A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH)

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Primary ObjectiveThe primary objective is to evaluate the effectiveness of adding Epanova to statin therapy (with or without ezetimibe) for lowering MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergent/elective...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON47312

Source
ToetsingOnline

Brief title
STRENGTH

Condition

- Heart failures
- Lipid metabolism disorders
- Vascular disorders NEC

Synonym
heart and vascular disease, increased glyceride (type of fat) levels

Research involving

Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Cardiovascular Risk, Epanova, Hypertriglyceridemia, Statin

Outcome measures

Primary outcome

The primary outcome measure is the time to first occurrence of any component of the composite of MACE: cardiovascular death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina. Patients will remain in the study until the required number of patients with MACE has occurred.

Secondary outcome

KEY Secondary outcome measures include:

* The composite measure of CV events that include the first occurrence of cardiovascular death, non-fatal MI, and non-fatal stroke.

* The composite measure of coronary events that include the first occurrence of cardiovascular death ((including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal MI, emergent/elective coronary revascularization, or hospitalization for unstable angina.

* Time to CV Death

Other Secondary outcome measures include:

a) Emergent/elective coronary revascularization

b) Hospitalization for unstable angina

c) Fatal or non-fatal MI

d) Non-fatal MI

e) Fatal or non-fatal stroke

f) Non-fatal stroke

g) All-cause death

Study description

Background summary

Few prospective studies have explicitly examined the predictive CVD risk of non-HDL-C levels versus LDL-C levels in persons with hypertriglyceridemia, however, several lines of evidence favor use of non-HDL-C over LDL-C in clinical evaluation of risk.

In patients with hypertriglyceridemia, non-HDL-C goals are frequently not achieved. In order to reduce non-HDL-C in patients with hypertriglyceridemia, combination therapy with statins is frequently necessary to maximize goal achievement. The National Cholesterol Education Program (NCEP) panel recognized that statins are not powerful TG-lowering drugs, and therefore recommended the use of specific add-on therapies to lower TG levels in patients with hypertriglyceridemia (fish oils to replace some long-chain TG levels in diet, as well as fibrates or nicotinic acid).

There are no long-term CV outcomes studies that specifically assess the impact of adding omega-3 fatty acids to statins in reducing the risk of cardiovascular events associated with persistent hypertriglyceridemia. The current protocol will investigate the effectiveness of adding Epanova to statin, with or without ezetimibe, as needed, for lowering MACE (cardiovascular death, nonfatal MI, nonfatal stroke, emergent/elective
coronary revascularization, or hospitalization for unstable angina) in patients with persistent hypertriglyceridemia and high risk for CVD.

Study objective

Primary Objective
The primary objective is to evaluate the effectiveness of adding Epanova to statin therapy (with or without ezetimibe) for lowering MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina) in high cardiovascular risk patients with persistent hypertriglyceridemia and low HDL-cholesterol (HDL-C).

Study design

The study is a randomized, double-blind, placebol-controlled (corn oil), parallel group design that will enroll approximately 13,000 patients with hypertriglyceridemia and at high risk for CVD. Patients will be randomized to either Epanova or placebo (corn oil), administered once daily, for approximately 3-5 years as determined by the number of patients with MACE. There will be up to 3 screening/washout visits, depending on the need for a repeat lab for statin/ezetimibe adjustment, discontinuation of excluded lipid-modifying agent, or a borderline TG and/or highdensity lipoprotein (HDL-C) value. During the screening period, patients will maintain a stable diet, and after randomization, patients must be willing to adhere to the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) or equivalent diet. During the screening period, and thereafter, patients will not be permitted to use any excluded therapies or products, and will continue or adjust their prescribed statin regimen. Patients who meet all Inclusion Criteria and no Exclusion Criteria will be randomized 1:1 (6,500/arm) to receive double-blinded Epanova (4 g daily) or a matching placebo (corn oil) control (4 g daily) for the study duration. The randomization visit will be Month 0 and there will be 11 treatment visits at Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60. There will be a 3-week follow-up visit after an early termination (ET) visit for those patients who undergo early permanent IP discontinuation due to a serious adverse event (SAE).

Intervention

Patients will be randomized 1:1 (6,500/arm) to receive double-blinded Epanova (4 g daily) or a matching corn oil control (4 g daily) for the study duration.

* Epanova (omega-3 carboxylic acids) capsules: 4 g (four 1-gram capsules) orally, once daily for the duration of the study.
* Control (corn oil) capsules: 4 g (four 1-gram capsules) orally, once daily for the duration of the study.
* Statins will be prescribed by the investigator or patient*s health care

provider.

Study burden and risks

Subject participation in the study will be approximately 3-5 years. The exact duration of the study will be determined during the study, but will not be longer than 5 years.

Subjects are asked to take either Epanova® (4 g per day) or corn oil (4 g per day), once daily with his/her prescribed statin treatment orally.

