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

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Primary Objectives * To assess the efficacy of rosuvastatin in paediatric patients with familial hypercholesterolaemia. * To establish long-term safety, tolerability and efficacy of rosuvastatin in paediatric patients with familial...

Ethical review	Approved WMO
Status	Pending
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON36759

Source
ToetsingOnline

Brief title
CHARON (049/193)

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism

Synonym
hypercholesterolaemia

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Farmaceutisch bedrijf: Astra Zeneca

Intervention

Keyword: Children, Crestor, Hypercholesterolaemia, Rosuvastatin

Outcome measures

Primary outcome

Efficacy:

* Percent change from baseline in low-density lipoprotein cholesterol following

3 months, 12 months and 24 months of treatment with rosuvastatin 5 mg, 10 mg or

20 mg.

Safety:

* 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.

Pharmacokinetics:

* Single dose pharmacokinetics of rosuvastatin: Cmax, tmax, and AUC(0-24).

* Population pharmacokinetics of rosuvastatin: CL/F and AUC(0-24) at steady

state.

Secondary outcome

Efficacy:

* Percent change from baseline (Visit 3, Week 0) in HDL-C, total cholesterol,

triglycerides, non-HDL-C, LDL-C/HDL-C, total cholesterol/HDL-C, non-HDL-C/HDL-C, ApoB, ApoB/ApoA-1 and ApoA-1 at 3 months, 12 months and 24 months.

* Assessments of intima and media wall thickness of the carotid arteries by sonography at baseline, 12 and 24 months in at least 180 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 adverse events, including:

* The incidence and severity of adverse events.

* Rate of discontinuations due to adverse events.

* Abnormal serum laboratory values.

Pharmacokinetics:

* Single dose pharmacokinetics of rosuvastatin metabolites: Cmax, tmax, and AUC(0-24).

* Population pharmacokinetics of rosuvastatin: Model dependent.

Compliance:

* Assessment of rosuvastatin treatment adherence, ie, the treatment compliance during the 2-year study period.

Study description

Background summary

Background
Familial hypercholesterolaemia (FH) is a frequent, inherited disorder of lipoprotein metabolism caused by mutations in the low-density lipoprotein (LDL) receptor gene. The prevalence of FH is 1:500 people worldwide. Certain groups (eg, Finnish, Lebanese, Ashkenazi Jewish, Afrikaner, and French Canadian populations) have a higher prevalence. In men with untreated FH, the risk of coronary heart disease (CHD) is approximately 50% by the age of 50 years. In children with FH, the disease is mostly asymptomatic. However, even in the general population, autopsy reports of healthy children show atherosclerotic lesions at a young age. The aggressive nature of vascular disease in young adult FH patients suggests that these atherosclerotic changes begin in early childhood. 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 events in FH.
The recommended therapy for FH children consists of dietary intervention, but the long term efficacy of such therapy in children is very poor. The United States (US) National Cholesterol Education Program (NCEP) recommends drug therapy for children aged >10 years whose low-density lipoprotein cholesterol (LDL-C) remains elevated after dietary therapy (American Academy of Pediatrics, 1992). Bile acid sequestrants have historically been used for lipid lowering, but the lipid-lowering efficacy is modest, and long term compliance remains poor.
Rosuvastatin produces its lipid-modifying effects in 2 ways; it increases the number of hepatic cell surface LDL receptors, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, therefore both VLDL and LDL are reduced.
To date, 3 clinical studies on rosuvastatin involving paediatric patients have been completed (Studies 54, 86 and 87). A pharmacokinetic (PK) study (Study 86) in children and adolescents (aged 10 to 17 years) showed that systematic exposure of rosuvastatin increased with dose following single administration of rosuvastatin from 10 mg to 40 mg to 80 mg in children and adolescents with FH. There were no clinically significant changes from screening in clinical chemistry parameters, urinalysis, vital signs, electrocardiograms (ECGs), or physical findings. Rosuvastatin was well tolerated in doses up to 80 mg for up to 7 days in this patient population. Overall, the clinical pharmacology of rosuvastatin in paediatric patients with FH appears to be similar to that observed in healthy adults.
Study 87 (the PLUTO study), evaluated the efficacy and safety of rosuvastatin once daily (5 mg, 10 mg or 20 mg) compared to placebo. The primary objective of the PLUTO study was to determine the efficacy of once-daily rosuvastatin in reducing LDL-C in children and adolescents aged 10 to less than 18 years with

