A Phase III Multicenter, Double-Blind, Crossover Design Study to Evaluate Lipid-Altering Efficacy and Safety of 1 g/10 mg Extended-Release Niacin/Laropiprant/Simvastatin Combination Tablets in Patients with Primary Hypercholesterolemia or Mixed Dyslipidemia

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2.1.1 Primary Objective1.Evaluate the LDL-C-lowering effects of ERN/LRPT/SIM 2 g/20 mg compared to ERN/LRPT 2 g coadministered with simvastatin 20 mg.Hypothesis: ERN/LRPT/SIM 2 g/20 mg is equivalent to ERN/LRPT 2 g coadministered with simvastatin 20...

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

Summary

ID

NL-OMON36032

Source
ToetsingOnline

Brief title
MK-143

Condition

- Other condition

Synonym
Patients with Primary Hypercholesterolemia or Mixed Dyslipidemia

Health condition

primaire hypercholesterolemie of gemengde dyslipidemie

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Scharp & Dohme BV

Intervention

Keyword: Efficacy and Safety, Hypercholesterolemia or Mixed Dyslipidemia, Niacin/Laropiprant/Simvastatin Combination Tablets

Outcome measures

Primary outcome

For the primary hypothesis, ERN/LRPT/SIM 2g/20 mg will be considered equivalent to ERN/LRPT 2g coadministered with simvastatin 20 mg if the 95% CI in LDL-C reduction for the difference between these two treatments falls within (-4%, 4%) interval.

Secondary outcome

The secondary hypothesis of equivalence in raising HDL-C will be tested using a similar ANOVA analysis, described above, applied to percent change from baseline to the end of the 8-week treatment period in HDL-C. The equivalence of ERN/LRPT/SIM 2g/20 mg and ERN/LRPT 2 g coadministered with SIM 20 mg in increasing HDL-C will be established if the 95% CI for the respective between-treatment difference in percent change from baseline in HDL-C falls

within ±4%.

Study description

Background summary

A fixed dose combination tablet of Extended-Release Niacin/Laropiprant (ERN/LRPT) has been approved for marketing in the European Union (TREDAPTIVE*) and a number of other countries around the world. ERN/LRPT is fixed dose combination tablet containing ERN 1 g and LRPT 20 mg (designated MK-0524A or ERN/LRPT 1 g).
To assist in patient convenience and compliance, a fixed dose tablet of ERN/LRPT 1 g and simvastatin is being developed and referred to as MK-0524B or ER niacin/laropiprant/simvastatin. This protocol will assess the lipid-altering efficacy of a tablet containing ER niacin 1 g, laropiprant 20 mg and simvastatin 10 mg designated as ERN/LRPT/SIM 1 g/10 mg.
The primary objective of Protocol 143 is to demonstrate clinically equivalent lipid-modifying efficacy of MK-0524B 2 g/20 mg (2 tablets of ERN/LRPT/SIM 1 g/10 mg) versus coadministered MK-0524A 2 g (2 tablets of ERN/LRPT 1 g) + simvastatin 20 mg (2 tablets of SIM 10 mg) in patients with primary hypercholesterolemia or mixed dyslipidemia.

Study objective

2.1.1 Primary Objective
1.Evaluate the LDL-C-lowering effects of ERN/LRPT/SIM 2 g/20 mg compared to ERN/LRPT 2 g coadministered with simvastatin 20 mg.
Hypothesis: ERN/LRPT/SIM 2 g/20 mg is equivalent to ERN/LRPT 2 g coadministered with simvastatin 20 mg in reducing LDL-C.
Note: For LDL-C primary hypothesis, the criterion for bioequivalence is that the 95% confidence interval (CI) of the difference in percent change from baseline between the two treatments falls within ±4%.

2.1.2 Secondary Objectives
1.Evaluate the HDL-C-raising effects of ERN/LRPT/SIM 2 g/20 mg compared to ERN/LRPT 2 g coadministered with simvastatin 20 mg.
Hypothesis: ERN/LRPT/SIM 2 g/20 mg is equivalent to ERN/LRPT 2 g coadministered with simvastatin 20 mg in raising HDL-C.
Note: For HDL-C secondary hypothesis, the criterion for bioequivalence is that the 95% confidence interval (CI) of the difference in percent change from baseline between the two treatments falls within ±4%.
2.Evaluate the tolerability of ERN/LRPT/SIM.

2.1.3 Tertiary Objectives

1.Estimate the differences in percent change in LDL-C from baseline between ERN/LRPT/SIM 1 g/10 mg and ERN/LRPT 1 g coadministered with 10 mg of simvastatin, respectively, for 4 weeks.
2.Estimate the differences in percent change in HDL-C from baseline between ERN/LRPT/SIM 1 g/10 mg and ERN/LRPT 1 g coadministered with 10 mg of simvastatin, respectively, for 4 weeks.

