A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Heterozygous Familial Hypercholesterolemia Not Adequately Controlled with Their Lipid-Modifying Therapy

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The primary objective of the study is to demonstrate the reduction of LDL-C by REGN727 as add-on therapy to stable, maximally-tolerated dialy statin therapy with or without other LMT in comparison with placebo after 24 weeks of treatment in patients...

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

Summary

ID

NL-OMON39622

Source
ToetsingOnline

Brief title
Odyssey FH II

Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
familial hyperchomesterolemia, inherited hyperlipidemia

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Regeneron Pharmaceuticals;Inc.

Intervention

Keyword: Heterozygous Familial hypercholesterolemia, LDL-C, REGN727/SAR236553

Outcome measures

Primary outcome

The percent change in calculated LDL-C from baseline to week 24, which is

defined as : 100x (calculated LDL-C value at week 24 - calculated LDL-C value

at baseline) / calculated LDL-C value at baseline.

The baseline calculated LDL-C value will be the last LDL-C level obtained

before the first double-blind IMP injection.

Secondary outcome

The percent change in calculated LDL-C from baseline to week 12.

The percent change in calculated Apo B from baseline to week 24

The percent change in calculated non-HDL-C from baseline to week 24

The percent change in calculated total-C from baseline to week 24

The percent change in calculated Apo B from baseline to week 12

The percent change in calculated non-HDL-c from baseline to week 12

The percent change in calculated total-C from baseline to week 12

The percent change in calculated LDL-C from baseline to week 52

The proportion of patients reaching LDL-C goal at week 24, i.e. LDL-C < 70 mg/dL in case of prior cardiovascular disease, or LDL-C < 100 mg/dL for patients without cardiovascular disease.

The proportion of patients reaching LDL-C < 70 mg/dL (1.81 mmol/L) at week 24

The percent change in Lp(a) from baseline to week 24

The percent change in HDL-C from baseline to week 24

The percent change in Lp(a) from baseline to week 12

The percent change in fasting TG from baseline to week 24

The percent change in fasting TG from baseline to week 12

The percent change in Apo A-1 from baseline to week 24

The percent change in Apo A-1 from baseline to week 12

The percent change in HDL-C from baseline to week 12

The percent change in calculated LDL-C from baseline to week 78

The proportion of patients reaching LDL-C goal at week 12, 52, and 78, i.e. LDL-C < 70 mg/dL in case of prior cardiovascular disease, or LDL-C < 100 mg/dL for patients without cardiovascular disease.

The proportion of patients reaching LDL-C < 100 mg/dL (2.59 mmol/L) at week 24

The proportion of patients reaching LDL-C < 100 mg/dL (2.59 mmol/L) at week 12

The proportion of patients reaching LDL-C < 70 mg/dL (1.81 mmol/L) at week 12

The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline to Weeks 12, 24, 52 and 78

The percent change in Apo B, non-HDL-C, total-C, Lp (a), HDL-C, fasting TG, and Apo A-1 from baseline to Week 52 and 78

The change in ratio Apo B / Apo A-1 from baseline to weeks 12, 24, 52 and 78

The proportion of patients with Apo B < 80 mg/dL (0.8 mmol/L) at weeks 12, 24, 52 and 78

The proportion of patients with non-HCL-C < 100 mg/dL at weeks 12, 24, 52 and 78.

The proportion of patients with calculated LDL-C < 70 mg/dL (1.81 mmol/L) and/or > or equal to 50*% reduction in calculated LDL-C (if calculated LDL-C > or equal to 70 mg/dL (1.81 mmol/L)) at weeks 12, 24, 52 and 78.

Anti-REGN727 antibody status and titers assessed throughout the study

The percent change in hs-CRP from baseline to weeks 24, 52 and 78

The absolute change in HbA1c (%) from baseline to weeks 24, 52 and 78

Response of each EQ-5D item, index score and change of index score from baseline through week 52

Study description

Background summary

The study will include patients with heterozygous familial hypercholesterolemia (heFH) with or without a history of MI or ischemic stroke. Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that predisposes a person to premature severe cardiovascular disease (CVD). Familial hypercholesterolemia has a high prevalence in Caucasian populations, were estimated 1 in 500 individuals are affected.
In the heterozygous form of FH, the cumulative risk of experiencing a coronary event by the age of 60 years without effective treament is at least 50% in men and approximately 30% in women.
In 4 observational studies, statin therapy was shown to reduce the risk of CVD by 50% to 80% in patients with FH. Unfortunately, even after treatment, the risk in heFH can still be almost 2-fold higher than the general population. In addition only a small fraction of treated heFH patients are able to reach recommended levels of LDL-C. Thus, the need for more intensive treatment in heFH patients is clear.

REGN727 is a fully human monoclonal antibody that binds Propotein Convertase Subtilisin Kexin type 9 (PCSK9).

PCSK9 which is highly expressed in the liver, is involved in regulating the levels of Low-density lipoportein receptor (LDL-R) protein. Once secreted into plasma, PCSK9 binds to the LDL-R and promotes its degeneration, which leads to reduced LDL-C removal or higher LDL-C circulating levels.
Therefor blocking PCSK9 can potentially benefit patients by decreasing their plasma LDL-C levels. In addition, PCSK9 messenger ribonucleic acid (mRNA) and protein levels are increased in response to statins, potentially attenuating their cholesterol-lowering effect.

