A randomized, double-blind trial comparing the efficacy and safety of a fixed combination of fenofibrate and metformin vs rosiglitazone in patients with type 2 diabetes mellitus and dyslipidemia

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Primary objective : Under conditions of first-line drug treatment in antidiabetic drug naïve/drug free patients (no antidiabetic drug treatment in the last 6 months), with type 2 diabetes mellitus and dyslipidemia, to show that : - the efficacy of a...

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

Summary

ID

NL-OMON30160

Source
ToetsingOnline

Brief title
fenofibrate and metformin FC vs rosiglitazone, Nr: C LF23-0121 05 01

Condition

- Diabetic complications

Synonym
diabetes mellitus type 2 and dyslipidaemia

Research involving

Human

Sponsors and support

Primary sponsor: Fournier Laboratories
Source(s) of monetary or material Support: farmaceutisch bedrijf

Intervention

Keyword: diabetes mellitus type 2 and dyslipidaemia, fixed combination of fenofibrate and metformin, rosiglitazone

Outcome measures

Primary outcome

Primary criteria: HbA1c, TG

Secondary outcome

Secondary criteria:

Efficacy parameters:

• FPG,

• TC, HDL-C, LDL-C, Non-HDL-C, LDL particle size, Apo AI, Apo B, Apo CIII,

• Body weight.

Safety parameters:

• Adverse events,

• Clinical examination including presence of peripheral edema and vital signs,

• Hematology: RBC, hemoglobin, hematocrit, platelets, WBC and differential

count,

• Biochemistry: CPK, AST, ALT, Gamma GT, alkaline phosphatase, total bilirubin,

creatinine, uric acid.

Study description

Background summary

Optimal management of individuals with type 2 diabetes mellitus (T2DM) to prevent both the macrovascular and microvascular complications requires a multifactorial approach and includes management of hyperglycemia, hypertension, body weight and the associated abnormal lipid profile. While the management of hyperglycemia and of hypertension have received considerable attention over the years, it is only recently that the importance of dyslipidemia - as a major risk factor for coronary heart disease (CHD) in diabetes - has been recognized as a key therapeutic target. The American Diabetes Association (ADA) guidelines [1] suggest that improved glycemic control alone will not be likely to completely eliminate excess risk of CHD in T2DM patients: clearly a multifactorial approach is necessary.

The dyslipidemia of T2DM typically includes hypertriglyceridemia (both in the fasting and
post prandial state), reduced HDL-C, normal total and LDL-C but with a preponderance ofsmall atherogenic dense LDL particles [2].

Cardiovascular disease, in particular CHD accounts for up to 80% of the morbidity
observed in patients with T2DM. In comparison to those without diabetes the risk of CHD is increased 2 - 4 times in patients with diabetes [3]. In a publication derived from
NHANES III, the age-adjusted prevalence of CHD in Americans over 50 years of age with
both metabolic syndrome and diabetes was 19.2% which was three fold higher than that observed in the diabetic patients without the features of metabolic syndrome [4]. TG elevation in T2DM clearly independently predicts cardiovascular events [5].

Specific drug treatments (oral antidiabetic drugs or insulin) which improve the glycemic
control have only a small lipid improving effect, and therefore drug treatments directed at the specific dyslipidemia of T2DM are now considered key therapies to reduce the high cardiovascular events in these patients.

The importance of tight glycemic control as demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS) [6] was confirmed with the use of metformin therapy in obese patients. Analysis of the results for overweight T2DM patients in the UKPDS [7] treated with metformin after failure of diet alone showed significant reductions of diabetesrelated deaths by 42%, of all cause mortality by 36%, and of risk of myocardial infarction by 39%.

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity [8]. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR (gamma)). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR (gamma) nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPAR (gamma)-responsive genes also participate in the regulation of fatty acid metabolism.

