A 12-Week, Randomized, Double-Blind, Olive Oil-Controlled Phase 3 Study to Assess the Efficacy and Safety of EPANOVA* in Subjects With Severe Hypertriglyceridemia

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Primary ObjectivesThe primary objectives of the study are:· To determine the efficacy of Epanova 2 g daily compared to olive oil 2 g daily for 12 weeks in lowering serum TG levels in subjects with severehypertriglyceridemia (TG levels *500 mg/dL [5....

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

Summary

ID

NL-OMON40969

Source
ToetsingOnline

Brief title
EVOLVE II

Condition

- Lipid metabolism disorders

Synonym
high tryglycerides, Hypertriglyceridemia

Research involving
Human

Sponsors and support

Primary sponsor: Omthera Pharmaceuticals
Source(s) of monetary or material Support: Omthera Inc

Intervention

Keyword: Epanova, Hypertriglyceridemia, Omega 3 fatty acids, Safety and efficay

Outcome measures

Primary outcome

Primary Objectives

The primary objectives of the study are:

· To determine the efficacy of Epanova 2 g daily compared to olive oil 2 g

daily for 12 weeks in lowering serum TG levels in subjects with severe

hypertriglyceridemia (TG levels *500 mg/dL [5.65 mMol/L] and <2500 mg/dL [28.25

mMol/L]) and

· To determine the safety and tolerability of Epanova.

Secondary outcome

Secondary Objectives

The secondary objectives are:

· To determine the effect of Epanova 2 g daily compared to olive oil 2 g daily

for 12 weeks in lowering serum TG levels in subjects with at least

1 qualifying TG >885 mg/dL (10 mMol/L) and <2500 mg/dL (28.25 mMol/L);

· To determine the effects of Epanova 2 g daily compared to olive oil 2 g daily

for 12 weeks in lowering TG levels in subjects with Fredrickson Type V

hyperlipidemia (TG/very low-density lipoprotein cholesterol [VLDL-C] *6); and

· To determine the effect of Epanova on non-HDL-C and HDL-C.

Tertiary Objectives

The tertiary objectives are:

· To determine the effect of Epanova on LDL-C, total cholesterol (TC), VLDL-C,

and TC:HDL-C ratio;

· To determine the effect of Epanova on apolipoprotein (apo) A-I, apo A-V, apo

B, apo C-III, and remnant-like particle cholesterol (RLP-C);

· To determine the effect of Epanova on lipoprotein(a) (Lp[a]) and lipoprotein

associated phospholipase A2 (Lp-PLA2);

· To determine the effect of Epanova on adiponectin and leptin; and

To determine the effect of Epanova on fatty acids (including EPA, DHA,

arachidonic acid [AA], and docosapentaenoic acid [DPA]) in RBC

membranes and as a percentage of total fatty acids in plasma.

Study description

Background summary

Epanova* is the name of the investigational study drug being tested to learn if it may lower high triglycerides and contains omega 3 fatty acids. Triglycerides are a type of fat found in your blood. When triglycerides are maintained at low levels, they are healthy. However, they can cause health problems if the levels become too high. High triglyceride levels can lead to increased risk of developing heart disease.
There is evidence that omega-3 fatty acids may reduce the risk of heart disease by lowering triglyceride levels.

Study objective

Primary Objectives
The primary objectives of the study are:
· To determine the efficacy of Epanova 2 g daily compared to olive oil 2 g daily for 12 weeks in lowering serum TG levels in subjects with severe hypertriglyceridemia (TG levels *500 mg/dL [5.65 mMol/L] and <2500 mg/dL [28.25

mMol/L]) and
· To determine the safety and tolerability of Epanova.

Study design

This is a double-blind, randomized, olive oil-controlled study to investigate the efficacy and safety of Epanova as an adjunct therapy to diet for reduction of TG levels in subjects with severe hypertriglyceridemia. The study consists of an approximately 8-week screening period
that includes a diet and lifestyle stabilization and washout period and a 12-week treatment period.
During the screening period and treatment period, all visits are to be within ±3 days of the scheduled time.
Screening Period
Visit 1 will occur at Week -8 for subjects requiring washout and/or statin, cholesterol-absorption inhibitor (CAI), or statin-CAI stabilization. This includes subjects who:
· Were previously on omega-3 drugs/supplements;
· Require adjustment to or addition of permitted statins, CAI, or statin-CAI combination;
· Have not been on a permitted stable dose of statin, CAI, or statin-CAI combination for at least 4 weeks prior to Visit 1; and/or
· Need to washout of bile acid sequestrants, fibrates, niacin, and other supplements known to alter lipid metabolism.
For these subjects who require washout and/or statin, CAI, or statin-CAI stabilization, at Visit 1 (Week -8) screening procedures will be performed. Subjects will return at Visit 1a (Week -2) for their first qualifying lipid measurement.

For subjects not requiring washout, Visit 1 will occur at Week -2. All screening procedures will be performed at this visit including the first qualifying lipid measurement.
At Visit 2 (Week -1), all subjects will return for their second lipid qualifying measurement. If at Visit 2 the subject does not have an average TG *500 mg/dL (5.65 mMol/L) and <2500 mg/dL (28.25 mMol/L), the TG measurement may be repeated one additional time after Visit 2 (Visit 2a). The subject*s qualifying measurement would be the average of Visit 1 or 1a + Visit 2 + Visit 2a (repeat measurement).

