A 52-Week Open-Label Extension and Safety Study of Pitavastatin in High-Risk Hyperlipidaemia in Childhood (NK-104-4.02EU).

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The primary objective of this study is to assess the safety of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD in children or adolescent patients with high-risk hyperlipidaemia over a period of 52 weeks.The secondary objective of this study is to assess...

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

Summary

ID

NL-OMON37642

Source
ToetsingOnline

Brief title
PASCAL402

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, pitavastatine

Outcome measures

Primary outcome

The safety endpoints of this study are the following:

- Adverse events;

- Clinical laboratory parameters (including assessment of renal function and

adrenal, gonadal, and pituitary hormones);

- Vital signs;

- Electrocardiogram (ECG) parameters; and

- Physical examinations (including Tanner staging).

Secondary outcome

The efficacy endpoints of this study are the following:

- Percent change in LDL-C from baseline over 52 weeks of treatment;

- 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 52 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

52 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 52 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 assess the safety of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD in children or adolescent patients with high-risk hyperlipidaemia over a period of 52 weeks.

The secondary objective of this study is to assess the persistence of efficacy with pitavastatin over 52 weeks by measuring lipid parameters and attainment of AHA minimal (130 mg/dL [3.4 mmol/L]) and ideal (110 mg/dL [2.8 mmol/L]) targets

for LDL-C.

Study design

This is a 52-week open-label safety study in children and adolescent patients with high-risk hyperlipidaemia, excluding patients with homozygous familial hypercholesterolaemia. This study will include patients who have completed the 12-week, double-blind study NK-104-4.01EU, but will also include eligible children and adolescents who were not enrolled in the double-blind study. Patients who were not enrolled in the double-blind study will participate in an up to 5-week screening/washout period prior to entering the 52-week treatment period.
All patients enrolled in the study will be assigned to treatment with pitavastatin 1 mg QD. During the study, the dose of pitavastatin may be up-titrated (to 2 mg at week 4 and to 4 mg at week 8) in an effort to achieve an optimum LDL-C treatment target of <110 mg/dL (2.8 mmol/L). The decision to up-titrate the dose of pitavastatin will be based on LDL-C values at Week 4 and Week 8. Patients will remain on their highest titrated dose of pitavastatin for the remainder of the study.
The goal is to randomize 120 patients, including 40 patients in The Netherlands.

Intervention

All patients entering the study will receive pitavastatin 1 mg QD and may have their dose up-titrated to 2 mg QD or 4 mg QD based on their LDL-C values at Week 4 and Week 8.

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 8 or 10 study visits, for which they will have to visit the hospital. The following procedures will be performed:
- Medical history check (verbal) (1x)
- Physical examination (3x)
- ECG (2x)
- vital signs (incl height and weight) (8x)
-urine sampling (for pregnancy test, among other things) (8x or 10x for girls, 5x for boys)
- diet assessment (8x or 10x)
- assess mentrual cycle (8x or 10x):
- administration of study drug: daily for 15 weeks

- BLOOD SAMPLES:
Screening visit : 20.0 mL
Lipid QV: 12.0 mL
Visit 1: 20.0 mL (without genotyping sample)
Visit 2: 12.0 mL
Visit 3: 16.5 mL
Visit 4: 16.5 mL
Visit 5: 20.0 mL
Visit 6: 20.0 mL
Visit 7: 20.0 mL
Visit 8: 20.0 mL
Total volume would differ for rollover patients, wash-out patients and patients with elevated LDL-C at visits 2 and 3.
For safety samples it would be maximum: 177.0 mL (washout period, visit 1, 3 and 4 included)
To be added with:
- 2 x 6.0 mL if a genetic sample is required
- 3.0 mL per plasma myoglobin sample that will be taken as needed

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 Visit 1;;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);;* 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
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-07-2012
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:	24-02-2012

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2013
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	EUCTR2011-004983-32-NL
CCMO	NL39388.018.12