Subjects participating in this study are expected to visit the study center 13 times. Until visit 4, the subject is expected to come every 4 months. The subject will only have to come to the study center every 6 months from visit 4 onwards. The subject will be contacted by phone between visits to assess how they are doing. At month 60 (or whenever the subject stops the study medication), he/she will have an end of treatment or Early Termination visit.

While participating in the study, the subject will be asked to follow a diet called the National Cholesterol Education Program (NCEP) Therapeutics Lifestyles Changes (TLC) diet or an equivalent diet. Some medications and dietary products are prohibited while on the study. The subject will need to stop taking any medication (apart from statins) that lower his/her triglyceride levels during the study starting during the screening period.

For some of the blood tests, it is recommended that the subject fasts for at least 9 to 14 hours before coming to the study center. This involves visits 1, 2,, 5, 7, 9, 11 and 13.

Female patients of child-bearing potential must agree to use effective contraception. Effective contraception must also be used for 14 days after stopping the study. There are no restrictions against fathering a child when treated with Epanova®.

There may be risks involved in taking this study drug (for side effects see E9) that have (not) been identified in the studies completed so far.
Taking part in this study does not guarantee that the subject will receive any medical benefit. However the subjects cardiovascular risk may be reduced as a result of taking part in this study. The close medical attention the subject gets during the study may result in him/her gaining new information about his/her health which may provide benefits for his/her general health and well-being.

Benefits: The beneficial effects of omega-3 fatty acids in fish oil formulations are associated with lowering of serum triglycerides.
Please also see the benefits and risks assessment document.

Contacts

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Scientific
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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. Men or women, *18 years of age.
2. Patient must be on a stable diet and statin* therapy at least 4 weeks prior to randomization
(Visit 2) and meet the following criteria, where the qualifying lipid parameters should be obtained from the same visit:
a. LDL-C <100 mg/dL (<2.59 mmol/L). Patient will also qualify if LDL-C *100 mg/dL (*2.59 mmol/L) and if on a high-intensity or maximally tolerated moderate- or lowintensity statin dose, with or without ezetimibe therapy, for at least 4 weeks (see Appendix D). The maximum tolerated dosage of a statin is defined as the approved dose per local label that the patient can tolerate without unacceptable adverse effects such as muscle aches/pain/weakness or elevations in liver enzymes or creatine kinase (CK) that are determined by the investigator to be clinically relevant and due to statin therapy.

b. TG *180 and < 500 mg/dL (*2.03 and < 5.65 mmol/L) and HDL-C
<42 mg/dL (1.09 mmol/L) for men or HDL-C <47 mg/dL (1.22 mmol/L)
for women.
3. Patient is at high risk for a future cardiovascular event if at least one of the following criteria
(3a, 3b or 3c)* is present via patient history, physical exam, or medical records at the time of screening:
a. Any atherosclerotic CVD as defined by one or more of the following:
* previous clinical myocardial infarction (MI) *30 days prior to randomization
* percutaneous coronary intervention (PCI) including balloon angioplasty and
coronary stenting * 6 months prior to randomization
* coronary artery bypass grafting (CABG) *30 days prior to randomization
* coronary angiogram including computed tomography angiogram (CTA)
showing<=> 50% stenosis in at least one native or graft
vessel
* anginal symptoms with a defect documented by stress testing with nuclear perfusion imaging or a wall motion abnormality determined by stress echocardiogram
* asymptomatic coronary ischemia documented by stress testing with nuclear
perfusion imaging or by stress echocardiogram
* peripheral vascular disease with symptoms of claudication and ankle brachial index
<0.9 performed by a vascular lab or angiogram (including CTA) showing <=> 50% stenosis)
* history of peripheral arterial revascularization (surgical or percutaneous) *30 days
prior to randomization
* carotid endarterectomy, carotid stenting or more than or equal to 50% stenosis in a carotid artery
determined by carotid ultrasound or angiogram *30 days prior to randomization
* history of abdominal aortic aneurysm confirmed by imaging, diagnosed *30 days prior to randomization
* ischemic stroke *30 days prior to randomization
* coronary calcium score >300 Agatston units (AU).
b. History of diabetes mellitus (type 1 or 2) and *40 years of age for men and *50 years of age for women, plus one of the following risk factors:
* chronic cigarette smoking at screening (at least 1 cigarette per day for > 1 month)
* history of hypertension (blood pressure >140/90 mm Hg) or taking antihypertensive medication
* high-sensitivity C-reactive protein (hs-CRP) > 2.0 mg/L (19.05 nmol/L) determined
at Visit 1
* history of albuminuria (urinary albumin:creatinine ratio [ACR] >30 mg/g).
c. Male patients >50 years of age or females >60 years of age, with at least one of the following risk factors:
* family history (mother, father or sibling) of premature coronary heart disease (father or brother <55 years of age, mother or sister <65 years of age)
* chronic cigarette smoking at screening (at least 1 cigarette per day for > 1 month)
* hs-CRP >2.0 mg/L (19.05 nmol/L) determined at Visit 1
* impaired renal function as estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for glomerular filtration rate (eGFR) <45 mL/min per 1.73 m2 (patients on dialysis are excluded).

