A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia for the Prevention of Recurrent Acute Pancreatitis

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Ethical review	Approved WMO
Status	Completed
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON52186

Source
ToetsingOnline

Brief title
R1500-HTG-20118 (ICON 0456/0418)

Condition

- Lipid metabolism disorders

Synonym
elevated fat levels in the blood, Severe Hypertriglyceridemia

Research involving

Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: The study sponsor as listed in B6/7.

Intervention

Keyword: Acute pancreatitis, Hypertriglyceridemia, Non-high-density-lipoproteïnecholesterol, Total cholesterol

Outcome measures

Primary outcome

Primary Efficacy: The primary endpoint is for efficacy: the proportion of

patients with at least 1 positively adjudicated AP episode during the 52 weeks

of the DBTP.

Secondary Efficacy:

Key Secondary Efficacy:

• Percent change in ApoC3 from baseline to week 52

• Percent change in fasting TGs from baseline to week 52

Other Secondary Efficacy:

• Percent change in other fasting standard lipid profile parameters (total

cholesterol [TC], non-high-density lipoprotein cholesterol [non-HDL-C]) from

baseline to week 52

• Percent change in other fasting specialty lipoprotein parameters (ApoB48,

ApoB100 levels, and NMR-determined particle size and number) from baseline to

week 52

• Number of independently adjudicated episodes of AP per patient during 52 weeks of the DBTP

Safety Endpoints:

• Incidence and severity of treatment-emergent adverse event (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and other safety variables in patients treated with evinacumab throughout the study

• Incidence of treatment-emergent ADA and NAb

Procedures and Assessments

Efficacy will be assessed by measurement of adjudicated events of AP, and measurement of lipids and lipoproteins. Safety will be monitored via AE reporting, physical examinations, routine vital signs, clinical laboratory tests (blood chemistry and hematology), and standard 12-lead ECG. Serum samples for the determination of total evinacumab and total ANGPTL3 concentrations, and ADA and NAb will be collected. Serum and plasma samples will be collected for analysis of additional biomarkers.

Secondary outcome

Other Endpoints:

• The percent change in fasting HDL-C and LDL-C from baseline to week 52

• Concentrations of total evinacumab and total ANGPTL3 over time

Study description

Background summary

Severely elevated levels of serum triglycerides (TGs) are associated with an increased risk for acute pancreatitis (AP). Episodes of AP secondary to severe hypertriglyceridemia (sHTG; TG >880 mg/dL [10 mmol/L]) frequently require hospitalization, and while most events can be treated with conservative therapy such as intravenous fluids and pain management, approximately 20% of patients suffer severe attacks associated with prolonged hospitalization and significant morbidity and mortality. Further, a prior episode of sHTG-associated AP markedly increases the risk for recurrent AP. While current lipid guidelines recommend lifestyle interventions and medications to lower TG levels to prevent AP, patients with sHTG often require robust (>50%) reductions in TG to lower the risk of AP. Indeed, a substantial proportion of patients have persistent hypertriglyceridemia (HTG), despite the use of multiple medications to lower TG levels. Current available therapies for lowering TG levels (eg, statins, fibrates, niacin, omega-3 fatty acids) typically provide 20% to 50% reductions in TG levels, which is often insufficient to lower TGs to a target level of <500 mg/dL (5.6 mmol/L).
Patients with TGs >880 mg/dL (>10 mmol/L) typically have chylomicronemia that may be either multifactorial (polygenic and environmental) in origin, or much more rarely, due to the presence of highly penetrant gene mutations in lipoprotein lipase (LPL) or genes encoding proteins in the LPL pathway (APOA5, APOC2, GPIHBP1, and LMF1), as observed in Familial Chylomicronemia Syndrome (FCS). Lipoprotein lipase is an endothelial bound enzyme involved in the hydrolysis of the TG content of very-low-density lipoproteins (VLDL) and chylomicron lipoproteins. Mutations in the LPL gene lead to varying levels of loss of LPL functional activity and elevated levels of plasma TGs, especially in chylomicrons. However, there is a high degree of genetic polymorphism and combinatorial effects of genes, diseases (such as type 2 diabetes), and environment. There is an unmet medical need for additional treatment options for patients with sHTG and a history of AP to further lower TG levels and the risk of recurrent attacks of AP, regardless of their genetic background.
Angiopoietin-like 3 (ANGPTL3) acts as a natural inhibitor of LPL and has emerged as a target for the treatment of elevated levels of TG and low-density lipoprotein cholesterol (LDL C). Loss of function of ANGPTL3 in humans has been associated with reductions in TG and LDL C.
Evinacumab (REGN1500) is a human IgG4 monoclonal antibody (mAb) specific for ANGPTL3. It is currently approved as an adjunctive treatment for homozygous familial hypercholesterolemia (HoFH, EvkeezaTM) and is being evaluated for treatment of dyslipidemia including HTG. Evinacumab has been studied in approximately 580 individuals with elevations in LDL C and TG and has been generally well tolerated up to single doses of 20 mg/kg intravenously (IV) and in multiple subcutaneous (SC) doses up to 450 mg administered weekly (QW), and 20 mg/kg IV administered every 4 weeks (Q4W) for approximately 8 weeks (ie 2 doses).
A phase 2, randomized, placebo-controlled study (R1500-HTG-1522) was conducted

