Double-Blind follow-on study of Pitavastatine (4mg)versus atorvastatine (20 mg and 40 mg), with a single extension of treatment in patients with type II Diabetes Mellitus and Combined Dyslipidemia

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To assess long-term safety and tolerability of pitavastatin 4 mg once daily (QD)To assess the efficacy of pitavastatin (4 mg QD) and simvastatin (40 mg and 80 mg QD) in terms of LDL-C target attainment (European Atherosclerosis Society [EAS] and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON30046

Source
ToetsingOnline

Brief title
A long term comparasion in DM II patients and Combined Dyslipidemia.

Condition

- Coronary artery disorders
- Diabetic complications
- Lipid metabolism disorders

Synonym
high cholesterol and diabets mellitus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: combined dyslipedemia, Diabetes Mellitus, Primary Hypercholesterolemia, statin

Outcome measures

Primary outcome

The primary efficacy variable is the proportion of patients achieving the LDL-C

target goal at Visit 4 (Week 16) for the double-blind treatment period and at

Visit 8 (Week 44) for the single-blind treatment period.

Secondary outcome

The secondary efficacy variables are the percent change from baseline in LDL-C,

TC, HDL C, TC:HDL C ratio, TG, Apo A1, Apo-B, Apo-B:Apo-A1 ratio, hs CRP,

oxidized LDL and non-HDL:HDL ratio. The baseline is defined as the mean from

Visits 2, 3 and 4 of the core study (NK 104 304) or Visits 3, 3A and 4, from

the core study, if Visit 3A was required as a qualifying visit.

Study description

Background summary

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of mortality in the developed world and accounts for more patient hospitalizations than any other single illness. The role of serum cholesterol, particularly low-density lipoprotein cholesterol (LDL C), in the development of atherosclerosis is well established. Interventional clinical trials, especially LDL-C lowering retards the development of atherosclerotic lesions and reduces

both cardiovascular morbidity and mortality.

There are 6 statins in clinical use in Europe. At their currently approved start doses, LDL-C levels can on average be reduced effectively. Despite the compelling evidence of the benefit of lowering cholesterol levels and the availability of effective cholesterol lowering agents, a large majority of patients with CHD or a significant cardiovascular risk still have LDL C levels greater than those recommended by the guidelines for primary and secondary prevention.

Pitavastatin is a statin, registered and launched in Japan and Korea. In European Phase II dose-ranging studies in patients with primary hypercholesterolemia and mixed hyperlipidemia, pitavastatin has been shown to safely lower LDL C by 41 to 44% after 3 months of treatment at daily doses of pitavastatin 4 mg. At these doses, pitavastatin is expected to bring most patients to reach their cholesterol targets with minimal dose adjustment required. Diabetes patients have an increased risk on recurrence of cardiovascular diseases. Use of lipid lowering medication for these patients can experience a larger risk fall of the cardiovascular diseases compared to non diabetics patients.

These follow-on study aims specifically at the security and effecacy of pitavastatine on the long period.

Study objective

To assess long-term safety and tolerability of pitavastatin 4 mg once daily (QD)

To assess the efficacy of pitavastatin (4 mg QD) and simvastatin (40 mg and 80 mg QD) in terms of LDL-C target attainment (European Atherosclerosis Society [EAS] and National Cholesterol Education Program [NCEP]) following 16 weeks and 44 weeks of study treatment in this study.

Study design

This is a 44-week double-blind, double-dummy follow-on study in patients from the core study NK 104 305 of the pitavastatin Phase III development program.

Intervention

Yes, Atorvastatine.

Study burden and risks

Not applicable

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

All patients entering this study must have satisfied inclusion criteria for the previous core study (NK-104-305) and received 12 weeks of active treatment.

Exclusion criteria

The exclusion criteria of the NK-104-305 study are still valid for the NK-104-310 study.
Patients participating in the study must not present any of the following conditions:
1. Homozygous familial hypercholesterolemia (heterozygous component of familial hypercholesterolemia is acceptable for inclusion);
2. Any conditions which may cause secondary dyslipidemia. This includes, but is not restricted to alcoholism, auto-immune disease, nephrotic syndrome, uremia, any viral or non

