A dose finding study to assess the safety and efficacy of K-877 in patients with statin-controlled LDL-C but abnormal lipid levels

Published: 07-08-2013
Last updated: 22-04-2024

The primary objectives of the study are the following:* To assess the dose response of the following parameters:* Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to Week 12* Percent change in TG from baseline to…

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

Summary

ID

NL-OMON40373

Source
ToetsingOnline

Brief title
K-877-201

Condition

- Lipid metabolism disorders

Synonym
abnormal cholesterol values, dyslipidemia

Research involving
Human

Sponsors and support

Primary sponsor: Kowa Research Europe

Source(s) of monetary or material Support: Kowa Research Europe Ltd.

Intervention

Keyword: Abnormal lipid levels, Dose-Finding, Safety and Efficacy, Statin-controlled LDL-C

Outcome measures

Primary outcome

The primary objectives of the study are the following:

* To assess the dose response of the following parameters:

* Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to Week 12

* Percent change in TG from baseline to Week 12

* To assess the safety and tolerability of K-877 in patients with residual cardiovascular risk despite statin-controlled LDL-C concentration as evaluated particularly by:

* Change and percent change in serum creatinine from baseline to Week 12

* Change and percent change in homocysteine from baseline to Week 12

Secondary outcome

The secondary objectives of the study are the following:

* Percent change in high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and apolipoprotein (Apo) B from baseline to Week 12

* Percent change in Apo A1 and Apo A2 from baseline to Week 12

* Percent change in LDL-C, small low-density lipoprotein (LDL) particles (small and dense LDL), very low-density lipoprotein (VLDL-C) (calculated as TC * LDL-C * HDL-C), Apo B48, Apo B100, Apo C2, Apo C3, adiponectin, fibroblast

growth factor 21 (FGF21), high-sensitivity C-reactive protein (hsCRP),

lecithin-cholesterol acyltransferase (LCAT) mass and activity, cholesteryl

ester

transfer protein (CETP) mass and activity, proprotein convertase

subtilisin/kexin

type 9 (PCSK9) mass, high-density lipoprotein (HDL) function (reverse

cholesterol transport, HDL driven endothelial production of nitric oxide), ion

mobility analysis, HDL sub-fractions (including pre-beta HDL), and lipid and

lipoprotein ratios TC/HDL-C, non-HDL-C/HDL-C, Apo B/Apo A1,

LDL-C/Apo B, and Apo C3/Apo C2, from baseline to Week 12

* To measure PK parameters in a subset of patients per dose group

Study description

Background summary

K-877 is a potent and selective peroxisome proliferator activated receptor (PPAR) agonist, which is several thousand times more selective for the PPAR* receptor than PPAR* or * receptors. K-877 is approximately 2,500 times more active than fenofibric acid, the active metabolite of fenofibrate, an existing PPAR* agonist, in terms of the half maximal effective concentration (EC50) for the transactivation of PPAR*. At doses of K-877 which have full agonist effects on lipids, it appears to modulate the effect of PPAR* agonism on some non-lipid effects, compared with full agonists like fenofibric acid. In pharmacological assessments, K-877 was shown to be a potent PPAR* agonist, with several fold lower activity associated with its metabolites.

Study objective

The primary objectives of the study are the following:
* To assess the dose response of the following parameters:
* Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to Week 12
* Percent change in TG from baseline to Week 12

* To assess the safety and tolerability of K-877 in patients with residual cardiovascular risk despite statin-controlled LDL-C concentration as evaluated particularly by:
* Change and percent change in serum creatinine from baseline to Week 12
* Change and percent change in homocysteine from baseline to Week 12

The primary efficacy objective is to evaluate the percent reduction in both TG and non-HDL-C with K-877 compared to placebo.