Study design

This is a multicenter, double-blind, randomized, crossover study in patients with primary hypercholesterolemia or mixed dyslipidemia.
Approximately 1268 patients >18-<85 years of age with primary hypercholesterolemia or mixed dyslipidemia, will be randomized in a 1:1 ratio.
Eligible patients must meet the following criteria based on NCEP ATP III guidelines at Visit 2:
High risk patients Not currently treated with lipid-modifying therapy (LMT) and LDL-C < 190 mg/dl (< 4,91 mmol/L).
Patients who are NOT high risk and LDL-C < 240 mg/dl (< 6,21 mmol/L)
Patients on simvastatin 40 mg or another LMT dose equivalent to or greater than simvastatin 40 mg are not eligible.
Patients washing off on LMTs which include niacin, statin, or fibrate must have a plasma TG level < 500 mg/dl (5,65 mmol/L) at Visit 2, and patients who are not on LMTs or on other LMTs (besides niacin, statin, or fibrate) must have TG level < 600 mg/dl (< 6,77 mmol/L) at Visit 2.
On-lipid-modifying therapy (LMT) will begin LMT wash-out at Week -10 or -8 at the Pre-screening Visit/Visit 1 (8 weks for washing-off on fibrates/6 weeks for washing-off other LMTs) followed by a 2-week placebo run in at Visit 2 (Week -2).
Not on LMTs will have a Pre-screening visit at Visit 1 (Week -4), followed by a 2-weeks placebo run-in at visit 2 (week -2).
Eligible patient will be randomized to one of the following 2 treatments groups at Visit 3 (Day 1):
Group 1:
ERN/LRPT/SIM 1g/10 mg + placebo (Weeks 0-4) continued by ERN/LRPT/SIM 1g/10 mg tablet x 2 + placebo x 2 (Weeks 5-12) and continuing with ERN/LRPT 1 g tablet x 2 + placebo (Weeks 13-20).
Group 2:
ERN/LRPT 1 g + SIM 10 mg (Weeks 0-4) continued by ERN/LRPT 1g tablet x 2 SIM 10 mg tablet x 2 (Weeks 5-12) and continuing with ERN/LRPT/SIM 1 g/10 mg tablet x 2 + placebo (Weeks 13-20).
After 4 weeks of treatment at visit 4 (Week 4), treatment doses of ERN/LRPT and SIM will be increased in both treatment groups for an additional 8 weeks (Weeks 5-12).
Beginning at Visit 6 (Week 12), patients in the ERN/LRPT/SIM 2g/20 mg combination treatment group will crossover to the corresponding ERN/LRPT 2 g + SIM 20 mg coadministration treatment, and patients in the coadministration treatment group will crossover to the corresponding ERN/LRPT/SIM combination

treatment.
There will be a total of 8 scheduled visits followed by a 14-day follow up telephone call to assess for serious adverse experience.
In addition patient who discontinue early will be contacted on the date of their intended final visit to assess for serious cardiovascular adverse events or death.

Intervention

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN
All study medication products used in this study will be provided by the Sponsor. ERN/LRPT/SIM 1 g/10 mg and ERN/LRPT 1 g tablets will be in the same image.
• ERN/LRPT/SIM combination will be supplied in Bottle A as 1 g/10 mg tablets.
• ERN/LRPT will be supplied in Bottle A as 1 g tablets.
• SIM will be supplied in Bottle B as 10 mg tablets.
• The placebo tablet in Bottle A will be in the same image as ERN/LRPT/SIM or ERN/LRPT (dispensed at Visit 2).
• The placebo tablet in Bottle B will be in the same image as SIM 10 mg.
All patients will take study therapy orally with food, in the evening or at bedtime
Placebo Run-In Period: Beginning at Visit 2 (Week -2), all patients will take 1 tablet from each bottle (Bottles A and B) daily for 2 weeks.
Treatment Period I (Weeks 0-4): Beginning on the day of Visit 3, all patients will take 1 tablet from each bottle (Bottles A and B) daily for 4 weeks.
Treatment Period II (Weeks 5-12): Beginning on the day of Visit 4, patients will take 2 tablets from each bottle (Bottles A and B) daily for 8 weeks.
Crossover of Treatments: Patients will have a crossover of treatments at Visit 6 and will remain on that treatment for the remainder of the study (Weeks 13-20):
• Patients on ERN/LRPT/SIM combination treatment during Weeks 0-12 will crossover to the ERN/LRPT + SIM coadministration treatment
• Patients on ERN/LRPT + SIM coadministration treatment during Weeks 0-12 will crossover to the ERN/LRPT/SIM combination treatment
Treatment Period III (Weeks 13-20): Beginning on the day of Visit 6, patients will continue to take 2 tablets from each bottle (Bottles A and B) daily for remainder of the study (8 weeks).

See table 2-1 "Treatment groups" in the protocol on page 20

Study burden and risks

The patient is at risk of side-effects of ER niacin/laropiprant:and Simvastatin (cfr. Annex 1: Risks and Side Effects of the ICF/PIF page 11-12)

Contacts

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US
Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient is male or female >=18 and <=85 years of age on day of signing informed consent.
2. A female patient must meet ONE of the following:
a. Of reproductive potential and agrees to remain abstinent* or use (or have their partner use) 2 acceptable methods of birth control for the study duration. An acceptable method of birth control is defined as: intrauterine device (IUD), diaphragm with spermicide, condom, vasectomy, non-cyclical hormonal contraception - must have been on a stable dose for greater than 6 weeks prior to Visit 1 and agree to remain on the same regimen for the duration of the study, contraceptive sponge (with spermicide) is acceptable as a single method of birth control but requires one of the following as a second method: intrauterine device (IUD), diaphragm, condom or vasectomy
3. Patient has a history of primary hypercholesterolemia or mixed dyslipidemia.

