A multicenter, randomized, double-blind, placebo-controlled, crossover trial to evaluate the effects of evolocumab added to standard lipid-lowering therapy on fasting and post fat load lipids in patients with Familial Dysbetalipoproteinemia.

Published: 01-08-2019
Last updated: 10-01-2025

To evaluate the effect of 12 weeks subcutaneous evolocumab (140 mg pre-filled pen every 2 weeks) compared to placebo on post fat load non-HDL-C levels in 30 subjects with FD, in a multicenter, randomized, placebo-controlled, double-blind, crossover...

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

Summary

ID

NL-OMON49866

Source
ToetsingOnline

Brief title
EVOLVE-FD

Condition

- Lipid metabolism disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym

Familial Dysbetalipoproteinemia, Fredrickson Type III hyperlipoproteinemia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: cholesterol, evolocumab, familial dysbetalipoproteinemia (FD), postprandial

Outcome measures

Primary outcome

The primary endpoint is non-HDL-C AUC (area under the curve).

Secondary outcome

1. Fasting, post fat load AUC and iAUC of total cholesterol (TC), LDL-C (directly measured), HDL-C, TG, ApoB and Lp(a); as well as fasting non-HDL-C after 12 weeks treatment with subcutaneous evolocumab (140 mg pre-filled pen every 2 weeks) compared to placebo in subjects with FD on standard lipid-lowering therapy.

2. Percentage change and absolute change from baseline in fasting and post fat load AUC and iAUC of non-HDL-c, TC, LDL-C (directly measured), HDL-C, TG, ApoB and Lp(a) after 12 weeks treatment with subcutaneous evolocumab (140 mg pre-filled pen every 2 weeks) compared to placebo in subjects with FD on standard lipid-lowering therapy.

3. Fasting and post fat load AUC and iAUC of lipoprotein (CM, VLDL, IDL, LDL

and HDL) concentrations and composition (triglycerides, cholesterol, ApoB and apolipoproteins) and metabolic parameters after 12 weeks treatment with subcutaneous evolocumab (140 mg pre-filled pen every 2 weeks) compared to placebo in patients with FD on standard lipid-lowering therapy.

4. Post fat load AUC and iAUC of ApoB48-containing lipoprotein concentrations (chylomicrons, chylomicron remnants) after 12 weeks treatment with subcutaneous evolocumab (140 mg pre-filled pen every 2 weeks) compared to placebo in patients with FD on standard lipid-lowering therapy.

5. Occurrence of adverse events after 12 weeks treatment with subcutaneous evolocumab (140 mg pre-filled pen every 2 weeks) compared to placbo in subjects with FD on standard lipid-lowering therapy.

Study description

Background summary

Patients with familial dysbetalipoproteinemia (FD) have increased triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C), beta VLDL, premature atherosclerosis and cardiovascular disease. They also have a delayed postprandial triglyceride and chylomicron (CM) remnant clearance. Postprandial hypertriglyceridemia is associated with increased vascular risk. Although combination therapy with statin and fibrate is recommended in the treatment of patients with FD, there is a substantial amount of patient who do not reach their treatment target with this medication. Furthermore no information is available about the postprandial effects of adding evocolumab to standard lipid lowering therapy in FD patients.

Study objective

To evaluate the effect of 12 weeks subcutaneous evolocumab (140 mg pre-filled

pen every 2 weeks) compared to placebo on post fat load non-HDL-C levels in 30 subjects with FD, in a multicenter, randomized, placebo-controlled, double-blind, crossover study.

Study design

Multicenter, randomised, placebo-controlled, double-blind, crossover trial. It consists of 2 treatment periods of 12 weeks in which patients receive evolocumab and placebo in a randomised order. Between treatment periods is an 8 week cross-over period. Before and at the end of the 2 treatment periods patients visit the hospital for an oral fat load. Before and after the oral fat load blood samples are collected through an intravenous catheter. Patients have to stay until 8 hours after the oral fat load and receive a meal at the end. Before the visits to the hospital people have to fast for at least 12 hours (meaning that they cannot eat or drink anything, except water). The study lasts 40 weeks excluding screening visit (-2 to -4 weeks prior to the first baseline visit).

Intervention

Evolocumab 140 mg subcutaneous every 2 weeks

Study burden and risks

Risks: low but known and unknown side effects of evolocumab can occur. Minimal risk concerning venapunctions are pain, hematoma or infection of injection site.