viral hepatitis clinically active within 12 months from study entry, obstructive hepatic or biliary disease, dys- or macroglobulinemia, multiple myeloma, glycogen storage disease, chronic pancreatitis, porphyria, and uncontrolled hypothyroidism or hyperthyroidism (controlled hypo- or hyperthyroidism [i.e., condition presenting with normal baseline serum thyroid stimulating hormone {TSH} and treatment stable during at least the last 2 months prior to study entry] will be permitted);
3. Uncontrolled diabetes mellitus as defined by glycosylated hemoglobin A1c (HbA1c) >7.5%.
4. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug. The investigator should be guided by the evidence of any of the following: history of major gastrointestinal tract surgery e.g. gastrectomy, gastroenterostomy, or small bowel resection, gastritis requiring active treatment, current active ulcers, gastrointestinal or rectal bleeding. Current active or recurrent irritable bowel syndrome (IBS) or history of inflammatory bowel syndrome. Patients with a past history of IBS without symptoms for at least the last 6 months prior to the study start will be allowed to enter the study;
5. Any history of pancreatic injury or pancreatitis, or impaired pancreatic function/injury as indicated by abnormal lipase or amylase;
6. Liver injury as indicated by serum transaminase levels (ALAT/serum glutamic pyruvic transaminase [SGPT], ASAT/serum glutamic oxaloacetic transaminase [SGOT]) >1.5 x upper limit of the reference range (ULRR) over the lead in period. The ALAT/SGPT and ASAT/SGOT levels must be *1.5 x ULRR on at least 2 of the 3 evaluations between Visit 1 (Week -8/-6) and Visit 3 (Week -1) for the patient to be eligible for further study participation. If ALAT/SGPT and/or ASAT/SGOT is >2 x ULRR at any time point between Visit 1 (Week 8/-6) and Visit 3 (Week -1), the patient will be immediately excluded from further study participation;
7. Impaired renal function as indicated by serum creatinine levels >1.5 x ULRR at Visit 1 (Week -8/-6). However, if creatinine is between 1.5 and 2 x ULRR, 1 retest will be permitted at Visit 2 (Week -2), provided all other criteria are fulfilled. Serum creatinine must be *1.5 x ULRR at the retest for the patient to be eligible for further study participation. If serum creatinine is >2 x ULRR at Visit 1 (Week -8/-6), the patient will be immediately excluded from further study participation;
8. Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions, which is likely to require intervention during the course of the study or is regarded as clinically meaningful by the investigator;
9. Serum CK >5 x ULRR. However, if at Visit 1 (Week-8/-6) serum CK is >5 x ULRR without a clinical explanation, one re-test will be allowed. If the repeat CK is >5 x ULRR in the absence of conditions explaining the CK elevation the patient will be immediately excluded from further study participation;
10. Uncontrolled hypothyroidism defined as TSH >ULRR. Patients with TSH >ULRR at Visit 1 are permitted to have a retest at Visit 2 and if TSH is also >ULRR at Visit 2 the patient will be excluded from the study;
11. Any severe acute illness or severe trauma in the last 3 months prior to Visit 1 (Week -8/-6);
12. Major surgery, during the 3 months prior to Visit 1 (Week -8/-6);
13. Significant CVD prior to randomization, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery or severe or unstable angina pectoris within the last 3 months;
14. Evidence of symptomatic heart failure (New York Heart Association [NYHA] class III or IV),

gross cardiac enlargement (cardiothoracic ratio >0.5); significant heart block or cardiac arrhythmias. History of uncontrolled complex ventricular arrhythmias, uncontrolled atrial fibrillation/flutter, or uncontrolled supraventricular tachycardias with a ventricular response rate of >100 beats per minute at rest. Patients whose electrophysiological instability are controlled with a pacemaker or implantable cardiac device are eligible;
15. In patients where the left ventricular ejection fraction (LVEF) is known this should be <0.25 (echographic confirmation of the LVEF is not a study requierment;
16. History of symptomatic cerebrovascular disease including cerebrovascular hemorrhage, transient ischemic attack or carotid endarterectomy within 1 month prior to randomization;
17. Any other medical or surgical conditions at the discretion of the investigator which place the patient at higher risk derived from his/her participation in the study, which could confound the result of the study, or are likely to prevent the patient from complying with the requirements of the study or completing the study period;
18. Known Human Immunodeficiency Virus (HIV) infection;
19. Poorly controlled or uncontrolled hypertension. Patients must have a systolic blood pressure (SBP) *160 mm Hg and diastolic blood pressure (DBP) *90 mm Hg with or without antihypertensive therapy;
20. Prior or current known muscular or neuromuscular disease of any type;
21. Current active neoplastic disease or patients who may require antineoplastic treatment during the course of the study. History of prior malignancy except those patients who have been cancer free for >10 years. Patients with prior history of basal cell carcinoma or squamous cell carcinoma of the skin remain eligible if they have been cancer free for >5 the past years;
22. Within the last 2 years, a history of drug abuse or continuous consumption of more than 65 mL pure alcohol per day (e.g., more than 4 x 125-mL glasses of wine or 3 glasses of spirits per day);
23. Exposure to any investigational new drug within 30 days of study entry (Visit 1/Week -8/-6) or ingestion of any drug known to be toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) within 12 weeks prior to the study entry (Visit 1/Week -8/-6);
24. Current or recent (within 4 weeks of Visit 1 [Weeks -8/-6]) use of supplements known to alter lipid metabolism e.g. soluble fibers (including >2 teaspoons Metamucil or psyllium containing supplement per day), or other dietary fiber supplements, fish oils, sterol/stanol products, or others at the discretion of the investigator;
25. History of hypersensitivity reactions to other HMG-CoA reductase inhibitors;
26. Any concomitant medication not permitted by this protocol (see Section 4.5.5, Concomitant Therapy);
27. History of being resistant to lipid-lowering medications. Known hypersensitivity or intolerance to any lipid lowering agent, i.e., elevated serum transaminases, myositis;
28. Excessive obesity defined as Body Mass Index (BMI) above 35 kg/m2 (BMI = body weight in kg divided by squared height [m2]). Body Mass Index values should be rounded to the nearest whole number: down at <0.5 and up at *0.5;
29. Any factor which makes regular clinic attendance in the morning impractical (e.g., shift and/or night work); and/or
30. Any signs of mental dysfunction or other factors (including language problems) likely to limit the ability of the patient to cooperate with the performance of the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-08-2006
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lipitor
Generic name:	Atorvastatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Livalo
Generic name:	Pitavastatin

Ethics review

Approved WMO

Date:	19-01-2006
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO Date:	01-05-2006
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	16-05-2006
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	08-09-2006
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	21-02-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	06-03-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	29-03-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	30-03-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	24-07-2007
Application type:	Amendment

Approved WMO Date:	16-11-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	13-06-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	25-06-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	01-07-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2005-006041-16-NL
CCMO	NL11362.003.06