Table 3 CHARON - Summary of Tanner Stage at baseline (Visit 3)

Parameter	Class	Treated patients (N=198)
Tanner stage at baseline	I	81 (40.9%)
	II	32 (16.2%)
	III	18 (9.1%)
	IV	44 (22.2%)
	V	22 (11.1%)
	Not recorded	1 (0.5%)

Table 4 CHARON - Summary of age and sex at baseline (Visit 3)

Parameter	Class/Statistics	Treated patients (N=198)
Age group (years)	6-<10	64 (32.3 %)
	10-<14	72 (36.4%)
	14-<18	62 (31.3%)
Age (years)	n	198
	Mean (SD)	11.6 (3.33)
	Median	11.0
	Min, max	6, 17
Sex	Male	88 (44.4%)
	Female	110 (55.6%)
Age (years) by sex	Male	
	n	88
	Mean (SD)	11.7 (3.42)
	Median	12.0
	Min, max	6, 17
	Female	
	n	110
	Mean (SD)	11.5 (3.27)
	Median	11.0
	Min, max	6, 17

The baseline characteristics of lipids levels and vital signs of the paediatric patients are summarized in table 5. Overall, small differences are observed in the characteristics of lipids between the different age groups.

Table 5 CHARON - Baseline characteristics (ITT analysis set)

Characteristic	Treated patients			
	6 -<10 years	**10 -<14 years**	**14 -<18 years**	**Total**
	n= 64 (32.5%)	**n= 72 (36.5%)**	**n= 61 (31.0%)**	**n= 197**
Sex n (%)				
Male	29 (45.3%)	30 (41.7%)	28 (45.9%)	87 (44.2 %)
Female	35 (54.7%)	42 (58.3%)	33 (54.1%)	110 (55.8 %)
Weight (kg)				45.9 (18.20)
Male Mean (SD)	29.9 (8.64)	45.8 (11.08)	70.1 (14.22)	
Female Mean (SD)	29.1 (5.85)	46.3 (17.54)	57.1 (8.14)	
Height (cm)				151.2 (17.26)
Male Mean (SD)	132.8 (9.52)	153.6 (9.89)	169.2 (9.26)	
Female Mean (SD)	132.9 (8.53)	151.5 (9.72)	163.4 (7.02)	
BMI (kg/m^2)				19.3 (4.32)
Male Mean (SD)	16.7 (2.81)	19.2 (3.61)	22.6 (4.62)	
Female Mean (SD)	16.3 (1.78)	19.8 (5.45)	21.3 (2.50)	
Waist circumference (cm)				67.7 (11.57)
Male Mean (SD)	59.0 (8.13)	68.8 (9.94)	80.1 (10.18)	
Female Mean (SD)	58.5 (5.29)	68.6 (11.72)	72.2 (7.95)	
LDL-C (mg/dL)				
Mean (SD)	233.6 (52.26)	234.3 (48.6)	240.5 (46.5)	236.0 (49.02)
HDL-C (mg/dL)				
Mean (SD)	52.4 (12.7)	51.8 (12.8)	46.2 (12.0)	50.3 (12.8)
TC (mg/dL)				
Mean (SD)	301.2 (56.6)	304.2 (49.3)	308.5 (50.0)	304.5 (51.8)
TG (mg/dL)				
Mean (SD)	75.9 (34.7)	90.3 (46.1)	109.1 (57.7)	91.4 (48.5)
Non-HDL-C (mg/dL)				
Mean (SD)	248.8 (53.6)	252.4 (50.3)	262.2 (48.2)	254.3 (50.8)
LDL-C/HDL-C				
Mean (SD)	4.70 (1.49)	4.83 (1.67)	5.57 (1.93)	5.02 (1.73)
TC/HDL-C				
Mean (SD)	6.02 (1.61)	6.21 (1.81)	7.10 (2.16)	6.43 (1.91)

Characteristic	Treated patients			
	6 -<10 years	10 -<14 years	14 -<18 years	Total
	n= 64 (32.5%)	n= 72 (36.5%)	n= 61 (31.0%)	n= 197
Non-HDL-C/HDL-C				
Mean (SD)	5.02 (1.61)	5.21 (1.81)	6.10 (2.16)	5.43 (1.91)
ApoB (mg/dL)				
Mean (SD)	152.7 (28.7)	153.0 (27.9)	158.9 (27.8)	154.7 (28.1)
ApoA-I (mg/dL)				
Mean (SD)	142.3 (21.8)	137.9 (22.7)	133.2(22.6)	137.9 (22.5)
ApoB/ApoA-I				
Mean (SD)	1.10 (0.26)	1.15 (0.32)	1.22 (0.30)	1.15 (0.30)
hCRP (mg/L)				
Mean (SD)	1.82 (6.74)	1.18 (2.57)	0.99 (1.15)	1.33 (4.19)

Numbers analysed

All 198 patients enrolled were treated with rosuvastatin. However, one patient left the study after 1 dose without presenting any post dose data due to a lack of follow-up. No explanation was given for the withdrawal and no adverse event was reported.

Another patient did not present any post dose data between baseline (Visit 3) and last visit (Visit 12). All available data are included in the safety and ITT analysis sets, meaning that there are 196 patients included at 3 and 12 months, and 197 patients at 24 months in these analysis sets.

170 patients (85.9%) were included in the PP analysis set, since a total of 27 patients (13.7%) had important protocol violations/deviations. The reason for violation/deviation was severe non-compliance to drug intake (13.2%) and failing the inclusion/exclusion criteria (2.0%).

Outcomes and estimation

Primary efficacy variable: Percent change from baseline in LDL-C following 3, 12 and 24 months.

The mean LDL-C ranged from 6.1 to 6.2 mmol/L across age groups at baseline, which decreased to a mean of 3.8 mmol/L after 3 months, 3.3 mmol/L after 12 months and 3.5 mmol/L after 24 months of treatment, a mean percent reduction of -37.86%, -43.67 and -42.88 ($p<0.001$), respectively, with significant LDL-C reduction observed as early as 1 month (-38.03% overall). PP analysis demonstrated a -39.98%, -47.07%, and -47.13% reduction, respectively.

Sustained efficacy was demonstrated after 12 months of treatment for each age group (-43.55%, -47.38%, and -40.78%, respectively) and after 24 months (-42.80%, -44.55%, and -35.15%, respectively, $p<0.001$). The younger age groups showed greater reductions in LDL-C than the 14 to <18 age group.