FH from baseline (Day 0) to the end of the 12 week double-blind treatment period. Secondary study objectives were to further characterise the lipid-lowering effects and the safety of rosuvastatin in the same populations.
The dose range corresponded to a minimum dose that is the lowest recommended adult dose and maximum dose that is half the highest recommended adult dose. This 4-fold range provided a robust assessment of the appropriate dose range in patients from 10 to <18 years of age. The 12 week duration in the double-blind phase was adequate to show efficacy, as the full effect has been shown to be demonstrable at 6 weeks in adults (Marais et al., 2002).
At the end of the double-blind phase, all patients (including those already treated with rosuvastatin) received rosuvastatin. The open-label starting dose of rosuvastatin was to be determined based on whether the dose received during the randomized phase resulted in achievement of an LDL-C target (<2.85 mmol/L). The patients were then to be titrated to their LDL-C target goal of <2.85 mmol/L recommended by the American Academy of Paediatrics Committee on Nutrition (American Academy of Pediatrics, 1992). The dose range from 5 mg/day to a maximum of 20 mg/day was adjusted at specified intervals and at the discretion of the investigator to obtain optimal efficacy and tolerability.
A dose-related reduction in LDL-C levels was observed with reductions ranging from 38% to 50% with the 5 to 20 mg doses of rosuvastatin. The reduction in LDL-C levels with the 20 mg dose in this study was similar to the reduction observed with the 20 mg dose in a previously reported study of adult patients with familial FH (Stein et al, 2003). Rosuvastatin was well tolerated in these young hypercholesterolaemic patients although CK elevation and muscle symptoms following exercise or increased physical activity (which resolved with continued treatment) were observed more frequently in paediatric patients. None of these patients had a SAE and did not have recurrence of marked CK elevations later in the course of rosuvastatin treatment.
The purpose of the current study (D3561C00002) is to establish the efficacy, tolerability and long-term safety, including growth and sexual development, of rosuvastatin in children with a history of FH between the ages of 6 and less than 18 years. Assessments of arterial-wall changes by means of cIMT will be assessed in at least 180 enrolled patients with representative age distribution. In addition, cIMT assessment will be performed in at least 60 enrolled healthy siblings of study participants or of other paediatric patients with FH not participating in the study. The single dose PK of rosuvastatin will be determined in a subset of patients aged from 6 years to less than Tanner Stage II.

Rationale

Familial hypercholesterolaemia is strongly associated with premature atherosclerotic cardiovascular disease but, despite documented evidence for benefit from treatment, a substantial number of patients fail to achieve recommended treatment targets. In general, the reluctance of physicians to use higher doses of statins to achieve therapeutic targets of LDL-C in children and adolescent patients with FH may be partially explained by perceived safety issues, particularly the potential for increases in liver enzymes and adverse muscle side effects. Therefore, the demonstration of a more efficacious and

safe statin may serve to minimize the concerns associated with titrating to higher doses. Use of statins, other than rosuvastatin, at recommended doses for the paediatric population have unfortunately not resulted in acceptable attainment of recommended LDL-C targets. Thus, there is the potential for rosuvastatin to fulfil an unmet need to achieve lipid goals for children and adolescent patients also.

Study objective

Primary Objectives
* To assess the efficacy of rosuvastatin in paediatric patients with familial hypercholesterolaemia.
* To establish long-term safety, tolerability and efficacy of rosuvastatin in paediatric patients with familial hypercholesterolaemia.
* To characterise the pharmacokinetic profile of rosuvastatin in paediatric patients, aged from 6 to less than Tanner Stage II, with familial hypercholesterolaemia.

Secondary Objectives
* To assess carotid artery intima and media wall thickness 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).
* To assess growth and maturation in children or adolescents with familial hypercholesterolaemia who are receiving long-term rosuvastatin treatment.
* 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.

Study design

This is an open-label study assessing the pharmacokinetics, efficacy and long-term safety of rosuvastatin in children and adolescents with familial hypercholesterolaemia.
Statin-naïve patients, including all patients aged 6 to less than 10 years, will qualify for the efficacy and 2-year safety study by meeting all inclusion, exclusion and low-density lipoprotein cholesterol criteria at Visit 1.
Statin-naïve patients will not have to attend Visit 2. Visit 3 will take place approximately 1 week after Visit 1, when low-density lipoprotein cholesterol results are available.

