A randomized, double-blind, placebo controlled study to assess efficacy, safety and tolerability of LCQ908 in subjects with Familial Chylomicronemia Syndrome

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The purpose of this study is to determine whether LCQ908 is effective and safe in lowering triglycerides in subjects with FCS (HLP type I).

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

Summary

ID

NL-OMON39328

Source
ToetsingOnline

Brief title
LCQ908 study

Condition

- Lipid metabolism disorders

Synonym
Familial Chylomicronemia Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: Familial Chylomicronemia Syndrome, LCQ908, Triglycerides

Outcome measures

Primary outcome

1. Percent change in fasting triglycerides from Baseline to 12 weeks.

Secondary outcome

1. To characterize the safety and efficacy of the LCQ908 20 mg and 40 mg doses.

2. To evaluate the proportion of subjects with FCS who respond to LCQ908 or

placebo at 12 weeks, 24 weeks and 52 weeks by dose as indicated by:

a. A relative reduction of fasting TG of at least 40% from baseline or final

fasting TG < 8.4 mmol/L

b. A relative reduction in fasting TG of at least 40% from baseline

c. Final fasting TG < 8.4 mmol/L

3. To assess the proportion of subjects achieving Final fasting TG < target

thresholds including TG < 11.4 mmol/L or < 22.8 mmol/L

at 12, 24 and 52 weeks

4. To assess the effects of LCQ908 20 mg or 40 mg as compared to placebo in

reducing fasting triglycerides after 24 weeks and 52 weeks.

5. To assess the effect of LCQ908 as compared to placebo on post-prandial

triglyceride levels after 12 weeks.

6. To evaluate the safety and tolerability of LCQ908 in FCS (HLP type I) up to

52 weeks.

7. To assess LCQ908 pharmacokinetics at steady state.

Study description

Background summary

Familial Chylomicronemia Syndrome (FCS) is a rare genetic disease due to loss of capacity to hydrolyze triglycerides (TG) circulating in TG-rich lipoproteins (primarily chylomicrons) resulting in severe hypertriglyceridemia (>8.4 mmol/L) in both the post-prandial and fasting state. The most severe consequence of FCS is acute pancreatitis, which can be severe and life-threatening

LCQ908 is a potent and selective DGAT1 inhibitor. DGAT catalyzes the final step in TG synthesis. LCQ908 may reduce plasma TG levels and chylomicrom synthesis in patients with FCS and may therefore have a beneficial effect on the pathophysiology of chylomicronemia.

Study objective

The purpose of this study is to determine whether LCQ908 is effective and safe in lowering triglycerides in subjects with FCS (HLP type I).

Study design

This is a multicentre, randomized, double-blind, placebo-controlled, parrallel-group study consisting of 3 periods: Screening/4-Week Dietary Lead-in (I), Double-Blind Treatment (II, Weeks 0-12), Double-Blind Treatment (III, Weeks 12-52), and a post safety follow-up (IV, Weeks 52-58).

Period I: After screening and eligibility all subjects will complete a 4 week dietary lead-in during which they will follow a severe fat restricted diet consistent with current recommendations for the management of FCS as stipulated: a diet with less than 15% of total caloric intake from fat, with less than 20-25 grams/day of fat each day.

Period II: After completion of the 4-week dietary lead-in, baseline fasting TG levels will be derived from the average of measures collected at day -3 and Week 0 (Randomization). At randomization, patients will be stratified by the use or non-use of statines. All subjects will be randomized to receive either LCQ908 20 mg, LCQ908 40 mg or placebo in a double-blind manner to be taken once daily for 12 weeks, while continuing the severe fat restricted diet.

Period III: Starting at week 12 all subjects will continue double-blind treatment but will be allowed to down titrate for safety or tolerability. Only one down titration will be allowed. All subjects will be treated for the remainder of the 52 weeks with either LCQ908 40 mg, LCQ908 20 mg, LCQ908 10 mg or placebo. The final study visit will be conducted at approximately Week 52.

Primary efficacy in this study will be assessed based on changes in fasting triglyceride levels. Additional measurements will include lipoprotein profiles, and levels of apoB58 and apoB100 to reflect chylomicron and VLDL levels. A Meal test will be administered at day -3 and week 12..

Intervention

Intervention consists of LCQ908 40 mg, LCQ908 20 mg or Placebo.

Study burden and risks

This study will last for 58 weeks and has 4 periods: 1) Screening period of 4 weeks and 3 visits; 2) Double blinded treatment phase of 12 weeks and 4 visits; 3) Double blinded treatment phase consisting of 7 visits in which it will be allowed to down titrate for safety and tolerability; 4) Post-treatment safety follow up period of 1 visit and a follow-up phone call over 6 weeks. During each visit a fasting blood sample will be taken and vital signs will be assessed. The EQ-5D and WPAI questionnaires will be assessed during 6 visits, ECG measurements will be assessed during 4 visits, fecal fat will be evaluated during 3 visits, physical exams will be performed during 3 visits and the standardized meal test will be assessed during 2 visits.

LCQ908 has been given to humans in single doses up to 300 mg and in multiple doses up to 20 mg for 12 weeks. All dose levels have been found to be safe. Over 1000 humans have been treated, including approximately 400 healthy volunteers, 600 patients with Type 2 diabetes, and 6 patients with FCS.
In general, a dose-dependent occurrence of watery diarrhea was found that was generally mild. Adverse events also included nausea and abdominal discomfort. Draft preliminary results of the study with 6 FCS patients indicate that LCQ908 use for 21 days was safe and well tolerated at 10, 20 & 40 mg, with no clinically significant laboratory abnormalities or clinical findings attributed to LCQ908. There were some mild gastrointestinal adverse events recorded, but the frequency and duration was less than in healthy volunteer studies.

There is a risk of hypersensitivity to sunlight at LCQ908 intake, although this has not been observed in humans.

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) Male and female subjects 18 years of age or above3) Fasting TG * 8.4 mmol/L at Screening
2) Fasting TG * 8.4 mmol/L at Screening
3) An established diagnosis of FCS (HLP Type I) confirmed through ultracentrifugation or by documented medical history of a fasting TG * 8.4 mmol/L and by documentation of any of the following at Screening or during the Screening Period:
a) Confirmed homozygote or compound heterozygote for known loss-of-function mutations in Type I-causing genes (such as LPL, apoCII, GPIHBP1, or LMF1)
b) Post heparin plasma LPL activity of * 20% of normal
c) Confirmed presence of LPL inactivating antibodies
4) History of pancreatitis.

Exclusion criteria

1) Although a history of pancreatitis is required, this must be inactive for at least 1 week prior to the Screening Visit.
2) Treatment with fish oil preparations within 4 weeks prior to randomization.
3) Treatment with bile acid binding resins (i.e., colesevelam, etc) within 4 weeks prior to randomization.
4) Treatment with fibrates within 4 weeks prior to randomization.
5) eGFR <30 ml/min/1.73m2 or history of chronic renal disease
6) Participation in any clinical investigation within 4 weeks prior to initial dosing or longer if required by local regulations, or any other limitation of participation based on local regulations.
7) Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive HCG laboratory test.
8) Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 100 days after discontinuation of investigational study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-10-2012
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LCQ908
Generic name:	LCQ908

Ethics review

Approved WMO Date:	23-04-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014
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	EUCTR2011-005535-68-NL
CCMO	NL39908.018.12