A Worldwide, Multicenter, Double-Blind, Randomized, Parallel, Placebo-Controlled 12-Week Study to Evaluate the Efficacy and Safety of Extended Release (ER) Niacin/Laropiprant When Added to Ongoing Lipid-Modifying Therapy in Patients with Primary Hypercholesterolemia or Mixed Dyslipidemia

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To evaluate the efficacy and safety of extended release (ER) Niacin/Laropiprant when added to ongoing lipid-modifying therapy in patients with primary hypercholesterolemia or mixed dyslipidemia.

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

Summary

ID

NL-OMON36069

Source
ToetsingOnline

Brief title
MK0524A-133

Condition

- Lipid metabolism disorders

Synonym
elevated cholesterol value, Hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Sponsor is Merck & Co.;Inc.

Intervention

Keyword: Mixed Dyslipidemia, Niacin/Laropiprant, Placebo, Primary Hypercholesterolemia

Outcome measures

Primary outcome

In patients with primary hypercholesterolemia or mixed dyslipidemia on stable

LMT and with elevated LDL-C: To evaluate the efficacy of ERN/LRPT 2 g relative

to placebo on plasma LDL-C at Week 12 of treatment.

Secondary outcome

In patients with primary hypercholesterolemia or mixed dyslipidemia on stable

LMT and with elevated LDL-C:

1. To evaluate the efficacy of ERN/LRPT 2 g relative to placebo on plasma

concentrations of LDL-C:HDL-C, HDL-C, TG, non-HDL-C, Apo B, ApoB:ApoA-I,

TC:HDL-C, Lp(a), Apo A-I, and TC at Week 12 of treatment.

2. To evaluate the efficacy of ERN/LRPT 2 g relative to placebo on plasma

concentrations of LDL-C, LDL-C:HDL-C, HDL-C, TG, non-HDL-C, Apo B, ApoB:ApoA-I, TC:HDL-C, Lp(a), Apo A-I, and TC in the following five LMT subgroups and four other key subgroups at Week-12 of treatment:

a. The LMT subgroup of patients on simvastatin alone

b. The LMT subgroup of patients on ezetimibe/simvastatin combination tablet

c. The LMT subgroup of patients on rosuvastatin alone

d. The LMT subgroup of patients on atorvastatin alone

e. The LMT subgroup of patients on simvastatin, rosuvastatin, or atorvastatin combined or coadministered with ezetimibe

f. Subgroup of patients with low baseline HDL-C per NCEP ATP III [<40 mg/dL (men), <50 mg/dL (women)]

g. Subgroup of patients with low baseline HDL-C per ESC [<40 mg/dL (men), <45 mg/dL (women)] guidelines

h. Subgroup of patients with metabolic syndrome (including patients with diabetes)

i. Subgroup of patients with metabolic syndrome (excluding patients with diabetes)

3. To evaluate the efficacy of ERN/LRPT 2 g relative to placebo on plasma concentrations of LDL-C, LDL-C:HDL-C, HDL-C, TG, non-HDL-C, Apo B, ApoB:ApoA-I, TC:HDL-C, Lp(a), Apo A-I, and TC in the following four other key subgroups at Week 12 of treatment:

a. Patients at combined (very high/high) CHD risk per NCEP ATP III

b. Patients at very high CHD risk per NCEP ATP III

c. Patients at high CHD risk per NCEP ATP III

d. Patients at moderate CHD risk per NCEP ATP III

4. To assess:

a. The proportion of patients who achieve NCEP ATP III LDL-C target levels after the addition of ERN/LPRT 2 g relative to placebo at Week 12 of treatment.

b. The proportion of patients who achieve ESC LDL-C target levels after the addition of ERN/LPRT 2 g relative to placebo at Week 12 of treatment.

5.To evaluate the efficacy of ERN/LRPT 1 g relative to placebo on plasma concentrations of LDL-C, LDL-C:HDL-C, HDL-C, TG, non-HDL-C, Apo B, ApoB:ApoA-I, TC:HDL-C, Lp(a), Apo A-I, and TC in all patients at Week 4 of treatment.