to evaluate the safety and TG-lowering effects of evinacumab in patients with various causes of sHTG, and at risk for AP, including homozygous/heterozygous loss of function (LoF) gene mutations in LPL, mutations in other genes in the LPL pathway, and other polygenic/environmental causes of severely elevated TGs. The 12-week, double-blind treatment period (DBTP) enrolled 52 patients who were randomized to receive either evinacumab 15 mg/kg or matching placebo administered IV Q4W, followed by a 12-week, single-blind treatment period (SBTP) in which all patients (N=47) received evinacumab Q4W.
The primary endpoint was predefined as the mean within-patient change in TGs, and the study did not meet the threshold of a clinically important reduction (>40%). This applied to the overall study population and also for genotypic strata based on the presence of LPL pathway LoF mutations. Several factors may have contributed to a lack of efficacy. There was large variability in TGs, which was compounded by the absence of a diet-stabilization period and efficacy determined by a single post-treatment TG measurement. In addition, there was variability in drug exposure, where patients with the lowest trough levels of evinacumab had little to no treatment response. In this context, when examining median percent changes to minimize the impact of outliers, the evinacumab treated patients overall showed a clinically important reduction (>40%) in fasting TGs at each post-baseline visit, culminating in a median reduction of approximately 57% at week 12 during the DBTP. The treatment effect was even more pronounced when excluding patients with FCS, where non-FCS patients had a median reduction in TGs of approximately 80%. When including patients that switched to evinacumab during the SBTP, the median percent reduction in TGs after 12 weeks of evinacumab exposure was approximately 70% for non FCS patients.
In the DBTP, 5 patients (3 in the evinacumab group; 2 in the placebo group) experienced an episode of AP (all serious adverse events or SAEs); all resolved within 7 days. For the evinacumab-treated patients, 1 participant had FCS and did not have a TG response to therapy; 1 patient had an episode of AP within 48 hours after receiving his first dose of evinacumab; 1 patient had persistently low trough concentrations of evinacumab. Treatment-emergent adverse events (TEAEs) that occurred more frequently in the evinacumab group compared to the placebo group included Abdominal pain (14.3% versus 12.5%), Headache (11.4% versus 6.3%), and Constipation (8.6% versus 0). In the SBTP, 12 (25.5%) patients had SAEs of Acute pancreatitis; none was considered related to the study drug. The majority of episodes occurred during the off-drug period (>4 weeks after the last dose of evinacumab) and episodes of AP were not independently adjudicated, with some patients diagnosed with AP despite the absence of pathologic findings on pancreatic imaging and/or elevated lipase/amylase levels.
The current study is a phase 2b randomized, placebo-controlled study intended to demonstrate that evinacumab can prevent recurrent episodes of HTG-associated AP in patients with sHTG, but without FCS due to mutations in LPL. The secondary aims are to evaluate the effects of evinacumab on safety and changes in biomarkers of TG-rich lipoprotein metabolism, including serum TG, ApoC3, ApoB48, and ApoB100 in this patient population.

Additional background information on the study drug and development program can be found in the Investigator*s Brochure.