Thirty-four of 196 (17.3%) patients achieved the LDL-C goal of <2.85 mmol/L after 3 months, 66 of 196 (33.7%) after 12 months, and 74 of 197 (37.6%) after 24 months.

Secondary efficacy variables: Lipids and lipoproteins.

Statistically significant mean changes from baseline values at 3 months, 12 months, and 24 months for the following secondary lipid and lipoprotein variables were achieved: 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 ($p<0.001$ for all variables at all time points except for TG/HDL-C: $p=0.003$, $p<0.001$ and $p=0.015$ at 3, 12, and 24 months, respectively). These changes from baseline were each in the direction of improved lipid responses and were sustained over 2 years.

The mean changes from baseline in HDL-C at 3 months, 12 months, and 24 months were + 5.7%, +6.4%, and +11.7%, respectively ($p< 0.001$ at all time points). Statistically significant mean changes from baseline in TG levels were observed following treatment with rosuvastatin at 3 months and 12 months (-8.0%, $p<0.001$ and -7.9% $p<0.004$). No significant differences in TG were observed at 24 months (-0.12%, $p=0.963$). In addition, rosuvastatin achieved significant mean changes from baseline in ApoA-1 levels at 3 months and 24 months ($p<0.001$ and $p=0.030$, respectively).

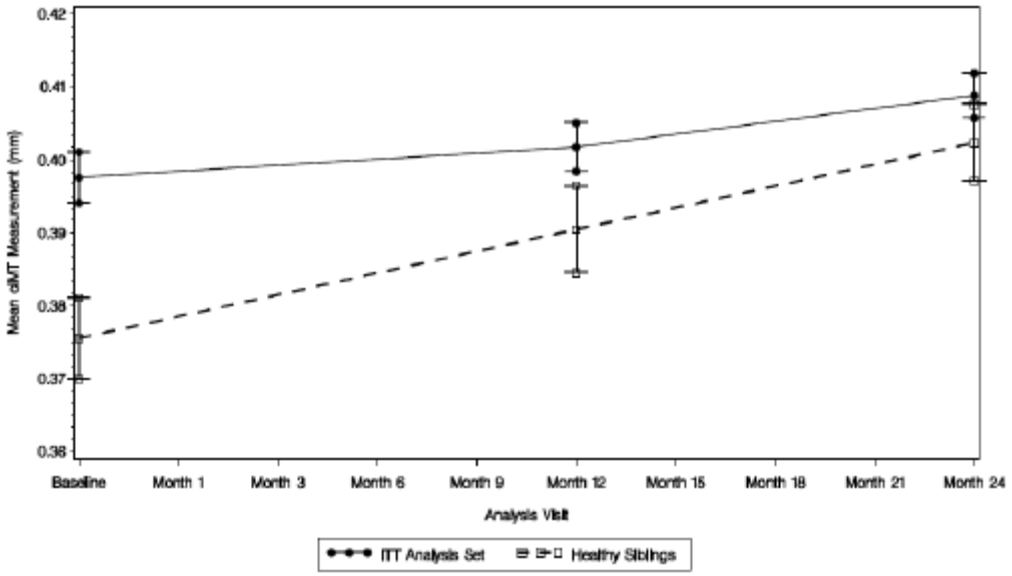
Ancillary analyses

Secondary efficacy variables: cIMT

The average mean cIMT measured was slightly higher for the patient population compared with the healthy siblings at baseline (0.39755 and 0.37551, respectively), 12 months (0.40173 and 0.39044, respectively) and at 24 months (0.40879 and 0.40233, respectively). Similarly, the average maximum cIMT measured by sonography was slightly higher for the patient population compared with the healthy siblings at baseline (0.48389 and 0.45791, respectively), 12 months (0.49274 and 0.47435, respectively) and 24 months (0.48676 and 0.46829, respectively).

The change from baseline in mean cIMT measurements (mm) was lower in the patient population compared with the healthy siblings at 12 months (0.002852 and 0.01564 [95% CI: -0.01197 – 0.00886];$p=0.77$, respectively) and at 24 months (0.01506 and 0.02779 [95% CI: -0.01463 – 0.00441]; $p=0.29$). Similarly, the change from baseline in maximum cIMT measurements (mm) was lower in the patient population compared with healthy siblings at 12 months (0.00626 and 0.01707 [95% CI: -0.01581 – 0.02103]; $p=0.78$, respectively) and at 24 months (0.00189 and 0.01202 [95% CI: -0.01181 – 0.01709]; $p=0.72$, respectively). 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 show 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 (figure 3). The smallest effect was observed in patients in the category of 10-14 years of age.

Figure 3 CHARON - Mean cIMT measurements (mm) over time



High sensitivity C-reactive protein (hsCRP)

No consistent changes were observed in hsCRP.

Number of patients on final dose

Twenty-one (21), 55 and 121 patients were on a final dose of 5, 10 and 20 mg, respectively. For the <10 year age group (n=64), the maximum dose reached was 5 mg for 5 patients, 10 mg for 40 patients and 20 mg for 19 patients. For the 10 to <14 years age group (n=71), the maximum dose reached during the study was 5 mg for 5 patients, 10 mg for 11 patients and 20 mg for 55 patients; for the 14 to <18 year age group (n=61), the maximum dose reached was 5 mg for 3 patients, 10 mg for 9 patients and 20 mg for 49 patients.

For each final dose, the percent of patients achieving treatment goal at month 24 were 47.6% in the 5 mg dose group, 45.5% in the 10 mg group, and 32.2% in the 20 mg group.

Summary of main study

The following table summarises the efficacy results from the CHARON study. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6 Summary of Efficacy for trial the CHARON trial

Title: CHARON		
Study identifier	D3561C00002	
Design	A 24-hour, single-dose, open-label PK phase and an efficacy and 2-year safety, open-label, multiple-dose phase IIIb	
	Duration of main phase:	24 Months.
	Duration of run-in phase:	minimum 4 weeks for patients being withdrawn from previous lipid therapy.
	Duration of extension phase:	not applicable.

