# A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Followed by an Open-Label Continuation Period to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Metabolic and nutritional disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON39591

**Source**
ToetsingOnline

**Brief title**
MIPO3801011 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:** Genzyme Corporation and its Affiliates
**Source(s) of monetary or material Support:** Genzyme corporation and its Affiliates;USA

## Intervention

**Keyword:** Familial hypercholesterolemia, LDL-C, Mipomersen

## Outcome measures

### Primary outcome

Percent change in LDL-C from Baseline to primary efficacy time point (PET) in

patients with LDL-C equal to or above 5.18 mmol/L plus CHD or LDL-C equal to or

above 7.77 mmol/L (cohort 1).

### Secondary outcome

Percent change in Apo B from Baseline to primary efficacy time point (PET) in

cohort 1;

percent change in L(p)a from Baseline to PET in cohort 1;

percent change in LDL-C from Baseline to PET in patients with LDL-C equal to or

above 4.14 mmol/L but lower than 5.18 mmol/L, plus a diagnosis of HeFH, plus

CHD (cohort 2);

percent change in Apo B from Baseline to PET in cohort 2;

percent change in L(p)a from Baseline to PET in cohort 2;

the longterm safety and tolerability of mipomersen;

to assess the systemic exposure to mipomersen.

# Study description

**Background summary**

Hypercholesterolemia is a common condition that in its untreated form is categorized by a broad range of elevated LDL-C levels.
Familial Hypercholesterolemia (FH) is a monogenic autosomal co-dominant form of hypercholesterolemia that results from mutation of the LDL receptor gene and produces a clinically recognizable pattern of severe hypercholesterolemia and a high risk of atherosclerosis with premature CAD.

The manifestations of the disease in heterozygotes (HeFH) are variable and may range from mildly elevated cholesterol to severe hypercholesterolemia (with median untreated LDL-C levels of 7.8 mmol/L). Young adults 20 to 29 years of age with HeFH have a 100-fold increased risk of fatality from a myocardial infarction (MI) compared to individuals with normal cholesterol.

There are currently 5 classes of approved therapeutic agents for the treatment of hyperlipidemia, all of which are administered orally. These include statins, the bile-acid sequestrants, fibrates, niacin, and cholesterol absorption inhibitors (e.g., ezetimibe). In order to optimize LDL-C reductions in clinical management of severe primary hypercholesterolemia, aggressive combination therapy is often required. Triple therapy with maximally-tolerated statins, ezetimibe, and a bile-acid sequestrant is common in many refractory patients or in patients with very high LDL-C levels. Despite recommendations for aggressive treatment in this patient population, large number of high-risk patients are not sufficiently treated.

Genzyme has chosen to develop mipomersen as an adjunct to other lipid-lowering medications in those patients who have severely elevated LDL-C and are at high CHD risk.

**Study objective**

The primary objective of this study is to determine whether mipomersen

significantly reduces atherogenic lipid levels in patients with severe HeFH, defined as LDL-C levels equal to or above 5.18 mmol/L plus the presence of CHD/risk equivalents or LDL-C levels equal to or above 7.77 mmol/L regardless of the presence of CHD/risk equivalents compared to placebo. Two different mipomersen dosing regimens will be studied: subcutaneous (SC) mipomersen 200 mg once weekly versus placebo, and SC mipomersen 70 mg thrice weekly versus placebo.

## Study design

This is a multicentre, randomized, double-blind, placebo-controlled, parallel-group study consisting of an 4-week screening period, during which patients will be evaluated for inclusion in the study, all eligible patients within each cohort will be stratified by geographic region and randomized in a 1:1 ratio to Regimen A (SC mipomersen 200 mg or placebo once weekly) or Regimen B (SC mipomersen 70 mg or placebo thrice weekly). Patients will then be stratified by gender and use of statins within each regimen group and randomized at a 2:1 ratio to receive mipomersen or placebo.

All eligible patients will participate in a 60-week blinded treatment phase during which investigational product (mipomersen or placebo) will be administered SC and patients will undergo monthly evaluations. During the first 8 weeks of the double-blind treatment, patients will receive an adjusted dosing regimen of investigational product (mipomersen or placebo), patients will begin receiving the target dosing regimen at Week 9.
For Regimen A: the adjusted dosing regimen will be 200 mg mipomersen or placebo SC administered once every other week, and for Regimen B the adjusted dosing regimen will be 70 mg mipomersen or placebo SC thrice weekly every other week.

Assessment of the primary efficacy endpoint will be 7 days post last dose of investigational product. Following completion of the treatment period and PET evaluation, patients can continue in an open-label extension study which will take 26 weeks. After this period the patient will be followed by a 24-week post-treatment safety follow-up evaluation period during which all patients, including those who discontinue prematurely and have received one or more doses of investigational product (mipomersen or placebo), will be asked to complete 2 or 3 post-treatment visits at specified times.

## Intervention

Intervention consists of: mipomersen 200 mg once weekly, mipomersen 70 mg thrice weekly or placebo.

