A Placebo-controlled, Double-blind, Randomised, Parallel-group, Long-term Phase III Trial Assessing the Safety and Efficacy of 50 microgram and 100 mircrogram/day of eprotirome in Patients with Heterozygous Familial Hypercholesterolaemia who are on Optimal Standard of Care

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

Summary

ID

NL-OMON36068

Source
ToetsingOnline

Brief title
KBT009/ Akka study

Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
familial hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Karo Bio AB
Source(s) of monetary or material Support: Karo Bio AB te Novum in Zweden

Intervention

Keyword: eprotirome, Familial hypercholesterolaemia, LDL-C

Outcome measures

Primary outcome

verandering in percentage van LDL-C tussen baseline en week 12

Secondary outcome

Percent change in LDL-C from baseline to Week 28, Week 52, Week 76, and Week

100;

percent change in other lipids and C-reactive protein;

the systemic exposure to the nitrated reaction product KB42899 ;

the effects on skeleton by bone mineral density;

the cardiovascular safety;

knee-joint function and symptoms;

the long-term safety and tolerability of eprotirome.

Study description

Background summary

There is an urgent need for new treatments for artherosclerosis. Although the death rates from artherosclerosis have decreased, the risk of mortality remains high.
There are patient groups, such as patients with familial hypercholesterolaemia (FH), in which there is a medical need for further treatments in addition to statin therapy. Since patients with HeFH have abnormally elevated LDL-C levels from birth, they have a high cumulative LDL-C exposure (cholesterol burden). Without treatment, the average age of onset of coronary heart disease is 40 to 45 years in men and 50 to 55 years in women while development of coronary atherosclerosis typically begins between 20 and 30 years of age.

Other available lipid-lowering therapies include ezetimibe, niacin, fibrates, and bile acid sequestrants, but all have limitations in terms of insufficient efficacy and/or poor tolerance in HeFH patients.
Karo Bio has chosen to develop eprotirome for HeFH patients with a high risk for CAD, where the unmet medical need is high and the potential benefit of cardiovascular risk reduction is substantial. Dyslipidaemia is built on the well known physiological role of thyroid hormones in lipid metabolism, an effect mainly exerted in the liver. Thyroid hormone lowers levels of serum LDL-C, TG and Lp(a) and has other potentially favourable actions on lipoprotein metabolism. Excess thyroid hormone is, however, associated with unwanted effects on the heart, bone and skeletal muscle. Consequently, the use of a thyroid hormone receptor analogue for the treatment of dyslipidaemia is only possible if the effects can be restricted to the liver and disturbance of thyroid hormone receptor mediated effects on organs other than the liver can be avoided. Thyromimetics with an adequate therapeutic window provide new opportunities for improved and targeted therapy against dyslipidaemia and atherosclerotic disease. Eprotirome is a thyroid hormone analogue that, as compared with triiodothyronine (T3), has minimal uptake in non-hepatic tissues. Eprotirome thus reduces LDL-cholesterol and reduces the cardiovascular risk.

Study objective

The primary objective of this study is to compare the efficacy of eprotirome 50 microgram and eprotirome 100 micorgram versus placebo in terms of the percent change in LDL-C from baseline to Week 12 in HeFH patients with CAD, or who are at high risk for CAD, and who are on optimal standard of care consisting of a statin with or without ezetimibe.

Study design

This is a multi-centre, randomised, double-blind, parallel-group study consisting of an up to 10-week run-in period, 100-week randomised treatment period (consisting of 52-76 weeks of double-blind treatment and 24-48 weeks of open-label treatment), and 12-week post-treatment follow-up period.
At randomisation (Visit 3 [Week 0]), patients will be randomised in a 1:1:1

ratio to placebo, eprotirome 50 microgram, or eprotirome 100 microgram g. During the initial 12 weeks of the double-blind treatment, patients will remain on their stable lipid-lowering treatment regimen; no other lipid-modifying agents are permitted to be used during the initial 12 weeks of randomised treatment.
Once all patients complete Visit 10 (Week 52) and 300 patients complete Visit 12 (Week 76), the main analysis of efficacy and safety will be performed. At this point, treatment assignment will be unblinded and all lipid values will be made available to the investigators. Patients will then continue with their randomised study medication in an open-label treatment period of up to 48 weeks. Patients receiving placebo will be permitted to add other lipid-lowering agents if deemed necessary by the investigator. Patients receiving eprotirome will be permitted to adjust statin dose, add ezetimibe, or add prescription fish oil products only.

Intervention

Intervention consists of: eprotirome 50 microgram per day, 100 microgram per day or placebo.

