A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Primary Hypercholesterolemia Who are Intolerant to Statins

Published: 19-12-2012
Last updated: 24-04-2024

The primary objective of the study is to demonstrate the reduction of low-density lipoprotein (LDL) cholesterol (LDL-C) by REGN727 in comparison with ezetimibe (EZE) 10 mg PO QD after 24 weeks in patients with primary hypercholesterolemia (...

Ethical review	Not approved
Status	Will not start
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON39721

Source
ToetsingOnline

Brief title
R727-CL-1119

Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
high cholesterol, primary hypercholesterolemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: primary hypercholesterolemia, REGN727/SAR236553

Outcome measures

Primary outcome

The primary efficacy endpoint is the percent change in calculated LDL-C from

baseline to week 24

Secondary outcome

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

* The percent change in ApoB from baseline to week 24.

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

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

* The percent change in ApoB from baseline to week 12.

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

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

* The proportion of patients reaching LDL-C goal at week 24, ie, LDL-C <70

mg/dL (1.81 mmol/L) in case of very high CV risk or LDL-C <100 mg/dL (2.59

mmol/L) for patients with moderate or high CV risk.

* 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 HDL-C from baseline to week 12.

* 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 ApoA-1 from baseline to week 24.

* The percent change in ApoA-1 from baseline to week 12.

Study description

Background summary

REGN727 is a fully human monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9). REGN727 is also referred to as SAR236553. In the context of this clinical study protocol, it will be referred to as REGN727
This study will include patients with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [heFH] and non-familial hypercholesterolemia [FH]) with or without a history of documented myocardial infarction (MI) or ischemic stroke
Current LDL-C lowering medications include statins, ezetimibe (EZE), fibrates, niacin, and bile acid sequestrants, of which statins are the most commonly prescribed, as they have shown a great ability to lower LDL-C and reduce CHD events. However, despite these available treatments, when used alone or in combination, many high-risk patients fail to reach the ESC/EAS guideline target level.
Proprotein convertase subtilisin kexin type 9 (PCSK9) belongs to the subtilisin family of serine proteases and is highly expressed in the liver. PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDLR) protein.
Once PCSK9 is secreted into plasma, it directly binds to the LDLR and promotes its degradation. The increased degradation of LDLRs leads to a decreased removal of LDL-C and therefore, higher circulating levels of LDL-C.
Blocking PCSK9 from binding to the LDLR can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels. In addition, PCSK9 messenger RNA 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

low-density lipoprotein (LDL) cholesterol (LDL-C) by REGN727 in comparison with ezetimibe (EZE) 10 mg PO QD after 24 weeks in patients with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [heFH] and non-familial hypercholesterolemia [FH]) who are intolerant to statins

Study design

This is a randomized, double-blind, double-dummy, active-controlled, parallel-group, multi-national, multi-center study in patients with primary hypercholesterolemia and moderate, high, or very high cardiovascular (CV) risk, who are intolerant to statins.

The study consists of 5 periods: screening; washout; single-blind placebo run-in; double-blind treatment; and follow-up.

Treatment groups:
* REGN727 75 mg SC Q2W + placebo voor EZE of atorvastatine PO QD
* EZE 10 mg PO QD + placebo voor REGN727 75 mg SC Q2W
* Atorvastatine 20 mg PO QD + placebo voor REGN727 75 mg SC Q2W

Study Drug schedules:

Study drug: Dose/Route/Schedule: REGN727 75 mg SC Q2W for 24 weeks, or 75 mg SC Q2W for 12 weeks followed by 150 mg SC Q2W for 12 weeks
Study Drug: Dose/Route/Schedule: Ezetimibe 10 mg PO QD for 24 weeks
Study Drug: Dose/Route/Schedule:Atorvastatin 20 mg PO QD for 24 weeks
Placebo: Dose/Route/Schedule: Placebo matching REGN727/Placebo matching EZE and atorvastatin SC Q2W for 24 weeks/PO QD for 24 weeks
Placebo Run-in: Route/Schedule: Placebo matching REGN727 and placebo capsule SC Q2W and PO QD

Intervention

Study drug: Dose/Route/Schedule: REGN727 75 mg SC Q2W for 24 weeks, or 75 mg SC Q2W for 12 weeks followed by 150 mg SC Q2W for 12 weeks
Study Drug: Dose/Route/Schedule: Ezetimibe 10 mg PO QD for 24 weeks
Study Drug: Dose/Route/Schedule:Atorvastatin 20 mg PO QD for 24 weeks
Placebo: Dose/Route/Schedule: Placebo matching REGN727/Placebo matching EZE and atorvastatin SC Q2W for 24 weeks/PO QD for 24 weeks
Placebo Run-in: Route/Schedule: Placebo matching REGN727 and placebo capsule SC Q2W and PO QD

Study burden and risks

Risks: side effects of the study drug

Burden
* 9 study visits + 1 follow-up visit
* come to the hospital in fasting condition almost every study visit (lipid panel test - bloodtests)
* 8 SC injections(self administration or done by somebody else), subject will be trained to do this
* physical examination (3x)
* vital signs (bloeddruk, pols): every study visit
* weight: 5x
* ECG: 2x
* diet review: 4x
* bloodtest: every study visit
* urine testing: every study visit (5x urine analysis) + every study visit for pregnancy test)
* pregnancy test: serum test 1x (screening), urine (elk studiebezoek)
* complete patient diary

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

Patients with primary hypercholesterolemia (familiaal of niet familiaal) with moderate, high or very high CV risk and a history of statin intolerance
*** Definition of statin intolerance: Inability to tolerate at least 2 previous statins at the lowest approved daily dose due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.

Exclusion criteria

- Calculated serum LDL-C <70 mg/dL (1.81 mmol/L) and very high CV risk (as defined in section 4.2) at the screening visit (week -7)
- Calculated serum LDL-C <100 mg/dL (2.59 mmol/L) and high or moderate CV risk (as defined in section 4.2) at the screening visit (week -7)
- diagnosis of fibromyalgia, history of severe neuropathic pain, history of reumatological disease, history of myalgia or myopathy, history of seizure disorder, history of transplant surgery
- presence of clinically significant uncontrolled endocrine disease known to influence serum lipids
- known loss of function of PCSK9 (genetic mutation)
- known homozygous FH
- < 18 years or legal age
- known HIV positivity
- previous participation in any clinical trial of REGN727 or SAR236553

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:	Will not start
Enrollment:	66
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	19-12-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	09-04-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Not approved

Date:	03-07-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2012-001221-27-NL
CCMO	NL42262.068.12