Hypothesis	Assess the PK, efficacy, tolerability and long-term safety, including growth and sexual development, of rosuvastatin, as compared to baseline, in children between the ages of 6 and <18 years with a history of HeFH		
Treatment groups	6 to<10 years		Rosuvastatin 5 mg up-titrated to maximum of 10 mg, 24 months treatment, 64 patients
	10 to<14 years		Rosuvastatin 5 mg up-titrated to maximum of 20 mg, 24 months treatment, 72 patients
	14 to<18 years		Rosuvastatin 5 mg up-titrated to maximum of 20 mg, 24 months treatment, 62 patients
Endpoints and definitions	Primary endpoint	Efficacy	To assess LDL-C reduction after 3, 12, and 24 months.
		Safety	To establish 2-year safety and tolerability.
		PK	To characterise the PK profile of rosuvastatin in paediatric patients aged from 6 to less than Tanner Stage II, with FH
	Secondary	Efficacy	To assess cIMT by sonography at baseline and every year in patients and healthy siblings.
		Safety	To assess growth and maturation in children or adolescents with FH who are receiving long-term rosuvastatin treatment.
		Adherence/ Compliance and acceptability	To assess adherence to rosuvastatin during a 2-year period of treatment.
			To assess the feasibility and acceptability of the current marketed tablet formulation of rosuvastatin for use in children.
Database lock	25 June 2013		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	ITT and PP Time points: 3, 12, and 24 months			
Descriptive statistics and estimate variability	Treatment group	6 to<10 years	10 to<14 years	14 to<18 years
	Number of subjects	64	72	62
	Percent change from baseline in LDL-C (3 months)	-40.96%	-40.52%	-34.73%
		p< 0.001	p< 0.001	p< 0.001
	Percent change from baseline in LDL-C (12 months)	-43.55%	-47.38%	-40.78
		p< 0.001	p< 0.001	p< 0.001

	Percent change from baseline in LDL-C (24 months)	-42.80%	-44.55%	-35.15%
		p< 0.001	p< 0.001	p< 0.001
Effect estimate per comparison	Treatment group	6 to<10 years	10 to<14 years	14 to<18 years
	Number of subjects	64	72	62
	Percent change from baseline in HDL, TG (3 months)	HDL 4.0%, P=0.123	HDL 4.14%, p=0.031	HDL 9.19%, p=0.004
		TG -7.04%, p=0.006	TG -7.04%, p=0.111	TG -11.67%, p=0.168
	Percent change from baseline in HDL, TG (12 months)	HDL 6.61%, p=0.007	HDL 2.43%, p=0.278	HDL 10.64%, P=0.001
		TG -7.69%, p=0.029	TG -5.77%, p=0.119	TG -10.43%, p=0.262
	Percent change from baseline in HDL, TG (24 months)	HDL 14,35%, p=0.001	HDL 8.47%,	HDL 14,35%, p=0.001
		TG -5.94%, , p=0.179	TG 4.96%, p=0.231	TG -0.03%, p=0.178

Comparison of CHARON with PLUTO

Rosuvastatin has been previously shown to effectively reduce LDL-C in paediatric patients 10 to<18 years of age with HeFH in a placebo-controlled study for 12 weeks with subsequent single-arm study until 52 weeks (the PLUTO study). Overall, the efficacy results in CHARON were similar to those observed in the PLUTO study.

Primary endpoint LDL-C reduction

When comparing the change in LDL-C for the rosuvastatin 5 mg dose of CHARON (all patients were on 5 mg during the first 3 months) with that of PLUTO, the LS mean change from baseline to 3 months in the present study (-37.9%) was similar to the LS mean change from baseline to 12 weeks in the PLUTO study (-38.3%). CHARON was an open-label study including the ages 6 to <18 years, whereas PLUTO included the ages 10 to <18 years with the first 12 weeks double-blinded and placebo-controlled with patients randomised to their treatment. The LS mean difference between rosuvastatin 5 mg and placebo in change from baseline to 12 weeks for the rosuvastatin 5 mg dose in PLUTO was -37.5% (95% CI: -42.8% to -32.3%).

Percentage at treatment goal

In the CHARON study, for the treatment goal of LDL-C <110 mg/dL (<2.85 mmol/L), 33.7% across age groups reached the treatment goal at 12 months, and 37.6% at 24 months. The highest success rate (43.7%) at 12 months was found in the age group 10 to <14 years (similar to that in PLUTO [40.5%]), while the other age groups had lower success rates (29.7% and 26.2% in the 6 to <10 years and the 14 to <18 years age groups, respectively). The percentage reaching this treatment goal was maintained (or somewhat increased) during the second year of treatment.

Secondary endpoints

In the CHARON study, the secondary endpoints show significant changes from baseline in the direction of improved lipid responses at 3, 12 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, and ApoB/ApoA-1. In the PLUTO study, the secondary endpoints show changes in the expected (beneficial) direction known from rosuvastatin use in adults, however, without reaching statistical significance.

Measurement of cIMT was not conducted in the PLUTO study.

2.4.2. Discussion on clinical efficacy

The CHARON study was an open label, single-arm study, whereas a placebo-controlled study might have been preferable. However, the use of placebo in children is subject to ethical concerns and the design of CHARON was considered appropriate for assessing both long-term efficacy and safety. In particular, the study duration of 2 year provides valuable long term effects both in terms of sustained efficacy and safety information, including growth, weight and sexual development, as this has been assessed in the PLUTO study only up to 52 weeks. Moreover, study design is in line with the PIP recommendations and the *Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/494506/2012)*.

However, the single arm open label design presents a risk of biased interpretation of the data. The assessment of all lipids that were measured in a central laboratory does however provide reassurance on the quality of the data. Similarly, the assessment of cIMT readings was blinded. A comparison to the PLUTO study for the overlapping population provides further reassurance on the robustness of the study results.

The inclusion and exclusion criteria of patients and healthy siblings – as a control group for cIMT assessments - are considered appropriate and in line with the inclusion and exclusion criteria of the PLUTO trial. Enrolment was actively managed, which is considered appropriate to achieve an equitable demographic distribution of patients by age, sex, and Tanner stage. In particular, genetic testing to document HeFH or documented evidence of FH in a first-degree relative could have provided reassurance on HeFH status in the view of eligibility of treating such young patients with statins. Nevertheless, it is unlikely that HoFH patients have been enrolled in the study as the HoHF phenotype is sufficiently distinctive from HeFH in terms of clinical presentation.