Study burden and risks

This study will last for 112 weeks and has 4 periods: 1) screening period; 2) double-blind treatment period; 3) unblinded extension period including a final visit; followed by 4) follow-up period. De screening consists of 2 visits followed by the double blind extension of a year with 8 visits. Hereafter there will be a maximum of 4 visits, dependent on when the patiënt starts, in the open label period of 1 year. The patient will then stop taking study drug and there is a follow-up visit 12 weeks later.
During each visit a fasting blood sample will be taken, vital signs and an ECG. (visit 7 isn*t fasting). At half of the visits patients should provide urine and women of childbearing potential should provide urine almost every visit. There are 7 physical exams. The first 300 patients will get 4 Dexa scans, 5 cardiac-echo*s and extra blood tests. 20 patients will be studied for 24 hours pharmacokinetics. 30 patients will have to carry a holter

So far 445 subjects have been treated with eprotirome, 303 of which have been treated for 10-12 weeks. The most frequent adverse events seen in these studies were respiratory tract infections, headache, musculoskeletal and gastrointestinal complaints These were mostly mild and short lasting. Eprotirome is similar to your body*s own thyroid hormones, but it differs by only having its effects in the liver, hence leaving the thyroid hormone balance in the rest of the body unchanged. No disturbances in the thyroid hormone balance have been seen during the clinical studies performed with eprotirome. However, in long term treatment it is not known if the thyroid hormone balance is maintained. If such effects would occur, they will be easily monitored and

reversible.
Eprotirome works in the liver, and similar to other lipid lowering drugs, eprotirome may increase your liver enzyme levels in the blood. As with any experimental drug, there may be side effects that are unknown and that could occur when the drug is taken alone or in combination with other drugs.
The effect of eprotirome on pregnancy is not known at this time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Patients with confirmed HeFH who are equal or above 18 years of age at screening.
2) Patients must also have:
Presence of clinical atherosclerotic disease that confers high risk for CAD events together with an LDL-C above 2 mmol/L at Visit 2; or

Presence of 2 or more risk factors for CVD (other than the HeFH diagnosis) together with an LDL-C above 2.5 mmol/L at Visit 2:
3) Patients should be on an optimal standard of care, defined as being on a stable dose of statin with or without ezetimibe for at least 8 weeks prior to randomisation. If lower doses of rosuvastatin, atorvastatin, or simvastatin or any dose of fluvastatin or pravastatin are used the reasons must be clearly documented.
4) Patients must understand the study procedures and agree to participate in the study by giving written informed consent at Visit 1; and
5) Women must not be pregnant or lactating. Women of childbearing potential must use a medically acceptable form of contraception at least 4 weeks prior to the start of the study and for at least 4 weeks after the patient*s last study visit. Subjects who are on systemic hormonal contraceptives must agree to use an additional method of contraception (barrier method).

Exclusion criteria

Patients should not have other dyslipidaemic or metabolic disorders that could affect the evaluation of eprotirome in HeFH, such as increased serum TG above 4.5 mmol/L, HbA1c above 8.5%, secondary dyslipidaemia or ongoing or planned apharesis.
Patients should also not have cardiac diseases that may interfere with the safety evaluation of eprotirome, such as congestive heart failure (NYHA III and IV), planned percutaneous coronary intervention, coronary artery bypass surgery, uncontrolled hypertension or evidence of cardiac electrophysiologic instability including uncontrolled sick sinus syndrome, sino-atrial or atrioventricular block, ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardia with a ventricular response heart rate or a QTcF above 450 ms prior to randomisation.
No other lipid-lowering medication with the exception of statins and ezetimibe are allowed.
Also patients with any medical or surgical condition which might significantly alter the absorption, distribution, metabolism, or excretion of the study medication are excluded.
As eprotirome is a thyroid hormone receptor agonist, patients with disturbed thyroid function, thyrotoxicosis, taking thyroid hormone or anti-thyroid medication are excluded. Drugs known to affect thyroid function tests are also prohibited.
As eprotirome exerts its pharmacological action in the liver, patients with liver dysfunction should be excluded prior to randomisation, such as: AST or ALT or ALP above 1.5 x ULN, total bilirubin >ULN, active hepatobiliary disease, cholestasis, or serologic evidence of past or active hepatitis B or hepatitis C, acquired immune deficiency syndrome, positive serological test for human immunodeficiency virus infection, substantial consumption of alcohol or drug abuse.
Patients with serum creatinine above 160 mmol/L or unexplained serum creatine kinase above 3 x ULN are exluded.
Patients on oral anticoagulant therapy other than vitamin K antagonists and anti-platelet agents are excluded.
Patients with the following diseases are excluded: rheumatoid arthritis; history of cancer, history of or current primary or secondary adrenal insufficiency or any other condition that in the opinion of the investigator confound the evaluation and interpretation of efficacy and or

safety data

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:	Recruiting
Start date (anticipated):	03-10-2011
Enrollment:	160
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	eprotirome
Generic name:	nvt

Ethics review

Approved WMO Date:	31-05-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2011

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2012
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	EUCTR2011-001483-21-NL
CCMO	NL36435.018.11