To be eligible for randomization, the subject must have a qualifying TG *500 mg/dL (5.65 mMol/L) and <2500 mg/dL (28.25 mMol/L). Of the total number of subjects, approximately 50% will have a qualifying TG >885 mg/dL (10 mMol/L) and <2500 mg/dL (28.25 mMol/L). Once approximately 50% of the total subjects has been reached for each TG group, enrollment of subjects with that specific TG criterion will stop. Subjects will be equally
allocated to each treatment group.
At the screening visit, all subjects will receive counseling regarding the

National Cholesterol Education Program Therapeutic Lifestyle Changes (TLC) diet and will receive basic instructions on how to follow this diet. Treatment Period At Visit 3 (Week 0), approximately 116 subjects will be randomized in a 1:1 ratio to receive daily olive oil 2 g or Epanova 2 g. Subjects will be stratified to ensure a balanced allocation of subjects who are users and non-users of lipid-altering drugs allowed at randomization. During the treatment period, subjects will return to the site at Visit 4 (Week 6), Visit 5 (Week 10), and Visit 6 (Week 12) for efficacy and safety evaluations.

Intervention

Eligible subjects will be randomly assigned at Visit 3 (Week 0) to receive orally Epanova 2 g daily or olive oil 2 g daily. Epanova and olive oil will be provided in 1 g polyacrylate-coated soft gel capsules. All capsules will be taken once per day, without regard to meals, for 12 weeks. At clinic visits, study drug will be administered at the clinic after fasting blood draws are complete.

Study burden and risks

Epanova* has been administered in a total of 731 patients for 6-12 weeks. The most common side effect (occurring in * 2% of patients treated with Epanova* are: -gastrointestinal (GI) disorders (such as diarrhea, nausea, gas (belching and/or flatulence), vomiting, abdominal pain, indigestion and irritable bowel), feeling tired, bruising, increased blood sugar, increased blood lipids, increased weight, diabetes, Joint and/or back pain, headache, an alteration in the sense of taste, rash and high blood pressure.

In general on the clinical trials, Epanova* was well tolerated and most effects were mild or moderate in severity and got better during the study.

It is hoped that the results of this study will help the sponsor learn which treatments for hypertriglyceridemia are well tolerated and effective.

This study has two periods. A Screening/Washout/Diet Stabilization and a Treatment period.

If the patient agrees to participate in this study:
* He/she will come in for approximately 6-8 visits at the study center. Each study visit may take a maximum of 2 hours, but often they take less time.
* Fasting blood samples will be collected at least 6 times throughout the study. A total of about 213 ml (12 tablespoons or a little more than 1/2 cup) of blood will be collected.

Contacts

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Omthera Pharmaceuticals

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Omthera Pharmaceuticals

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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. Qualifying (average of Visit 1 or 1a + Visit 2 + Visit 2a [repeat measurement]) serum TG *500 mg/dL (5.65 mMol/L) and <2500 mg/dL (28.25 mMol/L);
2. Body mass index *20 kg/m2;
3. Untreated dyslipidemia or dyslipidemia treated with a statin, CAI, or statin-CAI combination that has been stable for 6 weeks prior to randomization; and
4. Willingness to maintain current physical activity level and follow the TLC diet throughout the study.

Exclusion criteria

1. Allergy or intolerance to omega-3 fatty acids, omega-3-acid ethyl esters, or fish;

2. Known lipoprotein lipase impairment;
3. Known non-responder to omega-3 or fenofibrate therapy;
4. Use of any prescription medications containing EPA and/or DHA (eg, Lovaza® or Vascepa®) within 8 weeks prior to randomization. Up to 1 g capsule/day of an omega-3 dietary supplement will be permitted;
5. Unable to discontinue use of bile acid sequestrants, fibrates or niacin (other thanniacin-containing vitamins <200 mg), or any supplement used to alter lipid metabolism including but not limited to dietary fiber supplements, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols at Visit 1;
6. Use of tamoxifen, estrogens, or progestins that has not been stable for >4 weeks at Visit 1 or is unstable prior to randomization;
7. Use of oral or injected corticosteroids or anabolic steroids in the 4 weeks prior to Visit 1;
8. History of hospitalization for pancreatitis in the last 5 years;
9. Uncontrolled diabetes (hemoglobin A1c >10%);
10. Uncontrolled hypothyroidism or thyroid-stimulating hormone >5 mIU/L;
11. History of cancer (other than basal cell carcinoma) in the past 2 years;
12. Cardiovascular event (ie, myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient heart attack, unstable congestive heart failure requiring a change in treatment), revascularization procedure or vascular surgery within 6 months of randomization;
13. Use of simvastatin 80 mg or Vytorin 10/80 mg;
14. Recent history (within 6 months of randomization) of significant nephrotic syndrome, pulmonary, hepatic, biliary, gastrointestinal, or immunologic disease;
15. Poorly controlled hypertension (systolic blood pressure *180 mmHg and/or diastolic blood pressure *110 mmHg) at two consecutive visits prior to randomization at Visit 3;
16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal;
17. Exposure to any investigational product within 4 weeks of Visit 1; or
18. Any condition or therapy which, in the opinion of the Investigator, might pose a risk to the subject or make participation in the study not in the subject*s best interest.

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):	25-09-2014
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epanova
Generic name:	EPA+DHA

Ethics review

Approved WMO Date:	03-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2014
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	EUCTR2013-004682-14-NL
CCMO	NL48001.018.14