6. To evaluate lipid efficacy of ERN/LRPT 2g relative to placebo on plasma concentrations of LDL-C, LDL-C:HDL-C, HDL-C, TG, non-HDL-C, Apo B, ApoB:ApoA, TC:HDL-C, Lp(a), Apo A-I, and TC in subgroups defined by age, gender, race, region, CV risk status, diabetes status, metabolic syndrome status (including and excluding patients with diabetes), type of hyperlipidemia, low/otherwise baseline HDL-C (per NCEP ATP III and, separately, per ESC) and baseline LDL-C, HDL-C and TG levels at Week 12 of treatment.

7. To evaluate the safety and tolerability of ERN/LRPT 2 g across 12 weeks of treatment.

Study description

Background summary

LDL-C has been well established as a risk factor for cardiovascular disease, and a linear relationship exists between reductions in LDL-C and cardiovascular risk reduction. I addition, epidemiological and clinical studies suggest that low levels of HDL-C and high levels of triglycerides are also positively associated with increased cardiovascular disease risk. Statins are the gold standard therapy to lower LDL-C; however, a significant number of statin-treated patients remain at risk. Combination therapy to target LDL-C as well as other potentially atherogenic lipid parameters may result in incremental clinical benefit beyond that possible with statin therapy alone. In controlled trials only 30% of CV events are prevented by statin monotherapy. Niacin is the most effective approved agent for raising HDL-C and is also efficacious in lowering LDL-C and triglycerides. A major impediment to the optimal use of niacin is the flushing experienced by most patients. Bothersome side effects, such as flushing of the face and trunk have been reported in over 90% of patients receiving niacin, even at a commonly prescribed dose of 500 mg t.i.d. However, lipid efficacy minimally requires doses of 1 g/day with the greatest lipid efficacy seen at the 2-g/day dose. Thus, an agent that can reduce niacininduced flushing (NIF) will facilitate more widespread use of niacin in the treatment of lipid disorders and may allow dosing at therapeutic levels within a shorter period of time after initiation of therapy. The ability to escalate to therapeutic doses quickly is likely to improve the acceptance of niacin for the treatment of lipid abnormalities and allow more patients to reach target goals.

Study objective

To evaluate the efficacy and safety of extended release (ER) Niacin/Laropiprant when added to ongoing lipid-modifying therapy in patients with primary hypercholesterolemia or mixed dyslipidemia.

Study design

Multicenter, randomized, double-blind, placebo-controlled.

Study duration is 19 weeks which includes the 2-week poststudy telephone follow-up and screening period. There will be 6 visites plus telephone call.

A minimum of 306 patients will be randomized to each of the following LMT groups: simvastatin monotherapy, atorvastatin monotherapy, rosuvastatin monotherapy and ezetimibe/simvastatin combination therapy (same tablet). In addition, a maximum of 200 patients taking ezetimibe coadministered with

simvastatin or atorvastatin or rosuvastatin will be randomized.

Patients who have been on a stable dose of protocol-specified LMT for at least 6 weeks prior to Visit 1 may enter Visit 1/Week-5 for screening and to have laboratory samples drawn for screening (TSH, FSH, HbA1c), and Framingham Risk Score calculation.

The central laboratory*s LDL-C and TG values obtained at Visit 1 will be used to determine if the patient is likely to meet the lipid criteria needed for eligibility at Visit 2.

The central lab values obtained at Visit 2 will be used to determine if the patient meets the lipid and other lab criteria (ALT, AST, CK, eGFR) needed for randomization.

