A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, 12-Week Study of Pitavastatin in High-Risk Hyperlipidaemia in Childhood P/266/2011, P267/2011, P268/2011

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON37577

Source
ToetsingOnline

Brief title
PASCAL 401

Condition

- Other condition

Synonym
high cholesterol, Hyperlipidaemia

Health condition

hyperlipidemie

Research involving
Human

Sponsors and support

Primary sponsor: Kowa Research Europe
Source(s) of monetary or material Support: KOWA Research Europe;Ltd.

Intervention

Keyword: childhood, high-risk, hyperlipideamia, pitavastatin

Outcome measures

Primary outcome

The primary efficacy endpoint of this study is the percent change in LDL-C from

baseline to Week 12 endpoint.

Secondary outcome

The secondary efficacy endpoints of this study are the following:

- Percent change in LDL-C from baseline over 12 weeks of treatment (Week 4,

Week 8, and Week 12);

- Percentages of patients who achieve AHA minimal (130 mg/dL [3.4 mmol/L]) and

ideal (110 mg/dL [2.8 mmol/L]) LDL-C targets over 12 weeks of treatment;

- Percent changes in HDL-C, non-high-density lipoprotein cholesterol

(non-HDL-C), TC, TG, apolipoprotein A1 (Apo A1), and Apo B from baseline over

12 weeks of treatment; and

- Changes in TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and Apo B:Apo A1 ratio

from baseline over 12 weeks of treatment.

Study description

Background summary

Elevated serum cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), and its associated apolipoprotein B (Apo B), constitute a risk factor for the development of coronary heart disease (CHD). It is now well established that the atherosclerotic process begins in childhood. Based on the data in adults demonstrating reduced incidence of CHD with statin-induced LDL-C reduction, it is recommended that children considered at high risk for the development of premature CHD should start drug therapy during childhood. Statins, or 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors, are considered the drug of choice among adult patients with elevated LDL-C and therefore are often considered for use in the paediatric population.
The efficacy and safety data in the paediatric population are not as extensive as in the adult population, but statins have been shown to be an effective option for the management of childhood hypercholesterolaemia.
Pitavastatin calcium (pitavastatin) is a synthetic HMG-CoA reductase inhibitor currently approved for marketing in several countries. Pitavastatin is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), LDL-C, triglycerides (TG), and Apo B as well as to increase high-density lipoprotein cholesterol (HDL-C). Overall, pitavastatin has been shown to be safe and well tolerated in the adult population. Although the safety and efficacy of pitavastatin are well documented in adults, the use of this drug has not been studied in a paediatric population. Therefore, the goal of this study is to evaluate the safety and efficacy of pitavastatin in children or adolescent patients with high-risk hyperlipidaemia. The results of this study will complement the existing body of knowledge obtained from clinical studies of pitavastatin in adults and will be used to support broadening the indication of pitavastatin to allow for use in children and adolescents.

Study objective

The primary objective of this study is to compare the efficacy of pitavastatin 1 mg once daily (QD), 2 mg QD, and 4 mg QD (after up-titration) to placebo in terms of the percentage reduction in LDL-C in children or adolescent patients with high-risk hyperlipidaemia at steady state (Week 12).
The secondary objectives of this study are the following:
- To compare the efficacy of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD to placebo in terms of the change or percent change in secondary lipid parameters in children and adolescent patients with high-risk hyperlipidaemia over 12 weeks;
- To measure PK parameters at each dose level; and
- To compare the safety and tolerability of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD to placebo in children and adolescent patients with high-risk hyperlipidaemia over 12 weeks.

Study design

This is a double-blind, randomised, placebo-controlled, parallel-group study in children and adolescent patients with high-risk hyperlipidaemia, excluding patients with homozygous Familial Hypercholesterolaemia.
A Data Monitoring Committee (DMC) will be set up in accordance with EMEA guidelines to oversee the safety of the participants of the study
Patients who use lipid lowering medications will undergo a 5-week wash-out period.
After the screening visit (visit 1 or 2 depending on if a wash-out period is necessary) randomization will take place. Recruitment will commence into the pitavastatin 1 mg QD , Pitavastatin 2 mg QD and Placebo treatment groups initially, until sufficient data has been collected to reassure the DMC that the pitavastatin 4 mg QD (or placebo) dose group should be opened to recruitment. Within each dose group patients will be assigned to Pitavastatin and placebo in a 3:1 ratio.
The participants will receive treatment for 12 weeks. Patients who complete the 12-week treatment period will be eligible to enter a 52-week open-label extension study (Study NK-104-4.02EU) to examine the long term tolerance of pitavastatin.
The goal is to randomize 96 patients, including 40 patients in The Netherlands.

Intervention

Pitavastatin 1 mg QD (1mg pitavastatin) or placebo (matching placebo for 1 mg pitavastatin) for 12 weeks. OR
Pitavastatin 2 mg QD (2 mg pitavastatin tablet) or placebo (matching placebo for 2 mg pitavastatin) for 12 weeks. OR
Pitavastatin 4 mg QD (2 mg pitavastatin tablet for 4 weeks, 4 mg pitavastatin tablet for 8 weeks) OR
placebo (matching placebo for 2 mg pitavastatin for 4 weeks, matching placebo for 4 mg pitavastatin for 8 weeks).