Reduction of LDL-C in children has never been demonstrated to reduce CV risk. Therefore, beneficial effects have to be extrapolated from adults LDL lowering. In adults, LDL-C reduction, especially in statins, has been demonstrated to reduce CV risk and therefore accepted as a surrogate marker for clinical outcome. LDL-C is also considered as the most appropriate marker to assess beneficial effects in children and therefore the primary endpoint of LDL-C reduction is considered appropriate for assessing the efficacy of rosuvastatin, as outlined in the *Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/494506/2012).*

The secondary endpoints can be considered supportive to establish the effect of rosuvastatin on the total lipid spectrum and onset of action.

In addition, the percentage response rate and cIMT measurements to assess vascular damage in relation to lipid lowering may be valuable as supportive data in terms of intermediate data for CV outcome (see also *Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/494506/2012)*. Although cIMT is a relevant

measure of atherosclerosis it has currently not been accepted as a surrogate marker for clinical outcome.

A significant reduction of LDL-C of approximately 40% (from 6.1 mmol/L to 3.8 mmol/L, p<0.001 for all 3 age groups) was observed for all age groups after 3 months of treatment, with a slightly smaller reduction for the highest 14-18 age group (35%).

In all age groups, efficacy was maintained after 12 months (3.3 mmol/L) and after 24 months of treatment (3.5 mmol/L), with a mean percent reduction of -43.67 and -42.88 (p<0.001), respectively.

Furthermore, after 24 months of treatment, considerable number of patients achieved the LDL-C goal of < 110 mg/dL (2.8 mmol/L) with 37.5 % in the 6 to <10 age group, 45.8% in the 10 to <14 age group, and 27.9% in the 14 to <18 age group.

The primary data of LDL-C reduction are supported by significant beneficial changes for secondary endpoints HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL-C/HDL-C, ApoB, and ApoB/ApoA-1.

A trend for slowing of intima media thickening (cIMT) was observed within each age category, although the lowest effect was observed for the category of 10-14 years of age.

Similar efficacy has been demonstrated for CHARON study data compared to data from the PLUTO trial with the 5 mg dose during 3 months of treatment.

2.4.3. Conclusions on the clinical efficacy

In the current study, the efficacy of rosuvastatin in reducing LDL-C in paediatric patients 6 to 18 years of age with HeFH was demonstrated in an open-label single arm designed study and was maintained for 24 months of treatment. Beneficial effects on secondary lipid profiles supported the main effect. Also, a trend towards reduction in vascular damage could be observed, although these data are less easily interpretable due to higher baseline cIMT.

2.5. Clinical safety

2.5.1. Introduction

The purpose of the safety assessment in this application was to investigate whether there would be safety concerns associated with administering rosuvastatin to paediatric patients aged 6 to <10 years with HeFH, and to expand the safety database with regards to duration of exposure and numbers of HeFH patients exposed in the 10 to <18 years age range.

Patient exposure

The safety population included all subjects who were randomised and who started treatment. 198 patients were enrolled into the study, however, one patient received 1 dose of study drug but was not included in the efficacy and safety analyses. Therefore, there were 197 subjects in the safety population.

The mean total duration of rosuvastatin treatment was 704 days (Table 7). The mean duration of rosuvastatin treatment at 5, 10 and 20 mg treatment was 175, 268, and 439 days, respectively. Exposure by age group is presented below.

A total of 19 patients aged 6 to <10 years at baseline received 20 mg during the study. None of the patients exceeded the maximum dose of 20 mg rosuvastatin.

Table 7 CHARON - Summary of exposure by age group

Parameter (unit) Statistics	Treated patients (N=197)			
	6-<10 years (N=64)	10-<14 years (N=72)	14-<18 years (N=61)	Total (N=197)
Total duration of rosuvastatin (days)				
N	64	71	61	196
Mean (SD)	722.8 (48.67)	709.7 (75.54)	676.0 (142.77)	703.5 (97.25)
Median	729.0	728.0	725.0	728.0
Min, Max	342, 739	359, 751	86, 756	86, 756
Duration of rosuvastatin at 5 mg (days)				
N	64	71	61	196
Mean (SD)	206.7 (181.28)	172.1 (191.78)	146.6 (153.23)	175.4 (177.85)
Median	130.0	93.0	97.0	97.0
Min, Max	42, 735	42, 751	43, 729	42, 751
Duration of rosuvastatin at 10 mg (days)				
N	59	66	58	183
Mean (SD)	459.5 (195.41)	180.7 (167.93)	173.7 (156.53)	268.3 (217.73)
Median	550.0	91.0	93.5	152.0
Min, Max	1, 648	7, 646	13, 631	1, 648
Duration of rosuvastatin at 20 mg (days)				
N	19	55	49	123
Mean (SD)	297.5 (163.36)	474.9 (131.60)	452.2 (139.70)	438.5 (151.82)
Median	283.0	544.0	529.0	537.0
Min, Max	57, 556	154, 569	60, 571	57, 571

Adverse events

Overall number of AEs

The overall number of AEs is presented in the table below.

Table 8 CHARON - Overall number of adverse events by age category

Categories of AE	Treated patients (N=197)							
	Number of patients (%)				Number of AEs			
	6-<10 years (N=64)	10-<14 years (N=72)	14-<18 years (N=61)	Total (N=197)	6-<10 years (N=64)	10-<14 years (N=72)	14-<18 years (N=61)	Total (N=197)
Any AE	56 (87.5%)	62 (86.1%)	54 (88.5%)	172 (87.3%)	259	347	235	841
AE leading to death	0	0	0	0	0	0	0	0
AE leading to discontinuation	0	1 (1.4%)	2 (3.3%)	3 (1.5%)	0	1	2	3
Serious AE	2 (3.1%)	4 (5.6%)	3 (4.9%)	9 (4.6%)	2	5	4	11
Treatment related AEs	5 (7.8%)	12 (16.7%)	12 (19.7%)	29 (14.7%)	5	15	19	39
Treatment related AE leading to death	0	0	0	0	0	0	0	0
Treatment related AE leading to discontinuation	0	1 (1.4%)	2 (3.3%)	3 (1.5%)	0	1	2	3
Treatment related serious AE	0	0	0	0	0	0	0	0

Treatment emergent adverse events

The incidence of treatment emergent adverse events (TEAEs) during the treatment phase was 87.3% (Table 9) and was similar across each age group. The most common treatment-emergent AEs by SOC were infections and infestations (67.0%), gastrointestinal disorders (35.0%), nervous system disorders (26.9%), and musculoskeletal and connective tissue disorders (25.4%).

