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Proprietary Drug Name: [Product Name/Trade Name may vary by country or area (e.g. Tricor in the U.S., Lipanthyl in the EU)]*	Generic Drug Name: Fenofibrate	Condition: Type 2 Diabetes, Dyslipidemia
Name of Sponsor/Company: Fournier Laboratories Ireland Ltd.		
Title of Study: Assessment of insulin sensitivity in type 2 diabetics treated with metformin, fenofibrate and their combination Protocol No.: CLF23-0121 05 03		
Coodinating Investigator: Professor Eleuterio Ferrannini, Pisa (Italy) Principal Investigators: Professor Stefano del Prato, Pisa (Italy) Doctor Patricia Iozzo, Turku (Finland) and Pisa (Italy) Professor John Nolan, Dublin (Ireland)		
Study Center (s): Out of 4 sites initially selected only two were opened: the Turku PET Centre, University of Turku, Turku, Finland; and The Metabolic Research Unit, St James's Hospital, Dublin, Ireland.		
Publication (reference): Not applicable		
Studied Period (years): 13 OCT 2006 (First Subject First Visit) 17 JUL 2007 (Early Termination) 23 JUL 2007 (Last Subject Last Visit)	Phase of development: Phase IIb/III	
Objectives: <u>Primary objective:</u> To investigate changes of Endogenous Glucose Production (EGP), and Glucose Disposal Rate (GDR) by two-step hyperinsulinemic euglycemic clamp (HEC) under fenofibrate, metformin and their combination in patients with Type 2 Diabetes (T2DM) and dyslipidemia. <u>Secondary objectives:</u> To investigate the effects of metformin, fenofibrate and their combination on gluconeogenesis (GNG), glycogenolysis (GGL), skeletal muscle and liver fat content measured by magnetic resonance spectroscopy (MRS), abdominal fat content measured by magnetic resonance imaging (MRI), body energy expenditure and respiratory quotient measured by indirect calorimetry, lipids, lipoproteins and carbohydrate metabolism and other biochemical parameters and other safety test parameters.		
Methodology:		

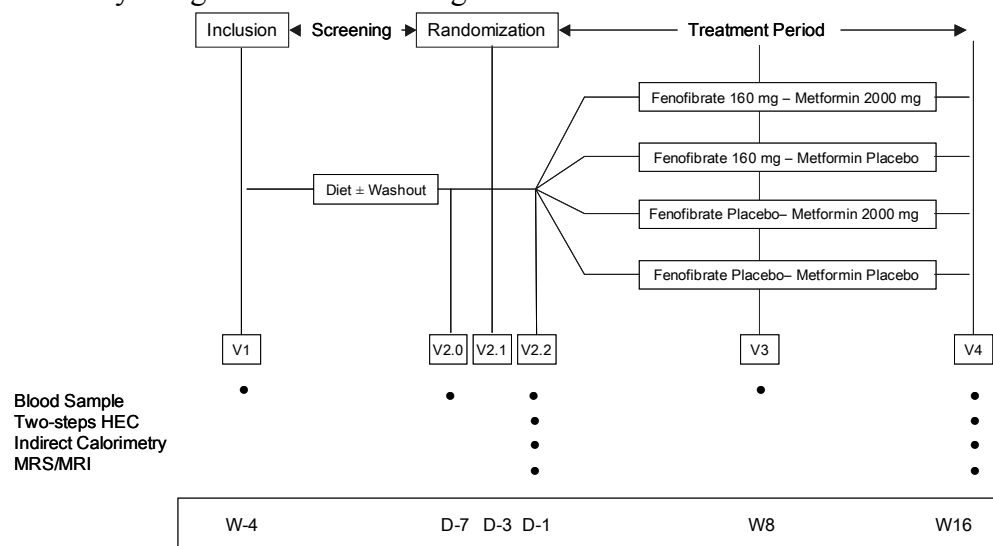
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It was a phase IIb/III, 2x2 factorial design, double-blind, randomized, placebo-controlled study. Patients with T2DM and dyslipidemia (increased TG and/or decreased HDL-C) were randomized to one of the following four treatment arms for 16 weeks: placebo, fenofibrate, metformin, or fenofibrate and metformin co-administration.

The study design is shown in the figure below.



V: Visit, D: Day, W: Week.

Number of Subjects (Planned and Analyzed):

Planned: A total of 100 (25 in each group) patients were to be randomized (visit V2.1) in order to obtain at least 80 patients (20 in each of the four groups) having completed the study in accordance with the protocol.

Analyzed: 30 patients were enrolled in the study and 8 were randomized; 2 in each group. 7 patients were treated, a patient in the metformin group was randomized but not treated (consent withdrawn).

The study was prematurely terminated, due to difficulties in the recruitment of T2DM patients who are not under statin therapy at inclusion.

Diagnosis and Main Criteria for Inclusion / Randomization:

For their inclusion into the study, patients were to be male or female, aged from 40 to 75 years at

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inclusion, with known T2DM as defined by ADA criteria:

- for patients under oral antidiabetic treatment at inclusion which will be stopped at inclusion (V1): fasting glucose ≥ 6.0 mmol/L or OGTT glucose at 120 minutes ≥ 10 mmol/L, or HbA1c $\geq 6\%$ and $<9\%$ at inclusion or during the last four months before inclusion,
- for patients which are not under oral antidiabetic treatment at inclusion, criteria are the same as randomization criteria: fasting glucose ≥ 7.0 mmol/L, and/or OGTT glucose at 120 minutes ≥ 11.1 mmol/L and/or HbA1c $\geq 7\%$ and $<10\%$ at inclusion or during the last four months before inclusion,

Patients were to have at least one of the following biochemical abnormalities:

- Triglycerides (TG) ≥ 150 mg/dL (≥ 1.69 mmol/L); and/or
- High-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL (≤ 1.03 mmol/L) for males or HDL-C ≤ 50 mg/dL (≤ 1.29 mmol/L) for females;
- BMI (body mass index) > 25 kg/m² and ≤ 40 kg/m²;
- And having signed a written informed consent.

