A Phase 4 Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Centre Study of Colesevelam as Add-on Therapy in Patients with Familial Hypercholesterolaemia.

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This study is being conducted in patients with familial hypercholesterolaemia (FH) to:1. Assess the efficacy of colesevelam added to a maximal tolerated and stable regimen of statin and ezetimibe in further decreasing the low-density lipoprotein (...

Ethical review	Approved WMO
Status	Pending
Health condition type	Endocrine disorders congenital
Study type	Interventional

Summary

ID

NL-OMON31385

Source
ToetsingOnline

Brief title
TRIPLE

Condition

- Endocrine disorders congenital

Synonym
Elevated LDL cholesterol level, familial hypercholesterolaemia

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme
Source(s) of monetary or material Support: Sponsor - Genzyme Europe B.V.

Intervention

Keyword: Colesevelam, Familial Hypercholesterolaemia

Outcome measures

Primary outcome

The primary efficacy endpoint is the relative reduction in LDL cholesterol at Week 6 compared to Baseline and the difference between colesevelam and placebo. Baseline is defined as the LDL cholesterol level taken the closest in time to the Day 1 visit.

Secondary outcome

The secondary endpoints will be the relative reduction in HDL cholesterol, total cholesterol, ApoA1, ApoB, ApoB/ApoA1 ratio, and triglycerides between Baseline and Week 6 and Week 12 and the differences between colesevelam and placebo; changes in fasting glucose, HbA1c level and hsCRP at Week 6 and Week 12; the percentage of patients being below their target for LDL cholesterol of 2.5 mmol/L (100 mg/dL) at Week 6 and Week 12 (goal rate); the percentage of patients with a relative reduction in their LDL cholesterol at Week 6 or Week 12 compared to Baseline of at least 15% or more (responder rate); and the relative reduction of LDL cholesterol at 12 weeks compared to Baseline and the difference between colesevelam and placebo.

Study description

Background summary

This is a prospective, randomised, double-blind, placebo-controlled, parallel-group, multi-centre, Phase 4 study of colesevelam administered to patients with FH as add-on therapy to a maximally tolerated and stable regimen of a statin and ezetimibe on which their LDL cholesterol level is still above their target (for either primary or secondary prevention).
Patients are known with FH, diagnosed by either presence of a documented LDL-receptor mutation or a combination of several clinical diagnostic criteria as described by Aalst-Cohen (van Aalst-Cohen, 2006, Eur Heart J) , based on a combination of criteria from the United Kingdom (Simon Broome register Criteria), The Netherlands (Dutch Lipid Clinic Network Criteria), and the USA (MEDPED criteria). Patients will be considered in screening after they have signed informed consent. Screening will comprise a 4 week run in period to assess stability of the lipid lowering effect of the statin and ezetimibe combination treatment patient has been on for at least 3 months. Patients will be screened and after confirmation of suitability will return for the baseline visit after a run-in period of 4 weeks. When the LDL cholesterol level at this baseline visit is within 10% of the level at Screening, patients will be randomised followed by start of daily treatment with colesevelam or placebo during the Day 1 visit. Upon meeting study eligibility requirements at Screening and Baseline, patients will be randomised to receive colesevelam or placebo at 1:1 ratio (i.e., 40 patients per group), using a central randomisation procedure, with stratification per site.
The investigational product consists of a daily dose of 6 tablets of colesevelam (625 mg per tablet) or matching placebo tablets to be taken during meals.

Dosing group Study treatment Total daily dose Total patients
1 colesevelam 6 tablets of 625 mg each 40
2 placebo 6 placebo tablets 40
Total 80
Patients will return for assessments at 6 weeks (±1 week) and 12 weeks (±1 week) after the Day 1 visit. After 12 weeks of blinded treatment all patients will receive open colesevelam treatment and continue for another 40 weeks on colesevelam. In the open treatment follow up period patients will have visits at Weeks 18, 26, and 52. The duration of each patient*s participation in the study will be maximal 13 months, inclusive of 4 week Screening and run-in period and 3 months blinded treatment period and 9 month open treatment follow-up. Safety and efficacy assessments will be performed at the designated study visits. Adverse events (AEs) and concomitant medications will be monitored and recorded throughout the study. Individual patients* randomisation assignments will remain blinded until the last patient has completed the 3 month blinded treatment period and the database with the 3

month data has been locked.

Study objective

This study is being conducted in patients with familial hypercholesterolaemia (FH) to:
1. Assess the efficacy of colesevelam added to a maximal tolerated and stable regimen of statin and ezetimibe in further decreasing the low-density lipoprotein (LDL) cholesterol level in terms of additional percentage decrease and in terms of reaching below target level of LDL cholesterol.
2. Evaluate the safety and tolerability of colesevelam added to a maximal tolerated and stable regimen of statin and ezetimibe.