The most common treatment-emergent AEs by PT were nasopharyngitis (44.2%), headache (23.4%), and influenza (10.2%). The most common TEAEs of specific interest (skeletal muscle events) were arthralgia (6.1%) and myalgia (5.6%). The majority of TEAEs were of mild or moderate intensity.

Table 9 CHARON - Number and percent of patients with treatment-emergent AE during the treatment phase by SOC and PT

PT	Treated patients (N=197)			
	6-<10 years (N=64)	10-<14 years (N=72)	14-<18 years (N=61)	Total (N=197)
Number of patients with treatment-emergent AEs during the treatment phase	56 (87.5%)	62 (86.1%)	54 (88.5%)	172 (87.3%)
Nasopharyngitis	30 (46.9%)	34 (47.2%)	23 (37.7%)	87 (44.2%)
Headache	14 (21.9%)	24 (33.3%)	8 (13.1%)	46 (23.4%)
Influenza	7 (10.9%)	10 (13.9%)	3 (4.9%)	20 (10.2%)
Vomiting	8 (12.5%)	8 (11.1%)	3 (4.9%)	19 (9.6%)

Gastroenteritis viral	12 (18.8%)	4 (5.6%)	2 (3.3%)	18 (9.1%)
Nausea	7 (10.9%)	3 (4.2%)	8 (13.1%)	18 (9.1%)
Abdominal pain upper	4 (6.3%)	8 (11.1%)	3 (4.9%)	15 (7.6%)
Influenza like illness	9 (14.1%)	4 (5.6%)	2 (3.3%)	15 (7.6%)
Abdominal pain	4 (6.3%)	8 (11.1%)	1 (1.6%)	13 (6.6%)
Oropharyngeal pain	2 (3.1%)	8 (11.1%)	3 (4.9%)	13 (6.6%)
Arthralgia	2 (3.1%)	7 (9.7%)	3 (4.9%)	12 (6.1%)
Gastroenteritis	8 (12.5%)	3 (4.2%)	1 (1.6%)	12 (6.1%)
Cough	5 (7.8%)	3 (4.2%)	3 (4.9%)	11 (5.6%)
Myalgia	0	5 (6.9%)	6 (9.8%)	11 (5.6%)
Pyrexia	6 (9.4%)	4 (5.6%)	0 (0.0%)	10 (5.1%)

Treatment related adverse events

The incidence of treatment-emergent related AEs during the treatment phase was 14.7%. The most common treatment-emergent related AEs by SOC were gastrointestinal disorders (8.1%), and musculoskeletal and connective tissue disorders (2.5%). Only 3 patients discontinued because of adverse events.

The safety profile of rosuvastatin treatment in the CHARON study was in line with the safety profile observed in the PLUTO study.

Other adverse events

Specific attention is given to hepatic, skeletal and renal adverse events. In the CHARON study, specific adverse events occurred in 10 patients (2 Asian and 8 Caucasian; 5.1%).

Hepatic AEs

Hepatic pain and hepatic enzyme increases were predefined as hepatic AEs. The percentage of patients with hepatic AEs was 1% (n= 2 patients). 1 Patient showed increased hepatic enzyme levels and 1 patient had hepatic pain.

Skeletal AEs

For CHARON, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle strain, and muscle weakness were predefined as skeletal muscle-related OAEs. The percentage of patients who reported skeletal muscles OAEs was 3.6% (n=7). No cases of rhabdomyolysis or myopathy were observed in CHARON. The most common skeletal muscle AEs were arthralgia (6.1%) and myalgia (5.6%). In addition, in 4 patients (2%) blood CK elevations were reported (3 patients with CK >5×ULN and 1 patient with CK >10×ULN).

Renal AEs

One patient (0.5%) was reported to have renal AEs (renal bruit). This patient had no abnormality of creatinine or estimated GFR. The patient's rosuvastatin dose was increased from 5 mg to 10 mg to 20 mg during the treatment phase.

All of these AEs were of mild intensity, except for hepatic pain, which was of moderate intensity. None of these AEs were serious nor did they result in the patient being discontinued from the study. A total

of 3 of these AEs were considered by the investigator to be possibly related to study treatment (hepatic pain and 2 separate events of musculoskeletal stiffness).

Deaths

There were no deaths during this study.

Serious adverse events

Eleven serious adverse events (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) (Table 10). All SAEs were considered by the investigator to be unrelated to study treatment and none resulted in study discontinuation.

Table 10 CHARON - Number and percent of patients with treatment emergent SAEs during the treatment phase by SOC and PT

SOC PT	Treated patients (N=197)
Number of patients with treatment emergent SAEs during the treatment phase	9 (4.6%)
Congenital, familial and genetic disorders	1 (0.5%)
Pectus carinatum	1 (0.5%)
Infections and infestations	3 (1.5%)
Appendicitis	1 (0.5%)
Toxic shock syndrome streptococcal	1 (0.5%)
Viral pericarditis	1 (0.5%)
Injury, poisoning and procedural complications	5 (2.5%)
Femur fracture	1 (0.5%)
Forearm fracture	1 (0.5%)
Lower limb fracture	1 (0.5%)
Multiple fractures	1 (0.5%)
Urinary retention postoperative	1 (0.5%)
Nervous system disorders	1 (0.5%)
Epilepsy	1 (0.5%)

#

Laboratory findings

Introduction

Laboratory findings of interest were glycosylated haemoglobin (HbA1c), certain liver, skeletal-muscle, and kidney-related clinical laboratory test findings (i.e., ALT >3×the ULN on 2 consecutive occasions at least 48 hours apart, CK >10×ULN at any time, urine protein/creatinine ratio above the normal range [defined as a transition from ≤0.2 mg/mg to >0.2 mg/mg], an increase in serum creatinine of ≥50%, and decrease in estimated GFR of ≥25% and ≥50% from baseline.

Hepatic enzyme elevation

No patients had ALT ≥3×ULN or AST ≥3×ULN and total bilirubin ≥2×ULN. As discussed under hepatic events, a 17-year-old Asian male had 2 separate events of hepatic enzyme increased.

