Impact of Triglyceride-Lowering on Inflammatory Activity in Patients with Hypertriglyceridemia

Published: 28-03-2022
Last updated: 05-04-2024

To study the impact of AKCEA-APOCIII-LRx on lipid and inflammatory measurements in the fasting and postprandial phase.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON51943

Source
ToetsingOnline

Brief title
CIRCE

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
high levels of triglyceride, Hypertriglyceridemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: IONIS,ISIS Pharmaceuticals

Intervention

Keyword: - Cardiovascular disease., - Hypertriglyceridemia, - Inflammation, - Lipoproteins

Outcome measures

Primary outcome

The primary outcomes are:

• The impact of ISIS 678354 on a mass cytometry monocyte phenotype panel;

expression markers such as CD14 and CD16.

• Postprandial triglyceride AUC change at the primary analysis time point from

baseline of the treatment group as compared to placebo.

Secondary outcome

The secondary outcome is:

• The mean percentage change in fasting apoC-III and triglyceride levels

between the treatment and placebo group, at the primary analysis time point,

compared to baseline.

Exploratory study parameters/endpoints

• The mean percentage change of the following parameters between the treatment

and placebo group, at the primary analysis time point, compared to baseline:

o Lipid parameters: LDL-C, HDL-C, VLDL-C, TC, (non-HDL-C), apoA-I, apoB,

apoB48, Lp(a), remnant cholesterol (RC) (by a deika-senken assay)

o Inflammatory parameters: hsCRP, IL-6, Il-1beta, IL-10, IL-18, E-selectin,

P-selectin, soluble ICAM, soluble VCAM, von Willebrand factor

• CD14-bead isolation of monocytes for:

o Lipid droplets, lipid size with Nile Red Quantifier (NRQ)

• Kinetic monocyte transendothelial migration (TEM) assay in the fasting and

postprandial phase, comparing the treatment with the placebo group

• Extracellular vesicle count and composition

• T-cell functionality assays, in vitro cytokine production and epigenetic

changes

Study description

Background summary

Hypertriglyceridemia is an independent risk factor for atherosclerotic cardiovascular disease with no therapeutic options currently widely adopted. AKCEA-APOCIII-LRx is a promising novel drug, targeting apolipoprotein CIII (Apo CIII), an important regulator of triglyceride metabolism. Is has been shown to effectively and safely reduce triglyceride levels. However, its effect on inflammatory pathways, an important driver of atherosclerosis, remains to be elucidated.

Study objective

To study the impact of AKCEA-APOCIII-LRx on lipid and inflammatory measurements in the fasting and postprandial phase.

Study design

A placebo controlled randomized clinical trial with 30 participants.

Intervention

The intervention group receives 80mg AKCEA-APOCIII-LRx twice subcutaneously with an interval of four weeks, as compared to a placebo group.

Study burden and risks

Participants will be randomized to either AKCEA-APOCIII-LRx or placebo and will be subjected to several blood testing, both in the fasting and the postprandial phase. AKCEA-APOCIII-LRx provides specific uptake in the lever, thereby increasing efficacy while minimizing side-effects. With only known injection site reactions, AKCEA-APOCIII-LRx can safely be administered, resulting in a

low risk for participants. The burden associated with participation entails multiple blood withdrawals and two oral fatloads. The yield for participants lies in the contribution to current knowledge of this drug. In the future, patients will benefit from an effective treatment when there is a drug on the market, this research will aid this purpose.

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

- Adults between 18 and 75 years old
- Triglycerides > 4mmol/l (350 mg/dl)

Exclusion criteria

- Molecularly diagnosed familial chylomicronemia syndrome (homozygous and/or compound heterozygous)
- Use of fibrates or fish oil: both have to be discontinued (if possible, triglyceride levels should not exceed 10 mmol/l) for at least 4 weeks prior to baseline visit
- Uncontrolled diabetes (HBa1C > 90 mmol/L)
- Body mass index (BMI) > 45.0 kg/m2
- Uncontrolled hypertension (systolic > 180mmHg; diastolic > 105mmHg)

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:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-09-2022
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	28-03-2022
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2021-003168-28-NL
CCMO	NL77458.000.21