An open-label study to evaluate the long-term safety and efficacy of evinacumab in patients with homozygous familial hypercholesterolemia

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The primary objectives of the study are- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg intravenous (IV) administered every 4 weeks (Q4W) in patients with homozygous familial hypercholesterolemia (HoFH).- To evaluate the...

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

Summary

ID

NL-OMON55891

Source
ToetsingOnline

Brief title
R1500-CL-1719 (0456/0171)

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 hypercholersterolemia, Phase 3

Outcome measures

Primary outcome

The primary endpoint is the incidence and severity of treatment-emergent

adverse events (TEAEs) and other safety variables during the open-label

treatment period in patients treated with evinacumab 15 mg/kg IV Q4W.

Secondary outcome

The secondary efficacy endpoints are:

- The percent and absolute change in LDL-C over time

- The percent and absolute change in Apo B over time

- The percent and absolute change in non-HDL-C over time

- The percent and absolute change in TC over time

- The percent and absolute change in TGs over time

Study description

Background summary

This study is being conducted in patients with HoFH , which may include patients who have participated in a previous evinacumab study and also evinacumab-naïve patients with HoFH. The study is intended to provide long-term safety, efficacy and pharmacokinetics (PK) information on evinacumab treatment of adult and adolescent patients in HoFH.

Hypothesis: Blockade of ANGPTL3 with evinacumab will reduce or maintain

consistent long-term reduction in LDL-C and demonstrate an acceptable safety profile in patients with HoFH.

Study objective

The primary objectives of the study are
- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg intravenous (IV) administered every 4 weeks (Q4W) in patients with homozygous familial hypercholesterolemia (HoFH).
- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg IV administered Q4W in adolescent patients with HoFH.

The secondary objectives of the study are:
- To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, low-density lipoprotein cholesterol [LDL-C], apolipoprotein B [Apo B], non-high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], and triglycerides [TG]) in patients with HoFH
- To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, LDL-C, Apo B, non-HDL-C, TC, and TG) in adolescent patients with HoFH
- To evaluate the potential development of anti-evinacumab antibodies

Study design

This is an open-label study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. Eligible patients for this study are male and female patients with HoFH, receiving stable lipid modifying therapy (LMT), as applicable. Lipid modifying therapy may include a maximally tolerated statin, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor antibody and lipoprotein apheresis. Patients with HoFH who have participated in a previous evinacumab study (eg, R1500-CL-1331 and R1500-CL-1629) and evinacumab-naïve patients with HoFH are eligible.

This study consists of 4 periods: a run-in period, a screening period, an open-label treatment period and a follow-up period.

Run-in Period
Patients whose HoFH diagnosis cannot be confirmed by the clinical criteria listed or from previous genotyping results, may enter the run-in period to determine their mutation status.

Screening period
All evinacumab-naïve patients who are on a stable background LMT will enter a 2-week screening period. Patients who participated previously in an evinacumab study and do not enter this study within 7 days of completing the end of study (EOS) visit of the previous study, must undergo screening.

Open-Label Treatment Period:
Patients who completed the EOS visit in the previous evinacumab study within 7 days of the baseline/day 1 visit for this open-label study do not have to undergo the screening visit and may enroll directly into this study if they fulfill all of the inclusion criteria and none of the exclusion criteria. The EOS visit from the previous study can serve as the baseline/day 1 visit for this open-label study and overlapping assessments do not need to be repeated in this study. Baseline assessments and procedures that do not overlap with assessments at the EOS visit of the previous study should be performed after all EOS assessments and procedures have been completed in the previous evinacumab study.

Starting on day 1 (baseline), all patients will receive evinacumab 15 mg/kg IV administered every 4 weeks (Q4W). Evinacumab treatment will continue until one of the following occurs: (1) Clinical development of evinacumab for the indication described in this study protocol is discontinued, (2) Clinical development of evinacumab is terminated, (3) Risk/benefit of evinacumab in this patient population is deemed unfavorable, (4) Evinacumab is approved by the regulatory authority governing the location of the study site, (5) For local discontinuation of study: a decision has been made not to seek approval of an indication for treatment of patients with HoFH in the regulatory region in which the study is being conducted (or, to discontinue efforts to obtain such an approval)

Follow-up period: Patients will be followed for 24 weeks after receiving the last dose of study drug.

Intervention

Evinacumab 15 mg/kg IV administered Q4W.

Study burden and risks

Please refer to the appendix in the subject information sheet for an overview of the risks and side effects.

Contacts

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US

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Regeneron Pharmaceuticals, Inc.

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US

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

A patient must meet the following criteria to be eligible for inclusion in the study:
1. Male and female patients >=12 years of age with HoFH. Patients aged >=12 years old will be enrolled only in countries where permitted by the Regulatory Agency and Institutional Review Board (IRB) or Ethics Committee (EC).
2. Diagnosis of functional HoFH by at least 1 of the following genetic or clinical criteria:
a. Documented functional mutation or mutations in both LDLR alleles
Note: patients who have null receptor mutations on both LDLR alleles, ie, double null, are eligible
b. Presence of homozygous or compound heterozygous mutations in Apo B or PCSK9
Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible
c. Untreated TC >500 mg/dL (12.93 mmol/L) and TG <300 mg/dL (3.39 mmol/L) AND
both parents with documented TC >250 mg/dL (6.47 mmol) OR cutaneous or tendinous xanthoma before the age of 10 years
3. For patients who have participated in a previous evinacumab or alirocumab study: completion of the study in which they participated.

4. Willing and able to comply with clinic visits and study-related procedures.
5. Provide signed informed consent.

Exclusion criteria

Exclusion Criteria for Evinacumab-Naïve Patients, A patient who meets any of the following criteria will be excluded from the study:
1. Concomitant medications and procedures that have not been stable prior to the baseline visit (see Section 7.7.2 for medications and procedures and their associated required duration of therapy).
2. Any new condition or worsening of an existing condition, which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
3. 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 baseline visit
4. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
Note: patients on thyroid replacement therapy can be included if the dosage of replacement therapy has been stable for at least 12 weeks prior to screening and the thyroid stimulating hormone (TSH) level is within the normal range of the central laboratory at the screening visit
5. Newly diagnosed (within 3 months prior to screening visit diabetes mellitus or poorly controlled (HbA1c >9%) diabetes
6. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to screening visit
Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as *systemic* and are allowed
7. Use of estrogen or testosterone therapy unless the regimen has been stable 6 weeks prior to the screening visit and no plans to change the regimen during the study
8. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit
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. History of New York Heart Association (NYHA) Class IV heart failure within 12 months before screening. Please refer to the protocol for exclusion criteria
11 - 19. Exclusion Criteria for Patients from a Previous Evinacumab Study, A patient who meets any of the following criteria will be excluded from the study:
1. Significant protocol deviation in the previous study based on the investigator*s judgment, such as non-compliance by the patient.

2. Concomitant medications and procedures that have not been stable prior to the baseline visit (see Section 7.7.2 for medications and procedures and their associated required duration of therapy).
3. Adverse event leading to permanent discontinuation from previous study.
4. Any new condition or worsening of an existing condition, which in the opinion of the
investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study. Please refer to the protocol for exclusion criteria 5 - 19.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-04-2018
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	evinacumab

Ethics review

Approved WMO

Date:	10-01-2018

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2021
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	EUCTR2017-003170-13-NL
ClinicalTrials.gov	NCT03409744
CCMO	NL64053.018.17