## Study burden and risks

This study will last for 88 weeks and has 4 periods: 1) screening period of 4

weeks and one visit; 2) blinded treatment phase of 60 weeks and 15 visits; 3) open label extention study of 26 weeks and 5 visits; 4) post-treatment safety follow up period of 2 visits over 24 weeks. During each visit a fasting blood sample will be taken, urine tests, vital signs. At half of the visits physical exams will be performed. MRI or CT imaging of the liver will be performed during 4 visits.

Mipomersen inhibits a molecular target not easily approachable by traditional drug modalities and has the potential to be an efficacious lipid-lowering agent. Because mipomersen has a mechanism of action that is distinct from that of the statins, mipomersen is hypothesized to have an additive effect when co-administered with statins and other approved lipid-lowering therapies. Furthermore, in patients with mutations in the LDLr gene, such as FH, mipomersen has the potential to demonstrate lipid-lowering activity beyond the magnitude observed for statins.

As of 31 August 2010, approximately 800 subjects have been exposed to at least 1 dose of mipomersen in clinical studies with approximately 100 subjects with at least 1 year of mipomersen exposure. Commonly related reported AEs observed with mipomersen treatment to date include injection site reactions, flu-like symptoms, and serum transaminase elevations.
As of 30 November 2011, a total of 119 severe side effects occurred during clinical trials in 83 patients. Seventeen (17) of these events were considered to be possibly or probably related to mipomersen (angina pectoris in 4 patients, alanine aminotransferase increased in 3 patients and coronary artery blockage, heart attack, fever, biliary colic, liver failure, liver fat, appendicitis, stroke and high blood pressure in one patient each). As with any other 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 mipomersen on pregnancy is currently unknown.

## Contacts

**Public**
Genzyme Corporation and its Affiliates

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US
**Scientific**
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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) The patient is willing and able to provide signed informed consent
2) The patient is a male or female, age equal to or above 18 years of age
3) Fasting LDL-C equal to or above 7.77 mmol/L regardless of the presence of CHD/risk equivalents;
or fasting LDL-C equal to or above 5.18 mmol/L plus at least 1 of the following: a) Documented CHD, or b) CHD risk equivalents;
or fasting LDL-C equal to or above 4.14 mmol/L but lower than 5.18 mmol/L, plus a diagnosis of HeFH (per Simon Broome Register, US MedPed, or Dutch Lipid Clinic Network Criteria) plus at
least 1 of the following: a) Documented CHD, or b) CHD risk equivalents.
4) Patients should be on a stable, maximally tolerated, lipid-lowering regimen for at least 12 weeks prior to Screening and the patient is expected to remain on this regimen through the completion of the primary efficacy assesment visit. The stable, maximally tolerated, lipid-lowering regimen is defined as: a) A statin with a dose >0. If the statin dose=0, the patient must be on at least 1 medication from another class of hypolipidemic agents. Therapy with fish oil must be accompanied by treatment with another hypolipidemic agent. b) A stable low-fat diet.
5) The patient should have a body mass index equal to or lower than 40 kg/m2 with stable weight (± 4 kg) longer than 6 weeks prior to screening
6) The patient should have a fasting triglyceride (TG) value above 3.95 mmol/L at Screening.
7) If sexually active: a) Females must be non-pregnant and non-lactating; either surgically sterile, post-menopausal, or patient or partner compliant with an acceptable and highly effective contraceptive regimen for 4 weeks prior to screening, and willing to remain compliant during and for 24 weeks after the last investigational product dose. b) Males must either surgically sterile or patient or partner is willing to utilize an acceptable and highly effective contraceptive method during and for 24 weeks after the last investigational product

dose.

### Exclusion criteria

1) The patient has experienced Myocardial Infarction, percutaneous transluminal coronary intervention, Coronary Artery Bypass Graft Surgery, cerebrovascular accident, unstable angina, or acute coronary syndrome within 24 weeks before screening.
2) The patient has had a clinically significant arrhythmia that was deemed to be uncontrolled at any time within 6 months before screening, or medication for an arrhythmia was started or dose was changed within 6 months before screening.
3) Type 1 diabetes, or if Type 2 diabetes, glycosylated hemoglobin A (HbA1c; glycohemoglobin) above 8% at screening.
4) Clinically significant hepatic disease (e.g. history of confirmed nonalcholic steathopatitis, renal disease, or Gilbert's syndrome).
5) Apheresis within 3 months of screening or is expected to start apheresis during treatment phase.
6) ALT and/or AST levels equal to or above 1.5 x upper limits of normal.
7) Serum creatinine above 8.8 µmol/L above upper limit of normal for women, or above 17.7 µmol/L above upper limit of normal for men
8) Proteinurie (>1000 mg protein/g creatinine on spot urine) confirmed on retetest
9) Total bilirubin above 1.2 x upper limit of normal.

## Study design

### Design

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| 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

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 15-11-2011 |

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| Enrollment: | 40 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 29-02-2012 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 27-04-2012 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 23-05-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 24-05-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 06-06-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 03-07-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 10-10-2012 |

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| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-11-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 21-03-2013 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 05-09-2013 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 22-10-2013 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 09-01-2014 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 17-02-2014 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 15-04-2014 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# 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 | EUCTR2011-001480-42-NL |
| CCMO | NL38572.000.11 |