Previously treated patients will qualify for the efficacy and 2-year safety study by meeting all inclusion and exclusion criteria at screening Visits 1 and 2 and by meeting low-density lipoprotein cholesterol criteria at Visit 2.
Potentially eligible patients will have current lipid therapy withdrawn after Visit 1. A minimum of 4 weeks later, low-density lipoprotein cholesterol will

be assessed at Visit 2. Visit 3 (baseline) dosing will take place approximately 1 week after Visit 2, when low-density lipoprotein cholesterol results are available.

Patients aged 6 to less than 10 years of age will not be required to attend screening Visit 2, as they must be statin-naïve. Patients aged 10 to less than 18 who are statin-naïve will not have to attend screening Visit 2. In the case of statin-naivety, Visit 1 low-density lipoprotein cholesterol results will determine whether the patient qualifies.

A total of 12 patients aged from 6 years to less than Tanner Stage II, will be enrolled in the pharmacokinetic portion of the study in conjunction with enrolment in the efficacy and 2-year safety phase. Patients participating in the pharmacokinetic phase must be statin-naïve; consequently they will not be required to attend the second screening visit (Visit 2). These 12 patients will be administered a single dose of 10 mg rosuvastatin at baseline (Visit 3) and assessed over a 24-hour period. After patients have received the single 10 mg dose for pharmacokinetic sampling, they will enter the efficacy and 2-year safety phase, receiving the starting dose of 5 mg rosuvastatin, after the 24-hour pharmacokinetic assessment has been completed. They will follow the remainder of the efficacy and 2 year safety study visits.
All patients will start 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 less than 10 years of age) will be eligible to titrate to treatment goal (low density lipoprotein cholesterol target of <2.85 mmol/L [110 mg/dL]) up to a maximum rosuvastatin dose of 10 mg once daily. However, should the single dose pharmacokinetic assessment results indicate that 5 mg rosuvastatin is the maximum tolerated dose, this lower dose will be the maximum daily dose administered to patients within this age group. If a patient reaches 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 may be allowed. Patients aged 10 to less than 18 years of age will be eligible to titrate to treatment goal (low density lipoprotein cholesterol target of <2.85 mmol/L [110 mg/dL]) up to a maximum rosuvastatin dose of 20 mg daily. Up-titration, to achieve the low density lipoprotein cholesterol target will be performed in 3-month intervals from baseline (ie, the first up titration visit would be Visit 5). If higher doses are not well tolerated, the patients may be down-titrated at the investigator*s discretion. The reason for down titration should be documented in the source documents and in the electronic case report form (eCRF). Patients may be up-titrated, if the low-density lipoprotein cholesterol target has not been met, at the investigator*s discretion.

Intervention

The investigational product for this study is clinically branded rosuvastatin in 5, 10 and 20 mg tablets that are to be taken orally, once daily, either in the morning or in the evening. Daily dosing should be consistent throughout

the study (ie, always in the morning or always in the evening). Study drugs will only be dispensed to patients in accordance with the protocol. Unused products will be accounted for and returned to the designated facility for destruction.

Study burden and risks

The burden for patients will be kept minimal in this study. During 12 visits blood samples will be taken. Additionally a small group of approximately 12 children worldwide between the age of 6 and 10 years will participate in a Pharmacokinetic phase. In this phase on day 1, blood will be taken at 11 set times spread over 24 hours. The child will have to stay in the hospital for the entire day and will get an intravenous (IV) line. Taking blood samples can lead to fainting, bleeding, bruises, discomfort, dizziness, infections and/or pain at the injection site. Applying the IV needle can be painful. There is a small chance that your child will have an allergic reaction to the gel for the cIMT measurement. When making the ECG sticky patches will be placed on the chest, arms and legs. These patches can cause itching or irritation. The assessment of the Tanner stage can be embarrassing for your child. Rosuvastatin frequently causes: headache, muscle pain, asthenia (a general feeling of weakness), constipation, dizziness, nausea and abdominal (stomach) pain.