Study design

Approximately 350 patients will be randomised at 50 sites in 9 European countries (Czech Republic, Denmark, Hungary, the Netherlands, Germany, Poland, Russia, Sweden, and the United Kingdom).
This is a Phase 2, multi-country, multi-centre, placebo-controlled, randomised, double-blind, parallel-group study in patients with statin-controlled LDL-C but residual abnormal lipid levels. The study consists of a screening period of up to 4 weeks, a 12-week treatment period, and a 2-week follow-up period.
Approximately 350 patients will be randomised to 1 of the following 7 treatment groups and will receive 2 tablets of study drug in the morning and 2 tablets in the evening:
* Placebo: morning dose: Placebo 2x, Evening dose: Placebo 2x
* K-877 50 mcg BID: morning dose: K-877 50 mcg + placebo, Evening dose: K-877 50 mcg + placebo
* K-877 100 mcg BID: morning dose: K-877 100 mcg + placebo, Evening dose: K-877 100 mcg + placebo
* K-877 200 mcg BID: morning dose: K-877 200 mcg + placebo, Evening dose: K-877 200 mcg + placebo
* K-877 100 mcg QD: morning dose: K-877 50 mcg × 2, Evening dose: Placebo × 2
* K-877 200 mcg QD: morning dose: K-877 100 mcg × 2, Evening dose: Placebo x2
* K-877 400 mcg QD: morning dose: K-877 200 mcg × 2, Evening dose: Placebo x2
(BID: twice daily, QD = once daily)

Patients must be on a stable dose (as per the national Summary of Product Characteristics [SPC]) of an allowed statin therapy for at least 12 weeks prior to screening and will continue therapy at an unchanged dose throughout the study.
In general, patients with dyslipidemia should be stabilized on an adequate statin therapy before being considered for an add-on therapy with another pharmacological group of products. Patients treated with pravastatin, lovastatin, or fluvastatin and still dyslipidemic are not considered to have received adequate statin therapy; therefore, patients receiving these types of statins are not eligible for enrollment in this study. Patients enrolled in the study will not be allowed to change the dose, dosing regimen (eg, morning or evening dose), or the type of statin during the Study Period. Any statin approved by the regulatory authority of each country (except for pravastatin,

lovastatin, and fluvastatin) is allowed and the maximum allowable dose will be specified for each drug according to the SPC in each country.

The Screening Period will be up to 4 weeks in duration and will consist of 1 or 2 visits: Screening Visit (SV) 1 for all patients and SV 2 for patients who fail to meet inclusion criteria #5 at SV 1. There should be an interval of * 1 weeks between the last SV and the Randomisation Visit (Treatment Visit [TV] 1 [Week 0]).
The patients, investigators, study staff, Medpace (except the unblinded statistician), and the Sponsor will remain blinded to lipid data from randomization to the end of the study.
Blood sampling for clinical laboratory tests (chemistry, haematology, and endocrinology) will be performed at every visit during the study except at the optional SV 2. At each of these visits, patients will report to the study centre after an overnight fast for * 10 hours (nothing by mouth except water).
The Treatment Period will be 12 weeks in duration and will consist of 5 visits (TV 1 [Week 0], TV 2 [Week 2], TV 3 [Week 4], TV 4 [Week 8], and TV 5 [Week 12]). Patients will be randomised at TV 1 and stratified to a treatment group by country, site, and prior statin treatment. At TV 2, patients who are enrolled at participating PK sites will undergo PK blood sampling. If the PK sampling is missed for any reason at TV 2, patients will undergo PK sampling at TV 3.
Study drug will be dispensed starting at TV 1 and patients will be instructed to take 4 tablets per day (2 tablets in the morning and 2 tablets in the evening), 30 minutes after eating a meal.
Patients will return for a Follow-up Visit 2 weeks after the last visit during the Treatment Period.