Study objective

The primary objective of the study is to determine the proportion of patients with elevated TGs, without Familial Chylomicronemia Syndrome (FCS) due to loss of function (LoF) mutations in lipoprotein lipase (LPL), and a history of hypertriglyceridemia (HTG)-associated acute pancreatitis (AP*) who experience a recurrent episode of AP after treatment with evinacumab versus placebo.

The secondary objectives of the study are:
• To determine the change in the standard lipid profile after therapy with evinacumab versus placebo
• To determine the changes in specialty lipoprotein parameters (ApoC3, ApoB48, ApoB100, and nuclear magnetic resonance [NMR] lipid profile) after therapy with evinacumab versus placebo
• To measure the number of AP episodes per patient
• To assess the safety and tolerability of evinacumab
• To assess the potential immunogenicity of evinacumab
• To assess the concentrations of total evinacumab and total angiopoietin-like 3 (ANGPTL3)
*Includes adult patients with 1) elevated baseline fasting TGs >880 mg/dL and history of 1 HTGassociated AP within 24 months of screening or 2) elevated baseline fasting TG values >500 mg/dL in patients with a history of 2 or more HTG-associated AP within 24 months or 3) elevated baseline fasting TG values >500 mg/dL with a prior documented fasted TG values >1000 mg/dL and a history of 1 or more HTG- associated AP within 24 months. All participants are without FCS due to LPL loss of function mutations.

Study design

This is a phase 2b, multicenter, international, randomized, placebo-controlled study intended to demonstrate that evinacumab can prevent recurrent AP in patients with severe hypertriglyceridemia (sHTG) and a recent history of HTG-associated AP. Approximately 120 adult patients will be randomized 1:1 to receive evinacumab or matching placebo.

The study consists of 3 periods: a screening period, a double-blind treatment period (DBTP), and a safety follow-up period. The screening period of up to 28 days will determine participant eligibility and will include an evaluation of prior episodes of HTG-associated AP, genotyping to exclude patients with familial chylomicronemia syndrome (FCS) due to loss of function mutations in lipoprotein lipase, and 2 measurements of fasting TG levels separated by at least 2 days. Patients must have baseline fasting TGs

>880 mg/dL on each of the 2 measurements and a history of HTG-associated AP within 15 months of screening to be enrolled in the study. Patients who fulfill all the eligibility criteria will be randomized and receive their first dose of assigned study drug on day 1, with subsequent doses administered approximately every 4 weeks (Q4W) during the 52-week DBTP. This will be followed by a 48-week off-drug follow-up period. Efficacy will be assessed by measuring the number of patients with at least 1 independently adjudicated positive event of AP over 52 weeks of treatment with evinacumab versus placebo. The study will have an independent committee to adjudicate these episodes in accordance with clinical standards for diagnosis of AP. Efficacy will also be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Safety will be assessed throughout the study by comparing the frequency and severity of adverse events (AEs) between the evinacumab and placebo groups, as well as evaluating abnormal laboratory findings, electrocardiogram (ECG) findings, and anti-drug antibody (ADA) and neutralizing antibodies (NAb) assessments.

Intervention

Study Drug: Evinacumab
Dose/Route/Schedule: 20 mg/kg administered intravenously (IV) over a 1-hour infusion Q4W, ±4 days
Placebo: Matching placebo
Route/Schedule: Intravenous infusion Q4W (±4 days)

Study burden and risks

See section 3.3 of the protocol Benefit/Risk assessment.

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
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. Adults 18 to 80 years of age without FCS due to LPL loss of function mutations
2. Documented history of 1 HTG-associated AP episode within 24 months of screening (can be determined by study investigator; does not need to be confirmed by independent adjudication committee).
3. Fasting serum TG value >880 mg/dL (10 mmol/L) on 2 occasions at least 2 days apart determined during the screening period. Triglyceride measurement can be repeated once for values >500 mg/dL (5.6 mmol/L) but <880 mg/dL (10 mmol/L)
OR
Fasting serum TG value >500 mg/dL (5.6 mmol/L) determined during the screening period in patients with a history of 2 or more HTGassociated AP episodes within 24 months of screening
OR
Fasting serum TG value >500 mg/dL (5.6 mmol/L) determined during the screening period and a documented fasted serum TG value >1000 mg/dL (11.3 mmol/L) and a history of 1 or more HTG-associated AP episode(s) within 24 months of screening.
4. Stable dose of lipid-lowering therapy (>=8 weeks) and willingness to maintain a stable regimen throughout the study
5. Body mass index >=18.0 and <=45.0 kg/m2
6. Compliance with a stable diet and exercise regimen at screening and willingness to continue the diet through the end of the study
7. Willing and able to comply with clinic visits and study-related procedures
8. Provide informed consent signed by study patient or legally acceptable representative
9. Able to understand and complete study-related questionnaires