CK elevation (skeletal muscle)

There were 3 patients (1.5%) with CK >5×ULN and 1 of these patients (0.5%) had CK >10×ULN during the treatment phase. All these patients had CK values above normal at enrolment.

The patient with the CK>10 x ULN had no associated muscle symptoms; hence, this patient did not meet the rosuvastatin programme criterion for myopathy (CK >10×ULN plus muscle symptoms). The rosuvastatin dose of the patient with the CK > 10 x ULN increased from 5 mg to 10 mg to 20 mg during the treatment phase. Only 1 of the 3 patients with CK elevation in CHARON had any musculoskeletal AE, and the only one seen within a time frame of ±7 months from a confirmed CK value >5×ULN was musculoskeletal stiffness. All patients continued the study as planned, whereof one had normal CK values at completion. In all 3 cases the AEs were considered by the investigator to be unrelated to the study treatment.

Serum creatinine elevation (renal)

After 24 months, there was 1 patient with creatinine increase from baseline ≥50% during the treatment phase. This patient had a normal GFR.

Urine protein-creatinine ratio

The urine protein-creatinine ratio increased >50% from baseline and was >200mg/g (>23 mg/mmol) in 7 patients. In 4 of these patients the urine protein-creatinine ratio value was <200 mg/g (<23 mg/mmol) at the last visit. The protein-creatinine ratio of the other patients were 276 mg/g, 213 mg/g, and 792 mg/g at 24 months and none of these 3 patients had abnormal creatinine or estimated GFR values.

HbA1c elevation

In this study, mean HbA1c actually decreased during the study; mean changes from baseline to 12 months and 24 months were -0.05 (SD 0.167) and -0.03 (SD 0.168), respectively. No individual clinically important changes in HbA1c were observed during the CHARON study. One patient had an HbA1c value outside of reference ranges, but this occurred at baseline. Collection of HbA1c was not included in PLUTO.

Safety in special populations

Tanner stage and sexual maturation

The primary safety outcome variable of the CHARON study was the assessment of growth by measurement of height together with the assessment of secondary characteristics of sexual maturation using Tanner staging at baseline, 12 months and 24 months. No signs of impact of treatment on normal sexual maturation were detected during 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.

Based on the mean z-scores at baseline (0.384), the height distribution of the study population was within the normal range but the average was higher than that of the general population. The percent change was 6% during the 2-year study period, and remained within the normal range for age and sex (mean z-score at 24 months: 0.422). There were no signs of impact of treatment on normal growth in height.

In general, the patients who were not already assessed as fully mature at baseline progressed in their sexual maturation during the study. Approximately, 82% (77 of 94) of the patients in Tanner stages II to IV progressed by at least 1 Tanner stage over the 2 years.

In addition, mean height, weight, and BMI were within normal ranges based on age and sex.

Discontinuation due to adverse events

Discontinuations

There were 3 patients who discontinued study treatment due to a AE: migraine in 1 patient aged 12 years (titrated to 10 mg and back titrated to 5 mg), nausea in 1 patient aged 15 years (on 5 mg titrated to 10 mg, interrupted and titrated to 5 mg), and paraesthesia in 1 patient aged 17 years (on 5 mg). These AEs were of mild intensity, and were non-serious. They were considered by the investigator to be related to study treatment.

Treatment adherence and usability

A secondary outcome variable was the assessment of rosuvastatin treatment adherence during the 2-year study period. In the current study, treatment adherence to rosuvastatin was high (89.6%) during the 2-year period, which indicates that rosuvastatin was well tolerated. The adherence rate was highest in the youngest age group (92.5% in the cohort aged 6 to <10 years, 89.0% in the cohort aged 10 to <14 years, and 87.1% in the cohort aged 14 to <18 years). Based on the high treatment adherence, it can be concluded that the currently marketed tablet formulation of rosuvastatin is acceptable and feasible for use in patients aged 6 to <18 years.

Post marketing experience

A comprehensive search of the MAH's safety database, which contains AEs from clinical studies as well as events reported from spontaneous sources such as healthcare professionals, Regulatory Authorities, literature, consumers, and others, was performed.

Of the 248 adverse events reported in paediatric patients on rosuvastatin, 187 were non-serious and 61 were serious. Most of the reports were in the SOC categories 'Injury, poisoning and procedural complications' (134 reports), 'Congenital, familial and genetic disorders' (21 reports) and 'Surgical and medical procedures' (20 reports) but most of these reports were related to off-label use. Otherwise, the reported events were generally spread amongst the preferred terms, and the types of events could be expected for children and adolescents or patients with HeFH.

2.5.2. Discussion on clinical safety

One objective of this study was to demonstrate the 2-year safety of rosuvastatin in children and adolescents, and especially in the children aged 6 to <10 years who had not been studied previously. Safety was evaluated by collecting information on AEs and laboratory changes, and measuring growth and development by z-scores and Tanner staging. No major deviations were observed in the growth pattern when the study population was compared to the general population.

No unexpected safety issue has been identified in the 2-year safety study. Although TEAEs were reported in 87% of the patients, mainly nasopharyngitis (44.2%), headache (23.4%), and influenza (10.2%), treatment related adverse events occurred in only 14.7% of the patients. These were mostly gastrointestinal adverse events. Treatment related adverse events occurred at the lowest rate in the youngest age group.

Another objective of this study was to assess the suitability of the tablet formulation for the youngest age group. Although the oral tablet formulation was originally designed for adults, the children and adolescents taking part in this study maintained high (89.6%) treatment adherence during the 2-year

period. This indicates that rosuvastatin was well tolerated and that the currently marketed tablet formulation of rosuvastatin is acceptable to use in patients aged 6 to <18 years.

Hepatic, renal and muscular events were assessed as events of special interest. Results on these events were reassuring. They were all of mild intensity, except for one hepatic pain AE, which was considered to be of moderate intensity. Although 10 events (2 hepatic, 7 muscular, 1 renal) of special interest were reported, only 3 were considered by the investigator to be possibly related to study treatment (hepatic pain and 2 separate events of musculoskeletal stiffness). Additionally, none of these AEs was serious nor did it result in the patient being discontinued from the study.