Study design

This is a prospective, randomised, double-blind, placebo-controlled, parallel-group, multi-centre, Phase 4 study of colesevelam administered to patients with FH as add-on therapy to a maximally tolerated and stable regimen of a statin and ezetimibe on which their LDL cholesterol level is still above their target level. Target level for LDL cholesterol is based on the 2003 European Guidelines for lowering LDL cholesterol in high risk patients defined as 2.5 mmol/L (100 mg/dL) (De Backer, 2003, Eur Heart J).
Patients with FH can be diagnosed by either presence of a documented LDL-receptor mutation or a combination of several clinical diagnostic criteria e.g., level of LDL cholesterol in patient and first degree relative and presence of xanthomas or proven coronary artery disease in patient or first degree relative, universally applied in the United Kingdom (Simon Broome Register Criteria), The Netherlands (Dutch Lipid Clinic Network Criteria), and the USA (MEDPED criteria) as described by van Aalst-Cohen (van Aalst-Cohen, 2006, Eur Heart J). A patient is considered to be in screening after he or she has signed informed consent. Patient will be asked to swallow a test dose of placebo tablets as part of the screening procedures to familiarise the patient with the tablets used. Screening will comprise a 4 week run in period to assess stability of the lipid lowering effect of the statin and ezetimibe combination treatment the patient has been on for at least 3 months. At the Baseline visit, it will be checked if LDL cholesterol level is within 10% of that level at Screening. Upon meeting the Screening and Baseline study eligibility requirements, patients will be randomised to receive colesevelam or placebo at 1:1 ratio (i.e., 40 patients per group).
The investigational product consists of tablets of colesevelam (625 mg per tablet) or matching placebo tablets. A total of 6 colesevelam or placebo tablets should be taken every day with a meal, either 6 tablets once a day or 3 tablets twice a day. Patients will need to continue their maximal tolerated dose of statins and ezetimibe.
The duration of each patient*s participation in the study will be maximal 13 months, inclusive of a 4 week Screening and run-in period, a 3 month double

blind treatment period a 9 month open treatment follow-up period. Patients will return for assessments at Week 6 (± 1 week), Week 12 (± 1 week), Week 18 (± 1 week), Week 26 (± 2 weeks), and Week 52 (± 2 weeks) after the Day 1 visit. Safety and efficacy assessments will be performed at the designated study visits.
Adverse events (AEs) and concomitant medications will be monitored and recorded throughout the study. Individual patients* randomisation assignments will remain blinded for the duration of the study until the last patient has completed the 3 month double blind treatment period.

Intervention

One group will receive 6 tablets/day Colesevelam and one group will receive 6 tablets/day Placebo for a period of 12 weeks. This procedure is dubbel blind

Study burden and risks

minimum risk

Contacts

Public
Genzyme

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1411 DD Naarden
Nederland
Scientific
Genzyme

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Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients must be males or females between 18 and 75 years of age, inclusive
2. Patients must have a clinical diagnosis of Familial Hypercholesterolaemia (FH) defined as EITHER
a. Presence of a documented LDL-receptor mutation OR
b. History of untreated LDL cholesterol level above the 95th percentile for sex and age in combination with documentation of at least one of the following:
i. Presence of typical tendon xanthomas in the patient or first degree relative
ii. An LDL cholesterol level above the 95th percentile for age and sex in a first degree relative
iii. Proven coronary artery disease in the patient or in a first degree relative under the age of 60
3. Patients must have been provided and undergone lifestyle changes for more than 6 months at time of Screening
4. Patients must have been treated for at least 3 consecutive months preceding the screening visit with a stable lipid lowering treatment regimen consisting of a maximal tolerated combination of a statin with ezetimibe and are still above their target for LDL cholesterol being 2.5 mmol/L (100 mg/dL)
5. Patients must be committed to following the protocol requirements as evidenced by written informed consent
6. Patients should be comfortable with swallowing at least 3 placebo tablets

Exclusion criteria

1. Patients with a known allergy to any of the components used in colesevelam or placebo or any other medications like statin or ezetimibe required for participation in this study
2. Patients with a bowel or biliary obstruction
3. Patients with secondary causes of hypercholesterolaemia, e.g., hypothyroidism, nephrotic syndrome (defined as proteinuria >2 g/L), dysproteinaemias, obstructive liver disease, other pharmacological therapies, alcoholism
4. Patients with triglyceride level of > 3.4 mmol/L.
5. Patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, inflammatory bowel disease, or major gastrointestinal tract surgery
6. Patients having undergone LDL-apheresis within one year prior to the screening visit and/or need to undergo LDL-apheresis
7. Patients with active liver disease or unexplained persistent elevations in transaminases
8. Patients on fenofibrates or on concomitant cholestyramine as this will affect the area under the curve (AUC) of ezetimibe

9. Patients with poorly-controlled diabetes (i.e., glycosylated haemoglobin (HbA1c) > 9% at Screening)
10. Patients with clinically significant (CS) abnormal haematology, renal, or other laboratory parameters that could be the result of an underlying malignancy or systemic infection as judged by the investigator
11. Patients with a heart transplant, concurrent congestive heart failure (New York Heart Association [NYHA] Class 3 or 4), life threatening ventricular arrhythmias, unstable angina, recent myocardial infarction within the past 6 month prior to screening or patients undergoing haemodialysis, or with active disease who may not be healthy enough to successfully complete all protocol requirements

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2007
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cholestagel
Generic name:	Colesevelam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-06-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2009
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	EUCTR2007-000582-37-NL
CCMO	NL16666.018.07