Burden: Patients are asked to keep a stable diet and alcohol consumption. They have to visit the hospital 5 times in total. Prior to each visit, patients are asked to fast for at least 12 hours and to fast 8 hours after the oral fat load. Four of the five visits include ingestion of an oral fat load (sweetened fresh cream). Patients might not like the taste of the cream. The four visit can lasts up to 9 hours. The screening visit lasts 60 minutes.

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. Subjects diagnosed with Familial Dysbetalipoproteinemia; defined as;
*known *2*2 genotype or known dominant APOE mutation genotype (confirmed by genotyping or isoelectric focusing) and a phenotype of familial dysbetalipoproteinemia (defined as an ApoB/TC ratio < 0.15, TC > 5 mmol/L and TG > 3 mmol/L or non-HDL-c/ApoB ratio > 6.55 mmol/g; with or without medication.
2. If using any lipid lowering treatment: dose must be stable for at least three months with non-HDL-C levels > 1.6 mmol/L.
3. >=18 or =< 80 years years old (on the day of signing informed consent).
4. Women are postmenopausal and not receiving systemic cyclic estrogen hormone agonist/antagonist therapy to prevent external effects due to estrogen on lipoprotein metabolism. Postmenopausal status is defined as:
*no menses for >=3 years or;
*no menses for >=1 year but <3 years and confirmed by FSH levels elevated into the postmenopausal range (15-150 IU/L).
5. Willingness to maintain a stable diet for the duration of the study.
6. Understanding of the study procedures, alternative treatments available, and risks involved with the study and voluntarily agreement to participate by giving written informed consent.

Exclusion criteria

1. Intolerance, known allergy or hypersensitivity to evolocumab (or other

PCSK-9 monoclonal antibodies), latex or any of the components of the medication.
2. Current or prior exposure ((< 1 year before screening) and not discontinued with PCSK9-inhibitor mAbs due to side effects) to evolocumab or another PCSK9-inhibitor mAb.
3. Unable or unwilling to drink an oral fat load.
4. Premenopausal women.
5. Uncontrolled diabetes as defined by a HbA1c >69 mmol/mol.
6. BMI >40 kg/m2.
7. Uncontrolled blood pressure with systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg.
8. Increased hepatic enzymes, defined as alanine transaminase (ALAT) or aspartate transaminase (ASAT) >3 times the ULN, or active liver disease defined as non alcoholic steatohepatitis (NASH), cirrhosis or Child Pugh B and C, or history of chronic active hepatitis B or C; subjects with documented resolution after treatment are permitted.
9. Impaired renal function, defined by an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2, and/or need of renal placement therapy or other clinically significant renal disease.
10. (Sub)clinical hypothyroidism defined as TSH >5.0 mcl/U/mL or (sub)clinical hyperthyroidism defined as TSH < 0.35 mcl/U/ml.
11. Increased levels of creatinine kinase defined as >3 times the ULN.
12. Increased fasting levels of triglycerides defined as >10 mmol/L.
13. History of organ transplantation.
14. Current use or use in the past 3 months of immunosuppressive medication.
15. Use of fish oil or red yeast rice, bempedoic acid, niacin, CETP inhibitors, lomitapide, mipomersen < 6 weeks prior to the study or the use of siRNA targeting PCSK9 inhibitors < 36 weeks prior to the study.
16. Active malignancy (<2 year prior to informed consent), except non-melanoma skin cancer or carcinoma in situ of the cervix.
17. Known infection with Human Immunodeficiency Virus (HIV) or AIDS.
18. Known celiac disease or other disorder associated with significant intestinal malabsorption, including short-bowel syndrome after intestinal resection or gastric bypass.
19. Known galactose-intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption.
20. Alcohol use, defined as >14 alcoholic consumptions per week for women and >21 alcohol consumptions per week for men. One alcohol consumption unit is defined as follows: 350 mL beer, 150 mL wine or 45 mL alcohol for mixed drinks.
21. Current participation or participation in a study with an investigational compound or device within 30 days of signing informed consent.
22. Any medical, social or physiological circumstance which interferes the study, based on judgement by the principal investigator.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-10-2019
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Repatha
Generic name:	Evolocumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-08-2019
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	12-09-2019
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	03-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	08-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-02-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-003476-12-NL
ClinicalTrials.gov	NCT03811223
CCMO	NL67476.041.19

Study results

Date completed:	07-10-2021
Results posted:	26-05-2023

First publication
26-05-2023