Intervention

* Placebo: morning dose: Placebo 2x, Evening dose: Placebo x 2
* K-877 50 mcg BID: morning dose: K-877 50 mcg + placebo, Evening dose: K-877 50 mcg + placebo
* K-877 100 mcg BID: morning dose: K-877 100 mcg + placebo, Evening dose: K-877 100 mcg + placebo
* K-877 200 mcg BID: morning dose: K-877 200 mcg + placebo, Evening dose: K-877 200 mcg + placebo
* K-877 100 mcg QD: morning dose: K-877 50 mcg × 2, Evening dose: Placebo x 2
* K-877 200 mcg QD: morning dose: K-877 100 mcg × 2, Evening dose: Placebo x 2
* K-877 400 mcg QD: morning dose: K-877 200 mcg × 2, Evening dose: Placebo x 2
(BID: twice daily, QD = once daily)

Study burden and risks

Risks
For K-877 it is not yet clear what specific side effects are associated with

its use alone or in combination with statins. Based on experience with drugs which work in a similar way and have been approved and are widely used in patients, hepatic disorder (including abnormal blood tests related to the liver), anaemia, low blood sugar, and muscle disorders might occur. Evaluation of the potential to produce cancer in animals has been completed for many products in the same mechanistic class as this investigational drug. The results of the completed carcinogenicity studies demonstrate that this class of compounds induces multiple tumour types in multiple species (mice, rats, hamsters). The mechanism by which these compounds produce tumours in rodents is not well understood, but the possibility that the rodent carcinogenicity findings may be relevant to humans cannot be ruled out at this time.
In studies conducted to date, 3 patients have had adverse events requiring admission to hospital, but only in one case, namely that of a patient who had a kidney stone, was it thought that there could be a relationship to K-877. Less serious events reported include hayfever, gastroenteritis, sore throat/cold symptoms, back pain, and headache, but it is not clear how these relate to K-877.

Benefits
K-877 may help to control your abnormal lipid levels and reduce your cardiovascular risks like stroke, hypertension, diabetes or heart attacks, but however there is no guarantee that this study will help you. The information that is collected from the study may help researchers find new treatments for future patients.

Contacts

Public
Kowa Research Europe

Wharfedale Road - Winnersh Triangle 105
Wokingham RG415RB
GB
Scientific
Kowa Research Europe

Wharfedale Road - Winnersh Triangle 105
Wokingham RG415RB
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients who meet the following criteria at screening will be eligible to participate in the study:;1. Able to understand and comply with study procedures and give written informed consent;2. Aged><=18 years;3. Have no clinically significant abnormal findings on medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory profiles of both blood and urine that would impair participation or safety in the trial or clinically relevant abnormal findings that in the opinion of the investigator could interfere with the objectives of the study or the safety of the patient;;4. After treatment with stable statin therapy for at least 12 weeks prior to screening, have a screening LDL-C of no more than 10 mg/dL (0.259 mmol/L) above the NCEP ATP III target (see note 2 below):;* - LDL-C<70 mg/dL (1.81 mmol/L) or <100 mg/dL (2.59 mmol/L) for patients with coronary heart disease (CHD) or CHD equivalent;* - LDL-C<130 mg/dL (3.36 mmol/L) for patients with multiple risk factors;* - LDL-C<160 mg/dL (4.14 mmol/L) for patients with 0-1 risk factor;Note 1: Any statin approved by the regulatory authority in the respective country is allowed with the exception of pravastatin, lovastatin and fluvastatin;Note 2: If LDL-C is greater than 10 mg/dL (0.259 mmol/L) above target, patients are only eligible for the study if they are on the maximum allowable statin dose as per approved SPC in the respective country or or on the maximum dose tolerated by the respective patient.;5. Fasting TG value at screening is><=175 mg/dL (1.97 mmol/L) and<<=500 mg/dL (5.65 mmol/L) Note: If the patient fails to meet this criterion at Screening Visit (SV) 1, a fasting re-test of TG will be allowed at a second SV;6. HDL-C value at screening is<<=50 mg/dL (1.30 mmol/L) for men and<<=55 mg/dL (1.43 mmol/L)for women;7. Women may be enrolled if all 3 of the following criteria are met:;* They are not pregnant;* They are not breastfeeding and;* They do not plan on becoming pregnant during the study;8. Women of childbearing potential must have a negative urine pregnancy test at screening. Women are not considered to be of childbearing potential if they meet 1 of the following criteria as documented by the investigator:;* - They have had a hysterectomy or tubal ligation at minimum 1 cycle prior to signing the Informed Consent Form;* - They are post-menopausal, defined as ><=1 year since their last menstrual period for women ><= 55 years of age or ><=1 year since their last menstrual period and have a follicle-stimulating hormone (FSH) level in menopausal range (defined as > 40 miU/mL) for women < 55 years of age;9. Women of childbearing potential must agree to use an effective method of contraception from screening to the end of the study. Effective methods of contraception are those contraceptive methods with a Pearl index of <1 used consistently

and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives or intrauterine devices;10. Male study participants will be required to use condoms with a spermicide during sexual intercourse from screening to the end of the study, even if their sexual partner is or may be pregnant.