Metformin is a biguanide widely used as an oral antidiabetic agent for the first line treatment of T2DM. It is marketed worldwide, and has been used for more than 40 years. Metformin does not increase pancreatic insulin secretion and, in contrast to sulphonylureas, does not produce hypoglycemia in either patients with T2DM or normal subjects. It has beneficial effects on body weight, fasting plasma insulin levels, fasting blood glucose levels in subjects with visceral obesity at risk of T2DM and in patient with T2DM [9] [10] [11].

The fibric acid derivatives, which are PPARα agonists, are important therapeutic drugs targeting the dyslipidemia of T2DM, in particular the reduction of TG and increase in HDL-C. The St Mary*s Ealing Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) [12] Study and the Veterans* Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) [13] both reported significant reductions in coronary events in patients with T2DM with effective TG lowering with fibrate therapy.

In the Diabetes Atherosclerosis Intervention Study (DAIS) [14] significantly lower progression of angiographic coronary disease was shown on fenofibrate. Currently both the ADA [1] and NICE Guidance (UK) [15] recommend the addition of fibrate therapy, either as monotherapy or in combination with statins for diabetic patients with low HDL-C (< 40mg/dL) and LDL-C between 100 and 129 mg/dl or patients needing treatment for all three lipid fractions.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [16], the largest intervention study ever conducted for the prevention of cardiovascular

events in
patients with T2DM, showed that in the subset of patients without prior CVD, the majority of the FIELD study population, fenofibrate significantly reduced the first occurrence of non-fatal MI or CHD death and total cardiovascular events.

Fenofibrate has been shown to be effective in improving lipid abnormalities in diabetic
patients receiving oral hypoglycemic agents or insulin without any change in glycemic
control [17]. Changes in the lipid profile, which are maintained during long-term treatment with fenofibrate, are believed to be consistent with a reduction in the cardiovascular risk.

As of now, no fixed combination of fenofibrate and metformin is registered. Therefore, coprescription of fenofibrate and metformin is common in diabetic patients. In France,
approximatively 9% of patients treated with metformin are also treated with fenofibrate, a total of more than 300,000 prescriptions per year. In the US, 3% of all prescriptions of products containing metformin (including other fixed combinations) are in co-prescription with fenofibrate.

Based on the complementary effects of fenofibrate and metformin and their individual
safety, a single combination tablet of these 2 compounds is being developed by FOURNIER S.A. achieve additive clinical benefits as well as improvement of medication
compliance by a reduced number of tablets to be administered. This fixed combination
(FC), LF23-0121, combines fenofibrate 160 mg and different strengths of metformin. The overall objective of the clinical development plan is to evaluate the efficacy and safety of the fenofibrate and metformin FC in patients with mixed T2DM and dyslipidemia (type IIb/IV).

This study, C LF23-0121 05 01, is part of the clinical development plan of LF23-0121 and will be conducted in such patients. The trial will be conducted in compliance with the
protocol, GCP and the applicable local regulatory requirement(s).

Study objective

Primary objective : Under conditions of first-line drug treatment in antidiabetic drug naïve/drug free patients (no antidiabetic drug treatment in the last 6 months), with type 2 diabetes mellitus and dyslipidemia, to show that :
- the efficacy of a fixed combination of fenofibrate and metformin on glycemic control is not inferior to that of rosiglitazone

- the efficacy of a fixed combination (FC) of fenofibrate and metformin on triglyceride control is superior to that of rosiglitazone

Study design

Methodology : This study is a double-blind, randomized, controlled, multicenter study comparing 2 treatments administered through forced titration over 2 periods of 12 weeks each, defined as Period 1 and Period 2. Study drug will consist of concomitant administration of active fenofibrate and metformin FC + placebo rosiglitazone or active rosiglitazone + placebo fenofibrate and metformin FC.