Laboratory evaluation of specific AEs was in line with these findings. Hepatic enzyme elevations were rare; only one patient demonstrated elevated ALT and AST at 2 time points and no patients with Hy's law were observed. For all patients with CK elevations, the events were transient and considered acceptable as all of these patients continued treatment and completed the study as planned. A single 16-year old male patient had CK levels>5 ULN with musculoskeletal symptoms (musculoskeletal stiffness), but did not meet myopathy criteria and could be maintained on the lowest 5 mg rosuvastatin dose throughout the study, although dose had to be reduced. Proteinuria was observed in a low number of patients, but there was no evidence of compromised renal function in any patient and therefore any association with the treatment of rosuvastatin cannot be concluded. No diabetogenic effect was observed.

Although eleven serious adverse events were reported by 9 patients, these were all considered to be unrelated to study treatment and none resulted in discontinuation from the study. Furthermore, no deaths occurred during this study.

Overall, rosuvastatin was well tolerated with only 3 patients discontinuing study treatment due to an AE: migraine in 1 patient aged 12 years, nausea in 1 patient aged 15 years, and paraesthesia in 1 patient aged 17 years, which were considered to be treatment related. In addition, for only 11 patients (5.6%) the dose of rosuvastatin was reduced or temporarily/permanently discontinued during the study due to an adverse event (n=1 in the 6-<10 age group, n=3 in the 10-<14 age group and n=7 in the 14-<18 age group; 8 were related to study medication), and lowest in the youngest age group.

The safety profile of rosuvastatin treatment in the CHARON study is in line with safety profile observed in the PLUTO study.

Because cholesterol is a key component of gonadal steroids (sex hormones), it was considered important to demonstrate that rosuvastatin treatment did not adversely affect sexual development. The safety in the previous PLUTO study has only be assessed during 1 year of treatment. In the CHARON study, rosuvastatin treatment in paediatric patients for 2 years seemed not to affect sexual development, growth and weight.

2.5.3. Conclusions on clinical safety

The safety profile of rosuvastatin treatment in the CHARON study confirmed the safety profile in paediatric patients previously established by the PLUTO study and extents these findings to a population in the lower age group of 6 to <10 years of age. Rosuvastatin was found to be well tolerated in paediatric patients over a 2 year treatment period, and the tablet formulation is suitable for these patients. Furthermore, the 2 year treatment data of CHARON provides additional reassurance on a lack of effect of rosuvastatin treatment on growth and maturation.

2.6. Risk management plan

A consolidated version of a Risk Management Plan (RMP) was submitted for rosuvastatin.

No additional pharmacovigilance activities or risk minimisation measures are required beyond those included in the product information. However, it was agreed that off-label use in patients below the age of 6 should be closely monitored.

Amendments were introduced to several modules of the RMP to reflect the updated information on the paediatric population. An updated RMP will be submitted to National Competent Authorities to reflect these agreed amendments.

2.7. Update of the Product information

Further to the assessment of all available data, the indication 'treatment of hypercholesterolaemia' within the section 'Therapeutic indications' was updated as follows:

Treatment of hypercholesterolaemia

*Adults, adolescents and children aged **6 years** or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.*

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

In addition, the paediatric information in the sections 'Posology and method of administration', Special warnings and precautions for use', 'Pharmacodynamic properties' and 'Pharmacokinetic properties' of the SmPC has been updated to reflect the latest data available from the paediatric studies.

The Package Leaflet has been updated accordingly.

2.8. Significance of paediatric studies

In the light of the EC's Communication 2008/C 243/09, the CHMP is of the opinion that studies PLUTO and CHARON, which are contained in the agreed Paediatric Investigation Plan, which is completed, and in the case of PLUTO has been completed after 26 January 2007, are considered significant *as per* article 45(3) of Regulation (EC) No 1901/2006.

PLUTO is a double-blind, randomised, multi-centre, placebo-controlled study to evaluate safety and efficacy in children aged 10 to 17 years with heterozygous familial hypercholesterolemia. CHARON is a pharmacokinetic study considered to provide meaningful data on the pharmacokinetics, efficacy, tolerability and long-term safety of rosuvastatin in children aged 6 to 17 years with heterozygous familial hypercholesterolemia.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the one pivotal open-label single-arm study (CHARON) conducted to demonstrate PK, efficacy, tolerability and long term safety study in children with HeFH from 6 to <18 years of age, a significant

reduction of LDL-C of approximately 40% (from 6.1 mmol/L to 3.8 mmol/L, p<0.001 for all 3 age groups) was observed after 3 months of treatment, with a slightly smaller reduction for the highest 14-18 age group (35%).

Efficacy was maintained after 12 months (3.3 mmol/L) and after 24 months of treatment (3.5 mmol/L), a mean percent reduction of -43.67 and -42.88 (p<0.001), respectively.

Furthermore, after 24 months of treatment, considerable number of patients achieved the LDL-C goal of < 110 mg/dL (2.8 mmol/L) with 37.5 % in the 6 to <10 age group, 45.8% in the 10 to <14 age group, and 27.9% in the 14 to <18 age group.

The primary data of LDL-C reduction are supported by significant beneficial changes for secondary endpoints HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL-C/HDL-C, ApoB, and ApoB/ApoA-1.

A trend for slowing of intima media thickening (cIMT) was observed within each age category, although the lowest effect was observed for the category of 10-14 years of age.

Similar efficacy has been demonstrated for CHARON study data compared to data from the PLUTO trial with the 5 mg dose during 3 months of treatment.

The PK of rosuvastatin in children and adolescents is predictable with respect to both dose and time. The relative impact of the increased accumulation factor is small due to the dose titration scheme and dose capping, and is not viewed to be clinically meaningful. In addition, the demographic variables, weight, age and gender do not appear to provide clinically meaningful changes in steady-state exposure.

Uncertainty in the knowledge about the beneficial effects

Although LDL-C is considered a surrogate to establish CV risk reduction in the adult population, no data are available on whether LDL-C reduction in childhood will reduce hypercholesterolemia in adulthood and whether CV risk is subsequently reduced.

The CHARON study was a single-arm, whereas a placebo-controlled study might have been preferable. However, taken into consideration the 2-year study duration and ethical principles with studies in the paediatric population, the use of a single-study seems appropriate. Also comparison of data has been made with the PLUTO study findings. The change in LDL-C from baseline to 3 months for the rosuvastatin 5 mg dose for all patients aged 10-<18 years in CHARON was comparable to the LDL-C change from baseline for the patients aged 10-17 years in PLUTO, which provides reassurance to the effect observed in this study.

