A Randomized, Double-blind, Placebo-controlled, Multi-center, Cross-over Study of Rosuvastatin in Children and Adolescents (aged 6 to <18 years) with Homozygous Familial Hypercholesterolemia (HoFH)

Published: 05-08-2014
Last updated: 21-04-2024

To assess the efficacy of rosuvastatin 20 mg on low-density lipoprotein cholesterol (LDL-C), compared to placebo, after 6 weeks of treatment in pediatric patients with HoFH.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON41938

Source
ToetsingOnline

Brief title
ROS304

Condition

- Lipid metabolism disorders

Synonym
hypercholesterolemia, Metabolism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Efficacy, LDL-C, Placebo, Rosuvastatin

Outcome measures

Primary outcome

LDL-C following 6 weeks of treatment with rosuvastatin 20 mg or placebo

Secondary outcome

- LDL-C following 6 weeks of treatment with rosuvastatin 20 mg or placebo in patients not treated with apheresis

- High-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), non-HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, apolipoprotein B (ApoB), ApoB/apolipoprotein A-1 (ApoA-1) and ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg or placebo

- Change in LDL-C from end of placebo period to 6, 12, and 18 weeks of therapy with rosuvastatin 20 mg

- Rosuvastatin trough concentrations

Study description

Background summary

Homozygous Familial Hypercholesterolemia is an inherited disorder most commonly caused by mutations in the low-density lipoprotein (LDL) receptor gene. The mutations mean that the LDL receptors don*t work properly resulting in high cholesterol in the blood. The onset of all forms of atherosclerotic cardiovascular disease can also be accelerated. The prevalence of HoFH is very

rare, occurring in about 1 in a million people worldwide. At this time no drug is approved for treatment of HoFH in pediatric patients.

Study objective

To assess the efficacy of rosuvastatin 20 mg on low-density lipoprotein cholesterol (LDL-C), compared to placebo, after 6 weeks of treatment in pediatric patients with HoFH.

Study design

D3561C00004 is a randomized, double-blind, cross-over study of rosuvastatin 20 mg once daily (QD) versus placebo QD in children and adolescents (aged from 6 to <18 years) with homozygous familial hypercholesterolemia (HoFH).

The study aims to enroll approximately 25 patients to provide an estimated 20 patients to complete the study.

Patients will qualify for the study by meeting all inclusion and none of the exclusion criteria at screening (Visit 1). Once eligibility is reconfirmed (Visit 2), patients will discontinue all lipid-lowering medication, with the exception of ezetimibe, and will be administered 10 mg rosuvastatin QD in a 4-week dietary lead-in phase. Patients who enter the study taking 20 mg or more of rosuvastatin will be administered rosuvastatin 20 mg in the lead-in phase. Patients who enter the study on ezetimibe therapy will be allowed to continue the medication throughout the entire study. The dose of ezetimibe should remain stable from the start of the lead-in phase (Visit 2) through the end of the efficacy maintenance phase. At the end of the rosuvastatin lead-in phase (Visit 3), patients will be randomized 1:1 to one of two treatment sequences: A or B. Treatment sequence A consists of 6 weeks of treatment with rosuvastatin 20 mg QD followed by 6 weeks of placebo QD. Treatment sequence B consists of 6 weeks of placebo QD followed by 6 weeks of treatment with rosuvastatin 20 mg QD.

Patients who enter the study taking 10 mg or more of rosuvastatin, and who do not require discontinuation of any lipid-lowering medication, will be asked to begin the dietary lead-in at the screening visit. Once eligibility is reconfirmed at the second visit, these patients will be permitted to forego the lead-in phase of the study and may proceed directly to the randomized, cross-over phase of the study.

Blood samples will be drawn at the end of each 6 week period in the cross-over phase (Visit 4 and Visit 5). The randomized, cross-over phase will be followed by a 12-week efficacy maintenance phase, during which all patients will receive rosuvastatin 20 mg QD. Blood samples will be drawn after 6 weeks of the efficacy maintenance phase (Visit 6) and at the end of the 12 week efficacy maintenance phase (Visit 7).

For patients who undergo apheresis, it is optimal to have blood drawn at least 7 days following the last apheresis. Because of the rapid changes that occur in LDL-C levels following apheresis, it is very important to ensure that blood samples taken during the 2 cross-over periods (and during the efficacy maintenance phase) are scheduled to be drawn the same number of days following the last apheresis and at the same time of the day in relation to the last apheresis. If patients are on a regular schedule for apheresis, eg, every 1 or 2 weeks, blood samples should be drawn in association with the apheresis, and must be obtained before (not after) the apheresis procedure.

After the efficacy maintenance phase, patients will have the opportunity to continue treatment in a separate Long Term Extension (LTE) study expected to extend through 2016.

Intervention

At the end of the lead-in phase of rosuvastatin (visit 3), the patients will be randomized 1:1 to one of the two treatment groups: A or B. Treatment group A consists of a treatment of 6 weeks with rosuvastatin 20 mg QD, followed by 6 weeks placebo QD. Treatment group B consists of 6 weeks placebo QD, followed by 6 weeks treatment with rosuvastatine 20 mg QD.