Double-blind on the product (not on the dose), double-placebo.
In Period 1, patients will take daily 2 tablets (1 active and 1 placebo) in the morning and 1 tablet (active or placebo) in the evening, i.e. a total of 3 tablets per day.
In Period 2, patients will take daily 2 tablets (1 active and 1 placebo) in the morning and in the evening and 1 tablet (active or placebo) at noon., i.e. a total of 5 tablets per day.

Active treatments and doses are the following:

Fenofibrate and metformin FC
Fenofibrate and metformin FC (study group)
Period 1 80 mg fenofibrate + 500 mg metformin bid (2 weeks)
80 mg fenofibrate + 850 mg metformin bid* (4 weeks)
Period 2 54 mg fenofibrate + 850 mg metformin tid (6 weeks)

Rosiglitazon (control group)
Period 1 4 mg rosiglitazon od (6 weeks)
Period 2 4 mg rosiglitazon bid (6weeks)

*In order to improve gastrointestinal tolerance to metformin, the FC dose of 80 mg fenofibrate + 850 mg metformin bid will be reached in Period 1 after 2 weeks of treatment at a lower dose of metformin (500 mg bid).

After a 4 to 6 week run-in period, with standard diet and exercise recommendations only, the patients will be randomized on the day of V1 to one of the 2 arms. A balanced stratification between arms will be made based on sex (male/female), concomitant use of statin (yes/no), and according to HbA1c value: 6.5% <= HbA1c <= 8% and 8% < HbA1c <= 9.5%.

A Lipid Data Safety Monitoring Board will be setup in order to monitor lipid values throughout the study. This Lipid Data Safety Monitoring Board will be constituted of at least two experienced physicians, independent from study participants.

Intervention

After a 4 to 6 week run-in period, with standard diet and exercise recommendations only, the patients will be randomized on the day of V1 to one of the 2 arms. A balanced stratification between arms will be made based on sex (male/female), concomitant use of statin (yes/no), and according to HbA1c value: 6.5% <= HbA1c <= 8% and 8% < HbA1c <= 9.5%.

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*In order to improve gastrointestinal tolerance to metformin, the FC dose of 80 mg fenofibrate + 850 mg metformin bid will be reached in Period 1 after 2 weeks of treatment at a lower dose of metformin (500 mg bid).

Study burden and risks

Burden: 5 visits to the trial center.
The screening visit should last 1,5 hour ans the other visits 1 hour.
During these visits there will be taken a blood sample.

The risks of fenofibrate, metformin and roziglitazone are well known, see the SmPCs of these separate registered drugs.

Contacts

Public
Fournier Laboratories

Anngrove, Carrigtwohill
Co. Cork
Ierland
Scientific
Fournier Laboratories

Anngrove, Carrigtwohill

Co. Cork
Ierland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

At inclusion (V0):
1. Male or female aged from 18 to 75 years old,
2. With type 2 diabetes mellitus and dyslipidemia inadequately controlled with lifestyle modifications (diet and exercise),
3. With antidiabetic drug status as follows:
• Antidiabetic drug naive patients: who have never been on prior antidiabetic drug treatment, or,
• Antidiabetic drug free patients: who have not received antidiabetic drug treatment in the last 6 months,
4. Having signed a written informed consent.
At randomization (V1):
5. FPG >= 126 mg/dL dL (>= 7.0 mmol/L) and < 300 mg/dL (< 16.7 mmol/L). Glycemic status of the patients will be confirmed based on two FPG assays, BV0 and BV1,
6. HbA1c >= 6.5% and <= 9.5%,
7. Hypertriglyceridemia with or without hypercholesterolemia, defined by TG >= 150 mg/dL and <= 400 mg/dL (TG >= 1.69 mmol/L and <= 4.52 mmol/L), assayed at BV1.

