A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia

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The primary objective of the study is:* To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by evinacumab 15 mg/kg intravenously (IV) in comparison to placebo after 24 weeks in patients with homozygous familial...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON48741

Source
ToetsingOnline

Brief title
R1500-CL-1629 (0456/0136)

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Lipid metabolism disorders

Synonym
hereditary abnormal high cholesterol level, homozygous familial hypercholesterolemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: evinacumab (REGN1500), Homozygous Familial Hypercholesterolemia (HoFH), phase 3

Outcome measures

Primary outcome

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

week 24.

Secondary outcome

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

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

* The percent change in TC from baseline to week 24

* The proportion of patients with *30% reduction in LDL-C at week 24

* The proportion of patients with *50% reduction in LDL-C at week 24

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

* The change in calculated LDL-C from baseline to week 24

* The proportion of patients who meet EU apheresis eligibility criteria (see

German Apheresis Working Group) from baseline to week 24

* The proportion of patients who meet US apheresis eligibility criteria (see US

[National Lipid Association] Lipid Apheresis Criteria) from baseline to week 24

Study description

Background summary

Hypothesis: Blockade of ANGPTL3 with evinacumab will reduce LDL-C in patients with HoFH.

Homozygous familial hypercholesterolemia (HoFH) is a rare and serious genetic condition resulting in severely elevated low-density lipoprotein cholesterol (LDL-C) and accelerated cardiovascular disease (CVD). Familial hypercholesterolemia results from mutations in the low density lipoprotein receptor (LDLR).
HoFH is frequently caused by mutations in both alleles of the LDLR gene and results in the decreased clearance of LDL particles from plasma. Patients with HoFH have severe hypercholesterolemia, often 3 to 6 times normal (500 to 1000 mg/dL), which can lead to an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis.
Many of the therapies for hypercholesterolemia are dependent on their stimulating an increase in activity of the LDLR. Part of the basis for the refractory nature of treatments is linked to the mutations in the LDLR that are the driver of HoFH. The presence of mutations in both LDLR alleles can result in far less efficacy for therapies that rely on the LDLR as part of their mechanism of action. Examples of such therapies include statins and PCSK9 inhibitor antibodies.
Despite treatment with lipid modifying therapies (LMTs), such as pharmacological agents, as well as mechanical removal by lipid apheresis, many patients with HoFH remain far from their LDL-C treatment goal. Therefore, the need for more intensive treatment in HoFH, especially those patients with double null mutations remains.
Angiopoietin-like 3 (ANGPTL3) has recently emerged as a potential target for the treatment of elevated levels of triglycerides (TGs) and for the treatment of elevated levels of LDL-C, both risk factors for the development of CVD. ANGPTL3 acts as a natural inhibitor of lipoprotein lipase, an endothelial-bound enzyme involved in the hydrolysis of the TG content of very low density lipoproteins and chylomicron lipoproteins. Inhibiting ANGPTL3 may be a meaningful and well-tolerated strategy for lowering serum LDL-C and TGs.
Evinacumab (REGN1500) is a fully human mAb, created with Regeneron*s VelocImmune technology platform, which specifically binds to ANGPTL3. Experiments performed in animals demonstrate that the administration of evinacumab results in a reduction of serum LDL-C and serum TGs.
In a phase 1, first-in-human, placebo-controlled, double-blind, ascending single-dose study the maximal mean percent LDL-C decrease from baseline of 27.8% was observed on day 15 in the 20 mg/kg IV group (n=11) compared to a decrease of 4.5% in the placebo IV group (n=12).
In a randomized, double-blind, placebo-controlled, multiple ascending dose study achieved a mean percent reduction from baseline in LDL-C of 34.7% at day 57. Those patients who received evinacumab 300 mg SC every 2 weeks (Q2W) achieved a mean percent reduction in LDL-C of 33.4% from baseline. Evinacumab

was well tolerated in doses up to 20 mg/kg IV Q4W.
In an open-label, single-arm, proof-of-concept study in patients with HoFH, (Study R1500 CL 1331), evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, with a duration of effect of at least 10 weeks after a 15 mg/kg IV dose (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients enrolled in Study R1500-CL-1331 are homozygous for null mutations in the LDLR. Evinacumab provided meaningful reductions in LDL-C in these 3 null/null HoFH patients (26-44% percent change in LDL-C by week 4).
Evinacumab has been well tolerated at all dose levels in these studies.

Study objective

The primary objective of the study is:
* To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by evinacumab 15 mg/kg intravenously (IV) in comparison to placebo after 24 weeks in patients with homozygous familial hypercholesterolemia (HoFH).