* coronary calcium score >300 Agatston units (AU) at any time in the past.
*If patient will meet CVD secondary prevention criteria (3a) AND primary prevention criteria (3b and/or 3c) at the same time, then patient will be considered as meeting CVD secondary prevention criteria (3a) for the purpose of identifying the inclusion criteria for that patient.
4. Patient must have been on a stable diet prior to randomization and willing to follow the NCEP TLC diet, or equivalent diet, throughout the study.
Note a) A patient can, in specific circumstances, be re-screened. For details, see section 6.4. of the protocol.

Exclusion criteria

1. Allergy or intolerance to omega-3 carboxylic acids, omega-3 fatty acids, omega-3-acid ethyl esters, or corn oil.
2. Known hypersensitivity to fish and/or shellfish
3. Use of fibrates, bile acid sequestrants, or niacin or its analogues (>250 mg/day) within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued for 4 weeks or more prior to Visit 2.However, niacin or its analogues at a dose less than or equal to 250 mg/day is permissible.
4. Statin naïve at Visit 1.
5. Use of simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg within 4 weeks prior to Visit 2.
Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued and replaced with a protocol acceptable statin treatment that is stabilized for 4 weeks or more prior to Visit 2.
6. Use of any prescription medications containing eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), e.g. Lovaza® or Vascepa®, within 4 weeks prior to Visit 2.
Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued for 4 weeks or more prior to Visit 2.
7. More than one capsule/day (any dose) of omega-3 dietary supplements. Patients taking >1 capsule/day of omega-3 supplements before Visit 1 DO NOT require a washout period but must agree to reduce the number of capsules per day to no more than 1 capsule of 1 g promptly after signing the informed consent. No new omega-3 supplements are permitted following initiation of screening procedures at Visit 1.
8. Use of prescription or over-the-counter (OTC) weight loss drugs at any time after Visit 1.
9. Chronic use of oral corticosteroids during screening (acute use for inflammation for example from poison ivy, or intranasal or inhaled steroids for allergies/asthma, or intraarticular injections are allowed).
10. Use of tamoxifen, estrogens, progestins, or testosterone, that has not been stable for >4 weeks at Visit 1, or is unstable prior to Visit 2.

11. Known lipoprotein lipase impairment or deficiency, or apolipoprotein C-II deficiency.
12. Hemoglobin A1c (Hb A1c) >12% at Visit 1.
13. Poorly controlled hypertension (resting blood pressure *180 mm Hg systolic and/or *100 mm Hg diastolic) at two consecutive visits prior to randomization at Visit 2.
14. Uncontrolled hypothyroidism, or thyroid stimulating hormone (TSH) >2.0 times upper limit
of normal (ULN) at Visit 1. Patients who are clinically euthyroid, on stable thyroid replacement therapy for 2 months prior to Visit 1 are allowed.
15. History of cancer (except non-melanoma skin cancer, or carcinoma in situ of cervix) within
the previous two years.
16. Patients on dialysis.
17. Females who are pregnant, planning to be pregnant during the study period, lactating, or women of childbearing potential who are not using an acceptable method of contraception. A woman is considered of childbearing potential if she is not surgically sterile or if her last menstrual period was <12 months prior to Visit 1. Acceptable methods of contraception for this study include use of double barrier contraception, intrauterine device, all
oral, patch, etc. hormonal contraceptives as long as dose and type is stable for 3 months prior
to Visit 1. In addition, true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject.
18. Creatine kinase >5.0 times ULN; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 times ULN; or total bilirubin (TBL) >2.0 times ULN (except with a confirmed diagnosis of Gilbert*s disease), at Visit 1. A diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) with stable elevations
of AST and/or ALT (>3.0 times ULN) is eligible for participation in the study.
19. Excessive use of alcohol or other substance abuse that in the investigator*s opinion would
jeopardize the patient*s participation in the study or interpretation of the data.
20. Exposure to any investigational agent within 4 weeks prior to Visit 1, including randomization in this study.
21. Previous clinical myocardial infarction (MI) <30 days prior to randomization
22. Percutaneous coronary intervention (PCI) including balloon angioplasty and coronary stenting<6 months prior to randomization
23. Coronary artery bypass grafting (CABG) <30 days prior to randomization
24. History of peripheral arterial revascularization (surgical or percutaneous) <30 days prior to randomization
25. Carotid endarterectomy or more than or equal to 50% stenosis in a carotid artery determined by carotid ultrasound or angiogram <30 days prior to randomization
26. History of abdominal aortic aneurysm diagnosed <30 days prior to randomization
27. Ischemic stroke <30 days prior to randomization

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-06-2015
Enrollment:	533
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epanova®
Generic name:	omega-3 carboxylic acids

Ethics review

Approved WMO Date:	11-12-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-06-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-11-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-03-2016

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-08-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
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Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
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Application type:	Amendment
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Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
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Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-04-2019
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2014-001069-28-NL
ClinicalTrials.gov	NCT02104817
CCMO	NL47269.068.14