Study objective

The primary objective of the study is to demonstrate the reduction of LDL-C by REGN727 as add-on therapy to stable, maximally-tolerated dialy statin therapy with or without other LMT in comparison with placebo after 24 weeks of treatment in patients with heFH.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-national study in patients with heFH who are not adequatley controlled with their LMT.
Pateints will be randomized in a 2:1 ratio to receive either 75 mg REGN727 or placebo by SC injection, every 2 weeks, on top of stable, maximally-tolerated dialy statin therapy with or without other LMT. Randomization will be stratified according to prior history of either myocardial infarction or ischemic stroke, and statin treatment
The study consists of :
1) A screening period of up to 2 weeks
2) A double-blind treatment period of 78 weeks, after completion of this period, patients may bbe eligible to enroll into a separate open-label extention study.
3) A follow-up period of 8 weeks

Intervention

Biweekly subcutaneous injections with 75mg/ml study drug or placebo.
At week 12, patients randomized to REGN727 will, in a blinded manner, dose up-titrate to REGN727 150mg every 2 weeks, if the week 8 LDL-C is higher or equal to 70 mg/dl (1.8 mmol/L).

Study burden and risks

This study consists of 3 periods:

1)screening period up to 2 weeks including an intermediate visit during which the patient will be trained to self-inject of the study medication.
2)Double-blind treatment period of 18 months with 10 visits. During each visit there will be a fasting bloodsampling, there will be 5 urine sampling except for the women of childbearing potential, they will give more urine samples (7) for pregnancy testing. During each visit bloodpressure and heartrate will be monitored . During the complete treatment period the patient will receive three ECG and six questionnaires. Between the visits the patient will keep a diary and follow a diet to decrease the cholesterol.
3) Follow-up period of 8 weeks after the end of the previous period for patients not consenting to participate in the open-label extension study or if prematurely discontinuing study treatment

REGN727 was well tolerated in all completed Phase 2 studies throughout the treatmentperiod and for all treatment groups. Injection site reactions were reported in patients including placebo-treated patients. These events were generally transient with no dose relationship. Rare cases of hypersensitivity reactions were reported. . No particular signal noted for "treament emergent adverse events" related to musculoskeletal or connective tissue disorders as well as no elevations in liver enzymes.
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 REGN727 on pregnancy or breast feeding mothers 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 heFH* who are not adequately controlled** with a maximally-tolerated daily dose*** of statin with or without other LMT, at a stable dose prior to the screening visit (week -2).;*Diagnosis of heFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria for definite FH (Appendix 1) or the WHO/Dutch Lipid Network criteria with a score of >8 points (Appendix 2).;***Not adequately controlled* is defined as LDL-C *70 mg/dL (1.81 mmol/L) at the screening visit (week -2) in patients with a history of documented CVD (Appendix 3), or LDL-C *100 mg/dL (2.59 mmol/L) at the screening visit (week -2) in patients without a history of documented CVD.;****Maximally-tolerated dose* is defined as (any of the following are acceptable):;*Rosuvastatin 20 mg or 40 mg daily;*Atorvastatin 40 mg or 80 mg daily;*Simvastatin 80 mg daily (if already on this dose for >1 year * see exclusion criterion #7);Note: Patients who are not able to be on any of the above statin doses should be treated with the dose of daily atorvastatin, rosuvastatin, or simvastatin which is considered appropriate for the patient, according to the investigator's judgment. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index, regional practices, local prescribing information, concomitant medications, co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose. The reason(s) will be documented in the case report form (CRF).;2.Provide signed informed consent

Exclusion criteria

1.Patient without diagnosis of heFH made either by genotyping or by clinical criteria;2.LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (week-2) in patients with history of documented cardiovascular disease;3.LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit (week *2) in patients without history of documented cardiovascular disease;4.Not on a stable dose of LMT (including statin) for at least 4 weeks and/or fenofibrate for at least 6

weeks, as applicable, prior to the screening visit (week -2) and from screening to randomization;5.Currently taking another statin than simvastatin, atorvastatin, or rosuvastatin;6.Simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose;7.Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than 1 year, who are eligible);8.Use of fibrates, other than fenofibrate within 6 weeks of the screening visit (week-2) or between screening and randomization visits;9.Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/amount for at least 4 weeks prior to the screening visit (week -2) or between screening and randomization visits;10.Use of red yeast rice products within 4 weeks of the screening visit (week-2), or between screening and randomization visits;11.Patient who has received plasmapheresis treatment within 2 months prior to the screening visit (week -2), or has plans to receive it during the study;12.Recent (within 3 months prior to the screening visit [week -2] or between screening and randomization visits) MI, unstable angina leading to hospitalization, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), uncontrolled cardiac arrhythmia, stroke, transient ischemic attack (TIA), carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease

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):	20-12-2012
Enrollment:	140
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	REGN727
Generic name:	nvt

Ethics review

Approved WMO Date:	31-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	23-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
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	EUCTR2012-001222-95-NL
CCMO	NL41314.018.12

Study results

Date completed:	17-12-2014
Results posted:	15-12-2015
Actual enrolment:	100

Summary results
Trial is onging in other countries

First publication
01-01-1900