Exclusion criteria

Patient with any of the following conditions will not be included in the trial:
1. Known Type 1 diabetes,
2. With LDL-C > 130mg/dL (3.35 mmol/L),
3. In cardiovascular secondary prevention,
4. Body mass index > 40 kg/m2,

5. Women who are not postmenopausal if they are not surgically sterilized (i.e. bilateral tubal ligation, bilateral or two unilateral oophorectomies, hysterectomy), or not using adequate contraceptive precautions,
6. Pregnant or lactating women,
7. Known hypersensitivity to fibrates, metformin, rosiglitazone or any of their components or known photoallergic or phototoxic reactions under treatment with fibrates or ketoprofen,
8. Known allergy to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions,
9. Having received an investigational drug in the last 30 days before date of inclusion,
10. Unable or unwilling to comply with the protocol and the standard diet and exercise recommendations,
11. Likely to withdraw from the study before its completion.;Concomitant medications:
12. Treated within the last 6 months before randomization with any antidiabetic drug treatment,
13. Treated within the last 2 months before randomization with a lipid-lowering drug (except statins). Patients who were on a statin before inclusion may be included provided the dose does not exceed the maximum daily dose authorized in the study) and is kept constant throughout the study.
14. Treated within the last 2 months before randomization with cyclosporin A, and any other immunosuppressive agent, with protease inhibitors (indinavir, ritonavir, saquinavir, *), for obesity by medical treatment (orlistat, sibutramine*) and/or surgery (gastroplasty, bypass,*), with rifampin (inducer of CYP2C8)
15. Change within the last 2 months before randomization, and during the course of the study, in the medications that could interfere with the lipid or glycemic profile.;Associated diseases or conditions:
16. Diabetic ketoacidosis, diabetic pre-coma,
17. Current chronic pancreatitis, or identified risk or known history of acute pancreatitis,
18. Known cholelithiasis without cholecystectomy,
19. Significant hepatic disease: AST and/or ALT > 2 times the upper limit of normal (ULN),
20. Musculoskeletal disease with increased creatine phosphokinase (CPK) > 3 times ULN,
21. Renal failure or renal dysfunction defined by a creatinine clearance < 60 mL/min as calculated with the Cockroft-Gault algorithm: creatinine clearance = [(140 - age) x weight (kg) / 7.2 x serum creatinine (mg/L)] for males and [x 0.85] in females,
22. Acute conditions with the potential to alter renal function (such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents),
23. Acute or chronic disease which may cause tissue hypoxia such as respiratory failure,
24. Known congestive heart failure or past medical history of congestive heart failure (class I to IV),
25. Known abnormal thyroid hormone levels, or high thyroid stimulating hormone (TSH) level. (clinically euthyroid subjects on stable replacement doses of thyroid hormone are eligible for inclusion),
26. Other uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins,
27. Patients particularly susceptible to hypoglycemic effects, such as debilitated, or malnourished patients, acute alcohol intoxication, excessive alcohol intake,
28. Known gastric or peptic ulcer or intestinal disease within the previous 3 months of randomization capable of modifying the intestinal absorption of the drugs,

29. Any other severe pathology such as cancer or mental illness or degenerative disease that would limit study evaluation or participation.;In addition in patients aged under 35 years the following exclusion criteria will apply:
30. Body mass index < 25 kg/m2,
31. Ever been treated by Insulin,
32. Family history of type 1 diabetes.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-02-2007
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AVANDIA 4 mg comprimés pelliculés
Generic name:	rosiglitazone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	LF23-0121 fenofibrate/metformin 54/850 mg
Generic name:	fixed-combination fenofibrate/metformin 54/850 mg
Product type:	Medicine
Brand name:	LF23-0121 fenofibrate/metformin 80/500 mg

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Generic name:	fixed-combination fenofibrate/metformin 80/850 mg

Ethics review

Approved WMO Date:	30-05-2006
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	30-08-2006
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:	30-09-2006
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	02-10-2006
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	07-11-2006
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO Date:	21-11-2006
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	02-01-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	22-01-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	23-01-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	06-08-2007
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	EUCTR2005-006060-63-NL
CCMO	NL12150.003.06