Although inclusion criteria were acceptable, further reassurance on inclusion of HeFH patients could be obtained by genotyping. It remains unclear how many patients were diagnosed based on genetic testing. It is however unlikely that HoFH patients have been enrolled in the study, as the HoFH phenotype is sufficiently distinctive from HeFH in terms of clinical presentation.

In the CHARON study, there were more patients in the younger age groups reaching the treatment goal at 3 months and throughout the study than in the oldest age group. This may reflect that some of the older (heavier) patients might have needed higher doses than permitted by study protocol. Additionally this may be due to less compliance of teenagers to treatment regimens and lifestyle recommendations.

Risks

Unfavourable effects

An objective of this study was to demonstrate the 2-year safety of rosuvastatin in children and adolescents, and especially in the children aged 6 to <10 years who had not been studied previously.

In general, the safety profile of rosuvastatin treatment in the CHARON study (6-18 years of age) seems in line with safety profile observed in the PLUTO study (10-18 years of age).

Rosuvastatin treatment was associated with an incidence of treatment-emergent related AEs of 14.7%. The most common treatment-emergent related AEs were gastrointestinal disorders (8.1%), musculoskeletal and connective tissue disorders (2.5%).

In addition, specific attention was given to hepatic, skeletal and renal adverse events. Results on these events were reassuring. They were of mild intensity, except for one AE of hepatic pain, which was of moderate intensity. Although 10 events (2 hepatic, 7 muscular, 1 renal) of special interest were reported, only 3 events were considered by the investigator to be possibly related to study treatment (hepatic pain and 2 separate events of musculoskeletal stiffness).

Laboratory evaluation on these specific AEs were in line with these findings. Hepatic enzyme elevations were rare; only one patient demonstrated elevated ALT and AST at 2 time points and no patients meeting Hy's law criteria were observed. For all patients with CK elevations, the events were transient and considered acceptable as all of these patients continued treatment and completed the study as planned, although in some cases dose levels were reduced. Proteinuria was observed in a low number of patients, but there was no evidence of compromised renal function in any patient and therefore any association with the treatment of rosuvastatin cannot be concluded. No diabetogenic effect was observed.

Although eleven serious adverse events were reported by 9 patients, these were all considered to be unrelated to study treatment and none resulted in discontinuation from the study. Furthermore, no deaths occurred during this study.

Overall, rosuvastatin was well tolerated with only 3 patients discontinuing treatment due to an AE.

In the CHARON study, 2 year data of rosuvastatin treatment in paediatric patients did not reveal any impact on the sexual development assessed by Tanner staging and growth.

Overall, rosuvastatin was found to be well tolerated in paediatric patients over a 2-year treatment period, and the tablet formulation is suitable for these patients.

Uncertainty in the knowledge about the unfavourable effects

Safety was assessed in a single arm open-label study, so no comparison to placebo treated patients is available for the entire 2 years of treatment.

The safety database is limited to 198 patients overall, and 64 patients in the 6-10 years age group.

Although safety follow-up has been extended in comparison to the PLUTO study, it is still limited to 2 years for what is considered a life-long treatment.

Even though 2 year treatment with rosuvastatin did not reveal any impact on the sexual maturation and growth, longer-term detrimental effects of rosuvastatin treatment in these children have not been studied, but these appear unlikely to occur.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Elevated LDL-C is a well-established risk factor for CVD. In adults, LDL-C reduction, especially with statins, has firmly demonstrated to reduce CV risk and is therefore accepted as a surrogate marker of clinical outcome. As a direct evaluation of lipid lowering treatment effects on CV outcome – expected to occur mostly in (early) adulthood - is unfeasible, LDL-C is still considered the most appropriate marker to assess beneficial effects in children. The chosen primary endpoint of LDL-C reduction is therefore considered appropriate for assessing the efficacy of rosuvastatin, as also outlined in the *Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/494506/2012).*

With regard to this endpoint, rosuvastatin demonstrated clinically significant reductions in LDL-C levels in patients aged 6-< 18 years with HeFH (40% reduction), which were maintained during 2 years with a slightly better effect size in the 6-10 year old patients compared to those patients who were 10-18 years old. This was similar to what has been observed in the placebo-controlled PLUTO study with the lowest 5 mg dose during the first 3 months in patients aged 10-< 18 years.

In the CHARON study, cIMT analyses were performed in patients and healthy siblings, who were included as a reference group. A trend for slowing of cIMT in the treated HeFH patients was observed. However these data should be interpreted with caution as cIMT is not considered to be an established surrogate marker for clinical outcome, patients had noticeable higher baseline values (as can be expected) and comparison was made with healthy subjects (without accelerated progression of CV disease) rather than patients.

In general, the safety profile of rosuvastatin observed during the 2 years of open-label treatment was as expected. Treatment related adverse events occurred in 14.7% of the patients and most of these were gastrointestinal adverse events. Discontinuation rate due to adverse events was low. Furthermore, specific AEs known to be associated with statins (hepatic, renal, musculoskeletal) occurred infrequently and were not severe, nor accompanied by important clinical laboratory findings. All patients who experienced these events continued rosuvastatin treatment, albeit in some cases at lower dose levels.

In this study, treatment with rosuvastatin did neither affect sexual development nor growth, which can be considered reassuring.

Benefit-risk balance

The beneficial effect of rosuvastatin on LDL-cholesterol as demonstrated in CHARON is considered to be clinically relevant for this patient population. The trend observed also towards beneficial effect in cIMT measurements is considered to be supportive.

Rosuvastatin was generally well tolerated and although the number in each group was limited, it can currently be assumed that in general no safety issues emerge within this paediatric population. Dose recommendations are considered acceptable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considered that the benefit-risk balance of Crestor and associated names in '*adults, adolescents and children aged 6 years or older with primary*

hypercholesterolaemia (mixed type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate' is favourable and therefore recommended amendments to the marketing authorisations of the medicinal products referred to in annex I of the Opinion.

Conditions and requirements of the marketing authorisation

Risk management plan (RMP)

An updated version of the Risk Management Plan will be submitted to National Competent Authorities within 3 months of the Commission Decision for this procedure, to reflect the updated information on the paediatric population as agreed by CHMP.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/229/2010 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/229/2010 have been completed after the entry into force of that Regulation.