Exclusion criteria

Patients will be excluded from participation in the study if any of the following criteria apply:;1. Patients who require other lipid lowering treatments in addition to study drug (K-877) and statin;2. Patients with body mass index *40 kg/m2;3. Patients with homozygous familial hypercholesterolaemia (heterozygous is permitted) or familial hypoalphalipoproteinaemia;4. Patients with type 1 diabetes mellitus;5. Patients with poorly controlled type 2 diabetes mellitus (haemoglobin A1c >10%);6. Patients who are receiving insulin or insulin analogue treatment except for stable basal insulin therapy with a single insulin;7. Patients with moderate or severe renal impairment (ie, estimated glomerular filtration rate <50 mL/min/1.73m2) at screening ;8. Patients with serious liver dysfunction; liver function test values >3 × upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at screening ;9. Patients with a creatine kinase level >3 × ULN at screening ;10. Patients with hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormalities), gall bladder disease or pancreatitis;11. Patients with a history of drug or alcohol abuse; allowed amounts of alcohol are an average of 20 g for women and 30 g for men per day as consumed in the course of a week ;12. Patients who have a hypersensitivity/intolerance to peroxisome proliferator-activated receptor * agonists or statins, or for whom statins are contraindicated as per approved statin Summary of Product Characteristics (SPC);13. Patients who had myocardial infarction, artery angioplasty, bypass graft surgery or severe/unstable angina pectoris within 3 months prior to screening;14. Patients who had symptomatic cerebrovascular disease including cerebrovascular haemorrhage, ischaemia (including transient ischaemic attack), or carotid endarterectomy within 3 months of screening;15. Patients with symptomatic heart failure (New York Heart Association class III or IV);16. Patients who have uncontrolled hypertension (seated systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg) Note: An average of 3 readings within an adequate time interval during the study visit may be used to determine blood pressure level. ;17. Patients who have used lipid modifying treatment other than statins within the 28 days prior to screening;18. Patients with a history of chronic active hepatitis B or hepatitis C or known to be infected with human immunodeficiency virus (HIV) 1 or HIV 2;19. Patients with known muscular or neuromuscular disease;20. Patients with known active or history (<10 years from previous event) of neoplastic disease (excluding basal cell cancer) or patients who may need to take antineoplastic treatment during the study period;21. Patients with uncontrolled hypothyroidism or hyperthyroidism;Note: controlled thyroid disease (normal serum thyroid stimulating hormone [TSH] and stable therapy for at least 3 months) is permitted;22. Patients who have participated in any other clinical studies within 3 months of screening;23. Patients who have experienced a loss of more than 400 mL of blood during the 3 months prior to screening, eg, as a blood donor;24. Patients with a clinically relevant abnormal history, physical examination findings, 12 lead ECG, or laboratory values at screening that in the

opinion of the investigator could interfere with the objectives of the study or the safety of the patient;25. Patients with a high possibility they will not be compliant with the requirements of the protocol (eg uncooperative attitude, inability to return for follow up visits and unlikelihood of completing the study);26. Patients who have a mental condition rendering them unable to understand the nature, scope, and possible consequences of the study

Study design

Design

Study phase:	2
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):	18-12-2013
Enrollment:	83
Type:	Actual

Ethics review

Approved WMO Date:	07-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	18-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2013
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:	11-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2014
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
Approved WMO	

Date:	08-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2014
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	EUCTR2013-001517-32-NL
CCMO	NL45192.018.13

Study results

Date completed:	19-09-2014
Actual enrolment:	52

Summary results
Trial is onging in other countries