Contacts

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SE
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SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

For inclusion in the study, patients should fulfil the following criteria:
1. Prior to any study related procedures being performed, provision of written informed consent from a parent/both parents or guardian and statement of assent from the child or adolescent (if required by institutional review board [IRB] or independent ethics committee [IEC] according to local regulations and guidelines). Communication between the investigator, patient/guardian and child/adolescent to confirm understanding and required compliance with the requirements of the study.
2. Male and female children and adolescents (aged 6 to less than 18 years) with FH* 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 cardiovascular disease (CVD), defined as onset of clinical atherosclerotic disease before age 55 in males or age 65 in females at Visit 1.
*FH is 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).
3. Patients aged between 6 and less than 10 years of age must be statin treatment naïve.
4. Negative serum pregnancy test (b-human chorionic gonadotropin analysis [b-HCG]) prior to baseline in females of child-bearing potential.
- Female patients of child-bearing potential must adhere to a pregnancy prevention method (abstinence, chemical or mechanical) during the study.
- Male patients should refrain from fathering a child (including sperm donation) during the study and up to 3 months following last dose.
5. Willing to follow all study procedures including adherence to dietary guidelines, study visits, fasting blood draws and compliance with study treatment regimens.
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, without lipid lowering medication.
*FH is 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).

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:
1. History of statin-inducted myopathy or serious hypersensitivity reaction to other HMG-CoA reductase inhibitors (statins), including rosuvastatin, at Visit 1.
2. Fasting TG * 2.87 mmol/L (254 mg/dL) at Visit 1 for statin-naïve patients and at Visit 2 for patients who were on prior statin treatment.
3. Fasting serum glucose of >9.99 mmol/L (180 mg/dL) or glycosylated haemoglobin (HbA1c) >9% at Visit 1 or patients with a history of diabetic ketoacidosis within the past year.
4. Uncontrolled hypothyroidism defined as thyroid stimulating hormone (TSH) >1.5 times the upper limit of normal (ULN) at Visit 1 (Week *4) or patients whose thyroid replacement therapy was initiated or modified within the last 3 months prior to Visit 3 (Week 0).
5. Current active liver disease or hepatic dysfunction (except a confirmed diagnosis of Gilbert*s disease) as defined as elevations of 1.5 times the ULN for any age in any of the following liver functions test at Visit 1 or Visit 2: ALT, AST, or bilirubin.
6. Serum CK * 3 times ULN (unless explained by exercise) at Visit 1.
7. Estimated glomerular filtration rate (GFR) by Schwartz formula <50 mL/min at Visit 1.
8. * 2+ proteinuria on urine dipstick at Visit 1 or Visit 2 (where applicable).
9. Stage 2 hypertension (systolic and/or diastolic blood pressure [BP] greater than 5 mmHg above the 99th percentile for age, gender and height) at Visit 1 and Visit 2 (where applicable).
10. History of solid organ transplantation at Visit 1.
11. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
12. Previous enrolment in the present study.
13. Participation in a clinical study where an investigational product was ingested during the last 30 days before Visit 3 (Week 0) of the current study.
14. Any acute illness within 2 weeks before the start of the study (Visit 1).
15. Any clinically significant abnormalities in clinical chemistry and haematology or urinalysis results at the discretion of the investigator.
16. Any contraindication from the following: a detailed medical and drug history, a complete physical examination including vital signs, blood chemistry, haematology, coagulation factors and urinalysis.
17. Definite or suspected personal history or family history of adverse drug reactions (ADRs), or hypersensitivity to drugs with a similar chemical structure to rosuvastatin as well as other statins.
18. History or presence of gastrointestinal, hepatic or renal disease or other condition known to interfere with absorption, distribution, metabolism or excretion of drugs.
19. Treatment in the previous 3 months with any drug known to have a well-defined potential for hepatotoxicity (eg, halothane).
20. Treatment with any lipid lowering medications within 4 weeks or less of initial dosing.
21. Clinical judgement by the investigator that the volunteer should not participate in the study.
22. Patients weighing <20 kg (44 lbs).
Healthy siblings should not enter the study if the following exclusion criteria are fulfilled:
1. Participation in a study requiring ingestion of a lipid lowering therapy.

2. Under the care of a specialist if deemed exclusionary per investigator discretion.
Procedures for withdrawal of incorrectly enrolled patients are presented in Section 5.3.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2010
Enrollment:	72
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rosuvastatin
Generic name:	CRESTOR
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-12-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2010

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-016492-29-NL
CCMO	NL30482.018.09