Exclusion criteria

A patient who meets any of the following criteria will be excluded from the study:
1. Hospitalization for AP within 4 weeks of screening
2. Known genetic FCS defined as homozygous or compound heterozygous LoF mutations in LPL, as documented by prior genotype result or determined from FCS genotyping at screening (see Section 9.2.7).
3. Symptomatic gallstone disease within 6 months prior to screening. Incidental and/or asymptomatic gallstones are permitted. Patients with symptomatic gallstone disease in the past 6 months who have undergone cholecystectomy >3 months prior to screening are permitted.
4. Use of any medication or nutraceutical known to alter serum lipids which has not been part of a stable therapeutic regimen for at least 8 weeks, and there are no plans to change the regimen during the study
5. Presence of any clinically significant, uncontrolled endocrine disease known to influence serum lipids, including but not limited to:
a. Newly diagnosed (within 3 months) diabetes by medical history, including screening value glycosylated hemoglobin (HbA1c) >6.5% without a prior history of diabetes
b. Diabetes with HbA1c >10.0%
c. Thyroid disease with thyroid-stimulating hormone (TSH) normal (LLN) or >1.5x ULN
d. Thyroid replacement therapy that has not been stable for at least 12 weeks

Note: For laboratory values, 1 repeat measurement is allowed. Other laboratory values that meet the inclusion/exclusion criteria do not need to be repeated.
6. Use of estrogen or testosterone therapy unless the regimen has been stable in the past 6 weeks and there are no plans to change the regimen during the study
7. Any clinically significant abnormality identified at the time of screening that, in the judgment of the investigator or any sub-investigator, would preclude safe completion of the study or constrain endpoints assessment; eg, major systemic diseases, patients with short life expectancy, or considered by the investigator or any sub-investigator as inappropriate for this study for any reason, including but not limited to:
a. Deemed unable to meet specific protocol requirements, such as scheduled visits
b. Deemed unable to tolerate injections, as per the patient or the investigator
c. Part of a vulnerable population such as the institutionalized
d. Presence of any other conditions (eg, geographic or social), either actual or anticipated, that the investigator feels would restrict or limit the patient*s participation for the duration of the study
8. Laboratory findings (for the reason that patients with these findings, who have a higher likelihood of liver, muscle, or kidney adverse events regardless of treatment assignment, are expected to be rare, they may not be evenly distributed across treatment groups and thus may confound the analysis of

safety):
a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 according to 4 variable Modification of Diet in Renal Disease study equation (MDRD, calculated by central laboratory)
b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN at screening
c. Creatine phosphokinase (CPK) >3x ULN at screening

Note: For all laboratory values, 1 repeat measurement is allowed.
9. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit or time of randomization (1 repeat allowed). The uneven distribution of these patients across treatment groups could confound the analysis of safety.
10. History of heart failure (New York Heart Association [NYHA] Class III-IV) within 12 months before screening. The uneven distribution of these patients across treatment groups could confound the analysis of safety.
11. Within 3 months of screening, a history of myocardial infarction (MI), unstable angina leading to hospitalization, coronary artery bypass grafting (CABG) surgery, percutaneous coronary interventions (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack (TIA), carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease. The uneven distribution of these patients across treatment groups could confound the analysis of safety.
12. Significant concomitant illness including, but not limited to: cardiac, renal, neurological, endocrinological, hepatic, metabolic, or lymphatic disease, that would adversely affect the patient*s participation in the study
13. 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

See protocol for further inclusion criteria

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-03-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evkeeza
Generic name:	Evinacumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-09-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-12-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2021-000437-13-NL
ClinicalTrials.gov	NCT04863014
CCMO	NL78035.100.21

Study results

Date completed:	02-02-2023
Results posted:	17-11-2023

Summary results
Trial ended prematurely

First publication
21-09-2023