4. Patient meets one of the following criteria at Visit 2: Patient is high risk (CHD or CHD risk equivalent based on NCEP ATP III guidelines) AND has LDL-C <= 190 mg/dL (<=4.91 mmol/L).
Patient is NOT high risk (based on NCEP ATP III guidelines) AND has LDL-C <=240 mg/dL (<=6.21 mmol/L).
5. Patient meets one of the following triglyceride (TG) criteria at Visit 2:
a. Patient who is on niacin, statin, or fibrate must have TG < 500 mg/dL (<5.65 mmol/L).
b. Patient who is not on an LMT or on LMT other than niacin, statin, or fibrate must have TG <600 mg/dL (<6.77 mmol/L).
6. Patient understands the study's procedures; alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.

Exclusion criteria

1. Patient consumes more than 3 alcoholic drinks on any given day or more than 14 drinks per week.
2. Patient has the following exclusionary central laboratory values. Creatinine clearance (eGFR) <30 mL/min (0.50 mL/s) ALT (SGPT) >1.5 x upper limit of normal (ULN) AST (SGOT) >1.5 x ULN CK >2 x ULN.
3. Patient is high risk (CHD or CHD risk equivalent based on NCEP ATP III) AND is on a LMT at Visit 1. Note: High risk patients not currently being treated with a LMT at Visit 1 are eligible.
4. Patient is on simvastatin 40 mg, or another LMT dose of equivalent or greater LDLC lowering efficacy than that of simvastatin 40 mg.
5. Patient with Type 1 or Type 2 diabetis mellitus and:
is on statin therapy
is poorly controlled (HbA1C>8%)
is newly diagnosed (within 3 months of Visit 1)
has recently experienced repeated hypoglycemia or unstable glycemic control
is taking new or recently adjusted anti-diabetic pharmacotherapy (with the exception of <=±10 units of insulin) within 3 months of Visit 1
6. Patient currently engages in, or during the study plans to engage, in vigorous exercise or an aggressive diet regimen. For example, patient has experienced weight change or has lost/gained more than 5% of body weight within 3 months prior to randomization.
7. Patient has uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins (i.e., secondary causes of hyperlipidemia such as hyper- or hypothyroidism):
Hyperthyroidism is defined as having a TSH below the central laboratory*s lower limit of the normal reference range (<0.30 mclU/ml)
Note: For patients on thyroid hormone replacement treatment at the time of screening, there is no lower TSH threshold for entry. The patient must have been on a stable dose of thyroid hormone therapy for >=6 weeks prior to the randomization visit.
Hypothyroidism is defined as having a TSH >20% above the central laboratory*s upper limit of the normal reference range (>6.0 mclU/ml)
8. Patient has nephrotic syndrome or other clinically significant renal disease.

9. Patient has chronic heart failure defined by the New York Heart Association (NYHA) Classes III or IV, uncontrolled/unstable cardiac arrhythmias, or poorly controlled hypertension (systolic blood pressure >160 mm Hg or diastolic >100 mm Hg
Note: The anti-hypertensive medications of a patient can be managed during the screening period and BP measurements can be repeated at subsequent visits prior to randomization.
10. Patient has had active peptic ulcer disease <=3 months of Visit 1.
11. Patient has had an episode of gout within 1 year of Visit 1, and is not on any medication to control gout.
12. Patient has a history of hypersensitivity or allergic reaction to niacin, simvastatin, niacin/laropiprant or other niacin-containing products.
13. Patient has history of myocardial infarction, stroke, coronary artery bypass surgery or other revascularization procedure, unstable angina or angioplasty within 3 months of Visit 1.
14. Patient has arterial bleeding.;15. Patient has history of ileal bypass, gastric bypass or other significant condition associated with malabsorption or rapid weight loss within 18 months of Visit 1.
16. Patient has active or chronic hepatobiliary or hepatic disease.
17. Patient has taken niacin >50 mg/day, bile-acid sequestrants, HMG-CoA reductase inhibitors, ezetimibe, CHOLESTIN , and other red yeast rice products and other red yeast products within 6 weeks or fibrates within 8 weeks of randomization visit (Visit 3).
18. Patient requires warfarin treatment and has not been on a stable dose with a stable International Normalized Ratio (INR) for at least 6 weeks prior to Visit 1.;Please refer to protocol for complete list

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2011

Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Niacin/Laropiprant/Simvastatin
Generic name:	Niacin/Laropiprant/Simvastatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	SIM
Generic name:	Simvastatine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TREDAPTIVE
Generic name:	niacine/laropiprant
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-07-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2011-001007-12-NL
ClinicalTrials.gov	NCT01335997
CCMO	NL37038.060.11