Study burden and risks

Nature and extent of the burden and risks for the patient:
- To read and sign the consent form and the assent form
- Visit the hospital on fixed timepoints
- Not taking certain medications during the study (e.g. prescription medications)
- To fast (no eating and no drinking, only water) for at least 12 hours before each visit
- To follow the fixed study procedures
- Regular collection of blood

Possible side effects of study drug:
Common (*1/100, <1/10) Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain, diabetes mellitus*.
Uncommon (*1/1000, <1/100) Pruritus, rash and urticaria.
Rare (*1/10000, <1/1000) Myopathy (including myositis), hypersensitivity reactions (including angioedema), rhabdomyolysis, pancreatitis.

Risk of the study procedures:
- Blood samples: faintness, inflammation of the vein, pain, bruising or bleeding at the site of the puncture. There's also a slight possibility of infection

- ECG: skin irritation

In order to ensure that the potential side effects are diagnosed by the doctor as early as possible, it is asked to report any muscle pain or weakness the child experiences during the treatment. Especially if the child feels unwell, has a fever or has reddish brown urine.

The patient may, or may not, benefit from participation in this study but information retrieved from this study can be of added value for the medical knowledge in this area and can help to develop a better treatment for people in the future.

Contacts

Public
Astra Zeneca

Pepparedsleden 1
Mölndal 431 83
SE
Scientific
Astra Zeneca

Pepparedsleden 1
Mölndal 431 83
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion 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 [EC] 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 <18 years) with at least 1 of the following criteria:
* Documentation of genetic testing confirming 2 mutated alleles of either the LDL receptor gene locus, ApoB, or PCSK9; and/or
* Documented untreated LDL-C >500 mg/dL (12.9 mmol/L) and triglyceride (TG) <400 mg/dL (4.5 mmol/L) and at least 1 of the following criteria:
o Tendinous and/or cutaneous xanthoma prior to 10 years of age; or
o Documentation of HeFH in both parents by:
* genetic and/or
* clinical criteria;
3. Negative pregnancy test (b-human chorionic gonadotropin analysis) 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 and 3 months following the last dose;
* Male patients should refrain from fathering a child (including sperm donation) during the study and up to 3 months following the last dose; and
4. Willing to follow all study procedures including adherence to dietary guidelines, study visits, fasting blood draws, and compliance with study treatment regimens.

Exclusion criteria

1. History of statin-inducted myopathy or serious hypersensitivity reaction to other HMG-CoA reductase inhibitors (statins), including rosuvastatin, at Visit 1;
2. Fasting serum glucose of >9.99 mmol/L (180 mg/dL) or glycosylated hemoglobin >9% at Visit 1 or patients with a history of diabetic ketoacidosis within the past year;
3. Uncontrolled hypothyroidism defined as thyroid stimulating hormone (TSH) >1.5 times the upper limit of normal (ULN) at Visit 1 or patients whose thyroid replacement therapy was initiated or modified within the last 3 months prior to Visit 2;
4. Current active liver disease or hepatic dysfunction (except a confirmed diagnosis of Gilbert*s disease) as defined as ALT or AST elevations of 2 times the ULN for any age, or bilirubin elevation of 1.5 times the ULN for any age at Visit 1;
5. Serum CK *3 times ULN (unless explained by exercise) at Visit 1. If CK *3 times ULN is assessed to be explained by exercise, retesting may be performed at Visit 2;

6. Estimated glomerular filtration rate by Schwartz formula <50 mL/min at Visit 1;
7. A *2+ proteinuria on urine dipstick at Visit 1;
8. Stage 2 hypertension (systolic and/or diastolic blood pressure greater than 5 mmHg above the 99th percentile for age, gender, and height) at Visit 1;
9. History of solid organ transplantation at Visit 1;
10. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and representatives and/or staff at the study site);
11. Previous randomization in the present study;
12. Participation in a clinical study where an investigational product was ingested during the last 30 days before Visit 2 of the current study;
13. Any clinically significant acute illness within 2 weeks before the start of the study (Visit 1);
14. Any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results at the discretion of the Investigator;
15. Any contraindication from the following: a detailed medical and drug history, a complete physical examination including vital signs, blood chemistry, hematology, coagulation factors, and urinalysis;
16. Definite or suspected personal history or family history of clinically significant adverse drug reactions (ADRs), or hypersensitivity to drugs with a similar chemical structure to rosuvastatin as well as other statins;
17. History or presence of gastrointestinal, hepatic, or renal disease or other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs;
18. Treatment in the previous 3 months with any drug known to have a well-defined potential for hepatotoxicity (eg, halothane);
19. Clinical judgement by the Investigator that the patient should not participate in the study;
20. Patients weighing <20 kg (44 lbs);
21. Pregnancy or currently lactating; or
22. Patients planning to start apheresis during the study period.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-11-2014
Enrollment:	7
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	05-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	16-09-2015
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	EUCTR2014-000972-24-NL
CCMO	NL49434.018.14

Study results

Date completed:	11-06-2015
Actual enrolment:	4