At Visit 3/Day 1, eligible patients completing the LMT stabilization/placebo run-in period will be randomized to one of the 2 blinded treatment groups (Table 2-3) in a 1:1 ratio: ERN/LRPT or placebo, using central randomization stratified by LMT via Interactive Voice Response System (IVRS). Patients in Treatment Group 1 will receive 1 g of ERN/LRPT (one 1-g tablet) for 4 weeks. After 4 weeks (Visit 4) of blinded treatment, Treatment Group 1 will be advanced to ERN/LRPT 2 g (two 1-g tablets) and remain on this treatment for the remainder of the study, an additional 8 weeks. Patients in Treatment Group 2 will receive 1 placebo tablet daily and will be advanced to 2 placebo tablets daily after 4 weeks (Visit 4) for the remainder of the study.

Intervention

At Visit 3/Day 1, eligible patients completing the LMT stabilization/placebo run-in period will be randomized to one of the 2 blinded treatment groups (Table 2-3) in a 1:1 ratio: ERN/LRPT or placebo, using central randomization stratified by LMT via Interactive Voice Response System (IVRS). Patients in Treatment Group 1 will receive 1 g of ERN/LRPT (one 1-g tablet) for 4 weeks. After 4 weeks (Visit 4) of blinded treatment, Treatment Group 1 will be advanced to ERN/LRPT 2 g (two 1-g tablets) and remain on this treatment for the remainder of the study, an additional 8 weeks. Patients in Treatment Group 2 will receive 1 placebo tablet daily and will be advanced to 2 placebo tablets daily after 4 weeks (Visit 4) for the remainder of the study.

Study burden and risks

A small, incremental increase in fasting serum glucose (FSG) is an expected effect of niacin therapy in some patients. This increase may be transient.

Niacine Induced Flushing (NIF) may occur in patients taking the study drug. Patients should be instructed not to drink alcoholic beverages around the time

of study drug dosing, as alcohol may intensify flushing symptoms.

Beginning at Visit 1, patients must be encouraged to follow the local dietary guidelines of the country or region. At each subsequent study visit, patients will be reminded to maintain this diet throughout the study. Refer to Appendix 6.3 of the study protocol for currently recommended NCEP TLC Diet (from the NCEP ATP III Guidelines).

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

- Patient has a history of primary hypercholesterolemia or mixed dyslipidemia
- Patient must meet one of the folowing risk categories and corresponding LDL-C criteria at visit 2: Very high risk, High Risk or Moderate Risk (see table at page 16 of protocol)

- Patient has been on a stable dose of one of the following LMT's for at least 6 weeks prior to Visit 1, and agrees to remain on the same type and dose of LMT for the duration of the study: Monotherapy:simvastatin or rosuvastatin or atorvastatin; Combination Therapy: ezetimibe/simvastatin in the same tablet; Co-administration Therapy: simvastatin or rosuvastatin or atorvastatin coadministered with ezetimibe
- Patient has TG levels <500mg/dL (<5.65 mmol/L)
- Patient is male or female and >< = 18 years of age on day of signing informed consent

Exclusion criteria

- Patient has taken a prohibited Lipid Modifying Therapy within 6 weeks of Visit 1
- Patient has had a change to the type or dose of acceptable LMT regimen within 6 weeks prior to Visit 1
- Patient is pregnant, breastfeeding, or expecting to conceive during the study including the 14-day post study follow-up
- Patient has a history of malignancy <= 5 years prior to signing informed consent
- Patient has had prohibited medical conditions like: poorly controlled Diabetes Type 1 or 2, an uncontrolled endocrine or metabolic disease, nephrotic syndrome or renal disease, active peptic ulcer disease (within 3 months of visit 1), cardiac disease, arterial bleeding, hepatic disease, malabsorption etc.
- Patient is on prohibited concomitant medication, e.g.: systemic steroids or systemic anabolic agents. antioxidant vitamins (certain vitamins at certain dosages) or patient is Chinese and is on simvastatin 80mg.

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: Pending

Start date (anticipated):	01-08-2011
Enrollment:	160
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ER Niacin/Laropiprant
Generic name:	Tredaptive
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-06-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2012
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	EUCTR2010-021627-27-NL
ClinicalTrials.gov	NCT01274559
CCMO	NL36288.018.11