The secondary objectives of the study are:
* To evaluate the effect of evinacumab 15 mg/kg IV on other lipid parameters (ie, apolipoprotein B [Apo B], non-high-density lipoprotein cholesterol [HDL-C], total-cholesterol [TC]) in patients with HoFH
* To evaluate the effect of evinacumab on LDL-C goal attainment
* To assess the effect of evinacumab on eligibility for apheresis (using German and US apheresis criteria)
* To evaluate the safety and tolerability of evinacumab 15 mg/kg in patients with HoFH
* To assess the pharmacokinetics (PK) of evinacumab in patients with HoFH
* To evaluate the potential development of anti-evinacumab antibodies

Study design

The study consists of 4 periods: up to 8-week run-in period (for patients who may require HoFH genotyping, for patients whose background medical lipid modifying therapy (LMT) has not been stable prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week double-blind treatment period (DBTP), and a 24-week open-label treatment period (OLTP), and a 24-week follow-up period after the last dose of study drug for those patients who choose not to enter the open-label study.
Patients who are not undergoing apheresis therapy, patients who have been on a stable apheresis schedule for at least 8 weeks before the screening visit, and patients on stable background medical LMT (as applicable) for at least 4 weeks (6 weeks for fibrates, 8 weeks for proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) before the screening visit, will enter a 2-week screening period.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to receive evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W for the double-blind portion of the study (24 weeks). Randomization will be stratified by apheresis treatment (Yes, No) and by region (Japan, Rest of World).
After completion of the DBTP, all patients will enter a 24-week OLTP and receive open-label evinacumab 15 mg/kg IV Q4W.
After completion of the 24-week OLTP, all patients who have successfully completed this study might have the opportunity to participate in a separate open-label (OL) study. All patients that enroll in the separate OL study will continue to receive open-label evinacumab at a dose of 15 mg/kg IV Q4W. Those patients who do not participate in the separate open-label study will undergo a 24 week follow-up after the last dose of study drug.

Intervention

In the double-blind treatment period, eligible patients will be enrolled to receive evinacumab 15 mg/kg IV Q4W
In the open-label portion of the study, all patients will receive evinacumab 15 mg/kg IV Q4W starting at week 24

Study burden and risks

Patients with HoFH have extremely high LDL-C levels, are far from their target level and will require significant reductions to get to their goal. Despite the approval of newer treatments including evolocumab, lomitapide and mipomersen, the need for more intensive therapies remains. Evinacumab could be a new addition to the armamentarium of LMT that could contribute to lowering the LDL-C of patients with HoFH. As mentioned above, in study R1500 CL-1331, evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, with a duration of effect of at least 10 weeks after a 15 mg/kg IV dose (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients in the study are homozygous for null mutations in the LDLR. Treatment with evinacumab in these difficult-to-treat patients reduced LDL-C by an average of 37.3% at week 4 with peak reductions up to 59.5%. Based on these data, it is expected that the addition of evinacumab to existing treatments will lead to significant LDL-C reductions in the HoFH population. The body of evidence from the statin literature shows that the relationship between LDL-C reduction and CV event reduction is approximately linear and for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C there is a corresponding 22% risk reduction in CV events (Cholesterol Treatment Trialists* Collaboration 2010). Moreover, the results from the recent outcomes trials with ezetimibe (IMPROVE-IT [Cannon 2015], alirocumab (ODYSSEY OUTCOMES [Steg 2018]) and evolocumab (FOURIER [Sabatine 2017]) reinforce this concept, providing additional evidence for the relationship between LDL-C lowering and reductions in CV events and the importance for patients to achieve their target LDL-C. Within the context of

this study in the HoFH patient population, additional reduction in LDL-C may get patients closer their LDL-C target, which could translate into significant benefits.
It is also expected that treatment with evinacumab will be well tolerated and have an acceptable safety profile. The accumulated safety information from the completed and ongoing clinical studies is marked by the absence of any important identified risks. There are potential risks that include systemic hypersensitivity reactions, immunogenicity, and embryofetal toxicity. These risks will be managed through careful patient selection and monitoring. For the potential embryofetal toxicity risk, there is a strict risk mitigation plan, including requirements for consistent use of contraception.
See protocol page 25-26 for more information.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Key inclusion criteria:
1. Male or female *12 years of age at the time of the screening visit
2. Diagnosis of functional HoFH
3. If undergoing LDL apheresis, must have initiated LDL apheresis at least 3 months prior to screening and must have been on a stable weekly or every other week schedule and stable settings for at least 8 weeks
4. Willing to consistently maintain his/her usual low fat or heart-healthy diet for the duration of the study, Note: Other protocol defined inclusion/exclusion criteria may apply.

Exclusion criteria

Key exclusion criteria:
1. LDL-C level <70 mg/dL (1.81 mmol/L) at the screening visit.
2. Background medical LMT (if applicable) that has not been stable before the screening visit
3. Lipid-apheresis schedule (every 7 or 14 days)/apheresis settings (if applicable) that have not been stable for at least 8 weeks before the screening visit
4. Use of nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit
5. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
6. Newly diagnosed (within 3 months prior to randomization visit) diabetes mellitus or poorly controlled (HbA1c >9%) diabetes
7. History of a MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit
8. Pregnant or breastfeeding women
9. Sexually active women of child bearing potential (WOCBP), who are unwilling to practice a highly effective birth control method prior to the initial dose, during the study, and for 24 weeks after the last dose of study drug
10. Sexually active men who are unwilling to use forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last dose of study drug, Note: Other protocol defined inclusion/exclusion criteria may apply.

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):	08-10-2018
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	evinacumab
Generic name:	evinacumab

Ethics review

Approved WMO Date:	26-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	23-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2021
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	EUCTR2017-001388-01-NL
ClinicalTrials.gov	NCT03399786
CCMO	NL64510.018.18