To be taken orally, once-daily, with or without food, in the morning.

Study burden and risks

The adverse events that have been reported as 'common' in the current version of the Investigator Brochure are:
Headache, Dizziness, Constipation, Diarrhoea, Dyspepsia, Nausea, Myalgia, Arthralgia, changes in liverfunction test.

The patients will have 6 study visits, for which they will have to visit the hospital. The following procedures will be performed:
- Medical history check (verbal) (1x)
- Physical examination (2x)

- ECG (2x)
- vital signs (incl height and weight) (5x)
- blood sampling:
Screening visit 1: 20.0 mL
Visit 3: 20.0 mL (without genotyping sample)
Visit 4: 12.0 mL
Visit 5: 12.0 mL (without PK)
Visit 6: 20.0 mL (without PK)
Total volume would therefore be: 84.0 mL
To be added with:
12.0 mL for washout patients that require visit 2
2 x 6.0 mL if a genetic sample is required
2 x 3.0 mL (trough + 1h post dose) for PK sample at visit
5 OR 6
3.0 mL per plasma myoglobin sample that will be taken as
needed

- urine sampling (for pregnancy test, among other things) (6x for girls, 3x
for boys)
- diet assessment (6x)
- administration of study drug: daily for 12 weeks

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female *6 years of age and <17 years of age at randomisation;;2. Have fasting LDL-C levels *160 mg/dL (4.1 mmol/L) or LDL-C *130 mg/dL (3.4 mmol/L) if any of the following additional risk factors are present:;* Male;;* A family history of premature cardiovascular disease defined as a myocardial infarction before age 50 in a second-degree relative or before age 60 in a first-degree relative with at least 1 relative (parent, grandparent, or sibling) affected;;* Presence of low HDL-C (<45 mg/dL) or high TG (>150 mg/dL);;* Presence of high lipoprotein(a) (>75 nmol/L);;09 December 2011 vii12;* Presence of type 2 diabetes mellitus diagnosed by treating physician according to current guidances; or;* Presence of hypertension defined as systolic and diastolic blood pressures above the 95th percentile for age and size;;3. Have not taken any lipid-lowering medications in the 5 weeks prior to screening or in the 4 weeks prior to the lipid qualifying visit at Week -1;;4. Have been adherent to an appropriate diet for at least 8 weeks;;5. Females who are post-menarche must not be pregnant or breast feeding and, if sexually active, must be using a reliable form of contraception; and;6. Written informed consent and assent (if necessary) obtained as required per local regulations.

Exclusion criteria

1. Unable or unwilling to take study drug;;2. Fasting TG >400 mg/dL (4.5 mmol/L);;3. Homozygous familial hypercholesterolaemia;;4. Other secondary causes of hyperlipidaemia (eg, hypothyroidism, human immunodeficiency virus infection, systemic lupus erythematosus, organ transplantation, previous malignancy, nephrotic syndrome, glycogen storage disease);;5. Previous history of statin intolerance, adverse effects with other statin use, or hypersensitivity to any components of the study drug;;6. Need for non-statin lipid-lowering medications;;7. Apheresis therapy;;8. Use of any concomitant medication which may interfere with the objectives of the study;;9. Type 1 diabetes mellitus;;10. Poorly controlled type 2 diabetes mellitus defined as haemoglobin A1c >9.0% at screening;;11. Severe renal impairment defined as serum creatinine >2.0 mg/dL at screening;;12. Uncontrolled hypertension;;13. Untreated thyroid disease;;14. Severe hepatic impairment, active liver disease, or persistent elevation of alanine transaminase or aspartate transaminase >3 × the upper limit of normal (ULN);;15. Active muscle disease or creatine kinase >3 × ULN (unless explained by exercise);;16. Screening laboratory values within the following age/gender appropriate reference ranges as assessed by the central laboratory:;* Haemoglobin <10 g/dL for males or <9 g/dL for females or;* Alkaline phosphatase >2 × ULN for age;;17. Any other

laboratory abnormality that could compromise patient safety because of study participation;;18. Malignancy during the past 5 years;;19. Current smoker or history of drug or alcohol abuse;;20. Hospitalisation for any cause within 30 days prior to the administration of study drug;;21. History of major surgery in the 3 months prior to screening;;22. Any medical condition which, in the judgment of the Investigator, would jeopardize the evaluation of safety and/or constitute a significant safety risk to the patient; or;23. Participation in another clinical study involving an investigational drug during the course of this study or within 30 days prior to signing the informed consent/assent form for this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-04-2012
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Livazo, Vezepra, Alipza
Generic name:	pitavastatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2012
Application type:	First submission
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	EUCTR2011-004964-32-NL
CCMO	NL39387.018.12

Study results

Date completed:	08-03-2013
Actual enrolment:	40

Summary results
Trial is onging in other countries