A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Varying Doses and Dose Regimens of Evinacumab in Patients with Persistent Hypercholesterolemia Despite Maximally Tolerated Lipid Modifying Therapy

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Ethical review	Approved WMO
Status	Completed
Health condition type	Metabolism disorders NEC
Study type	Interventional

Summary

ID

NL-OMON48629

Source
ToetsingOnline

Brief title
0456/0137 R1500-CL-1643

Condition

- Metabolism disorders NEC
- Vascular disorders NEC

Synonym

hyperlipidemia; high cholesterol

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Evinacumab, Persistent Hypercholesterolemia

Outcome measures

Primary outcome

The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 16 in the intent to treat (ITT) population, using all LDL-C values regardless of adherence to treatment.

Secondary outcome

The secondary efficacy endpoints are:

* Percent change in ApoB from baseline to week 16

* Percent change in non-HDL-C from baseline to week 16

* Percent change in TC from baseline to week 16

* Proportion of patients with * 30% reduction in calculated LDL-C at week 16

* Proportion of patients with * 50% reduction in calculated LDL-C at week 16

* Percent change in TGs from baseline to week 16

* Percent change in Lp(a) from baseline to week 16

* Proportion of patients with calculated LDL-C < 100 mg/dL (2.59 mmol/L) at week 16

* Proportion of patients with calculated LDL-C < 70 mg/dL (1.81 mmol/L) at week

16

* Proportion of patients with calculated LDL-C < 50 mg/dL (1.30 mmol/L) at week

16

* Percent change in calculated LDL-C, ApoB, non-HDL-C, TC, TG, and Lp(a) from

baseline to week 24 (only applicable to those patients receiving IV route of

study treatment administration)

Study description

Background summary

No randomized placebo-controlled clinical CV outcome trials of statin treatment have been conducted in patients with HeFH due to ethical concerns of withholding recommended therapy in this population. Clinical management of HeFH is largely based on extrapolation from the results of clinical outcomes trials conducted in patients with polygenic hypercholesterolemia, from studies in FH patients that used carotid intima-media thickness as a surrogate outcome, and from a small number of prospective observational studies in patients with FH. In 4 observational studies, statin therapy was shown to reduce the risk of CHD by 50% to 80% in patients with FH (Harada-Shiba 2010, Huijgen 2010, Vermissen 2008). Unfortunately, even after treatment, the risk in HeFH can still be almost 2-fold higher than the general population (Neil 2008).

Study objective

The primary objective of the study is to evaluate the reduction of low density lipoprotein cholesterol (LDL-C) by evinacumab in comparison to placebo after 16 weeks in patients with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH], or non-HeFH with a history of clinical atherosclerotic cardiovascular disease [clinical ASCVD]) persistent hypercholesterolemia despite receiving maximally-tolerated lipid-modifying treatment (LMT). Persistent hypercholesterolemia is defined as LDL C * 70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL C * 100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD.

Study design

The study consists of 4 periods: run-in period of up to 8 weeks (for patients whose background lipid modifying therapy [LMT] has not been stable prior to

screening, who are not already receiving a PCSK9 inhibitor, or whose background LMT has not been optimized), 2-week screening, 16 week double-blind treatment period for SC group and 24 week double blind treatment for IV group, and follow-up period that lasts 24 weeks after the last dose of study drug.

Intervention

Patients will be randomized 1:1:1:1:1:1:1 to one of 7 treatment groups as follows:
* 300 mg SC of evinacumab (REGN1500) once every week (QW), or
* 300 mg SC of evinacumab once every 2 weeks (Q2W) (alternating with placebo on opposite weeks), or
* 450 mg SC of evinacumab once every week (QW), OR
* 5 mg/kg IV of evinacumab once every 4 weeks (Q4W), or
* 15 mg/kg IV of evinacumab once every 4 weeks (Q4W), or
* Placebo SC once every week (QW)
* Placebo IV once every 4 weeks (Q4W)

Study burden and risks

A risk benefit assessment is provided in the protocol:

Section 3.2.3.
Of the current medications for lowering LDL-C, statins are the most commonly prescribed because they are inexpensive and have demonstrated the ability to reduce CHD events. PCSK9 inhibitor antibodies are a newer class of agents that significantly lower LDL-C and recently demonstrated a reduction in the risk of CV events (Sabatine 2017). Despite all of the available treatment options, particularly statins and PCSK9 inhibitor antibodies, some patients still do not reach their LDL-C goal and continue to have residual CV risk. In the Odyssey FH 1 and FH 2 studies, up to 19% and 28% in FH1 and FH2, respectively, did not meet their LDL-C target despite 24 weeks of treatment with alirocumab. Patient populations that continue to need additional LDL-C lowering include those with severe HeFH as well as severe non-FH patients with polygenic etiologies of their disease. It is important for all patients to achieve their LDL-C target because the body of evidence from the statin literature shows that the relationship between LDL-C reduction and CHD 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 CHD events (CTT study). Moreover, the results from recent outcomes trials with ezetimibe (IMPROVE-IT) and evolocumab (FOURIER) reinforce this concept, providing additional evidence for the relationship between LDL-C lowering and reduction in risks for CV events, thereby emphasizing the importance for patients to achieve their target LDL-C.
Evinacumab is a new treatment option that could get patients to their target LDL-C when added to a stable lipid-lowering regimen, including statins and a

PCSK9 inhibitor antibody. In the early clinical studies in healthy subjects, monotherapy treatment with evinacumab resulted in up to 40% reduction in LDL-C and up to 80% reduction in TG. In the R1500-CL-1331 study in patients with HoFH, treatment with evinacumab on top of a stable lipid lowering regimen resulted in peak mean LDL-C reductions of approximately 58%.
It is 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.
Taken together, these data show the positive benefit/risk assessment of treatment with evinacumab in patients with HeFH, or non-HeFH with clinical ASCVD, that have an LDL-C * 100 mg/dL (2.59 mmol/L), despite receiving a stable maximally tolerated statin and PCSK9 inhibitor antibody therapy.

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. Men and women, ages 18 through 80 at the screening visit;2. Diagnosis of primary hypercholesterolemia, either HeFH or non-HeFH with clinical ASCVD;3. A history of clinical ASCVD, for those patients who are non-HeFH.;4. Receiving a stable maximally tolerated statin (± ezetimibe) for at least 4 weeks at screening;5. Receiving alirocumab 150 mg SC Q2W, OR evolocumab 140 mg SC Q2W or 420 mg SC Q4W for at least 8 weeks prior to the screening visit;6. Serum LDL-C * 100 mg/dL at screening (1 repeat lab is allowed);7. Provide signed informed consent

Exclusion criteria

1. Known history of homozygous FH (clinically, or by previous genotyping);2. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins;3. Newly diagnosed diabetes (within 3 months prior to screening);4. Use of thyroid medications (except for replacement therapy which has been stable for at least 12 weeks before screening);5. Laboratory findings during screening period (not including randomization labs):;- Triglycerides > 400 mg/dL (> 4.52 mmol/L) for patients without a known history of diabetes mellitus; OR Triglycerides > 300 mg/dL (> 3.39 mmol/L) for patients with a known history of diabetes mellitus;- Positive test for Hepatitis B surface antigen and/or Hepatitis C antibody (associated with a positive HCV ribonucleic acid [RNA] polymerase chain reaction);- Positive serum beta-human chorionic gonadotropin or urine pregnancy test in women of childbearing potential;- Estimated glomerular filtration rate < 30 mL/min/1.73 m^2;- TSH > 1.5 x ULN;- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN;-Creatinine phosphokinase (CPK) > 3 x ULN at screenin (1 repeat lab is allowed);6. Systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening visit or time of randomization;7. History of heart failure (New York Heart Association [NYHA] Class II-IV) within 12 months before screening;8. History of MI, unstable angina leading to hospitalization, CABG surgery, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, TIA, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior screening;9. History of cancer within the past 5 years (except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer);10. Having received LDL apheresis within 2 months before screening;11. Pregnant or breast-feeding women;12. Women of childbearing potential who are unwilling to practice a highly effective birth control method;13. Sexually active men unwilling to use acceptable birth control

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-05-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evinacumab intravenous
Generic name:	Evinacumab intravenous
Product type:	Medicine
Brand name:	Evinacumab subcutaneous
Generic name:	Evinacumab subcutaneous

Ethics review

Approved WMO

Date:	16-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	18-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2021
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	EUCTR2017-001508-31-NL
ClinicalTrials.gov	NCT03175367
CCMO	NL62911.094.17

Study results

Date completed: 14-12-2020

Results posted: 15-12-2021

First publication
10-12-2021