For their randomization at V2.1 to one of the 4 treatment arms, patients were to have:

- Fasting glucose ≥ 7.0 mmol/L (repeated on a different day) and/or OGTT glucose at 120 minutes ≥ 11.1 mmol/L and/or HbA1c $\geq 7\%$ and $<10\%$

Plus at least one of the following biochemical abnormalities: TG ≥ 150 mg/dL (≥ 1.69 mmol/L) and/or HDL-C ≤ 40 mg/dL (≤ 1.03 mmol/L) for males or HDL-C ≤ 50 mg/dL (≤ 1.29 mmol/L) for females.

Test Product, Dose and Mode of Administration:

Fenofibrate: tablets 80 mg bid

Metformin: commercial product, tablets 500 mg metformin chlorhydrate

500 mg bid for the two first weeks (1000 mg/day), then 2 x 500 mg bid for the remaining 14 weeks (2000 mg/day)

Oral route

The treatment period was preceded of a 4-week diet period following the inclusion visit.

Patients randomized in one of the four arms:

- Fenofibrate 80 mg bid (F160), metformin 1000 mg bid (M2000),
- Fenofibrate 80 mg bid (F160), metformin placebo bid (M0),

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- Fenofibrate placebo bid (F0), metformin 1000 mg bid (M2000),
 - Fenofibrate placebo bid (F0), metformin placebo bid (M0).
 Metformin (active or placebo) was initiated at 500 mg bid for the first 2 weeks.

Duration of Treatment:

- Wash-out period of 4 weeks with diet regimen adapted from the American Heart Association step 1 diet, Plus discontinuation of lipid-lowering drugs (other than statin therapy which is an exclusion criteria), antidiabetic agents (other than thiazolidinediones and insulin therapy which are exclusion criteria) and weight-lowering drugs (orlistat, sibutramine).
- Treatment period of 16 weeks.

Reference Therapy, Dose and Mode of Administration:
 Fenofibrate placebo and metformin placebo tablets
 Oral route

Criteria for Evaluation:
 The following efficacy and safety criteria for evaluation were initially planned.

Efficacy:

Primary criteria: Main primary criterion was the percent change of low-dose insulin-suppressed EGP as investigated by HEC ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$; where kg_{ffm} is the fat-free mass in kg). Other primary criteria were percent change of basal EGP ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$), high-dose insulin-suppressed EGP ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$), basal GDR (same as basal EGP; $\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$), low-dose insulin-stimulated GDR ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$), high-dose insulin-stimulated GDR ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$).

Secondary criteria: Main secondary criteria were the percent change of gluconeogenic flux ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$), glycogenolytic flux ($\mu\text{mol}/\text{kg}_{\text{ffm}}/\text{min}$), skeletal muscle fat content, Liver fat content, abdominal fat mass, body energy expenditure and respiratory quotient at basal state and during each of the two steps of the HEC. The following biochemical variables were also evaluated: fasting blood insulin and fasting blood glucose, HbA1c, fructosamine, C-peptide, insulin sensitivity (HOMA-IS) assessed by the homeostasis model assessment of insulin sensitivity using the fasting parameters, fasting lipid parameters: TG, total cholesterol (TC), HDL-C, measured low-density lipoprotein cholesterol (LDL-C), very-low density lipoprotein cholesterol (VLDL-C), free fatty-acids (FFA), apolipoprotein (apo)-A1, apo-A2, apo-B, and apo-CIII.

Other secondary criteria were the percent change of fenofibric or drug plasma levels, fibrinogen,

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Plasminogen -1 Activation Inhibitor (PAI-1) activity, tissue Plasminogen Activator Antigen (t-PA Ag), high sensitivity C-reactive protein (hsCRP), tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), adiponectin and leptin, weight, BMI, waist circumference, hip circumference, waist-to-hip ratio, total body water and fat mass and subcutaneous fat.

Due to premature termination of the study, none of these efficacy parameters were measured.

Safety:

Main safety variables initially planned were adverse events (AEs) ; hemoglobin, hematocrit, MCV, MCH, MCHC, red blood cells count (RBC), white blood cells count (WBC), Platelet count ; creatinine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine and uric acid ; Supine blood pressure, heart rate.

All these parameters, except blood pressure and heart rate, were measured and analyzed.

Statistical Methods:

The statistical methods initially planned are described thereafter.

Statistical analysis of primary criteria:

The main efficacy analysis was conducted on the Full Analysis Set (FAS) according to the following stepwise procedure:

- 1°) The group fenofibrate plus metformin was compared to the Placebo group at 5% two-sided;
- 2°) If the previous analysis was statistically significant, the group fenofibrate plus metformin was then compared to the Metformin group and the Fenofibrate group at 2.5% two-sided;
- 3°) For each monotherapy, if the comparison (group fenofibrate plus metformin vs. monotherapy) was statistically significant at step 2, each monotherapy was then compared to the placebo group at 2.5% two-sided.

Statistical analysis of secondary criteria:

The multiple comparison to the best (MCB) procedure was used to compare four groups on the percent change from baseline to 16 weeks treatment for the main secondary criteria. Other secondary parameters, safety and biological parameters were only described by treatment group.

The following statistical methods were used:

Only descriptive analyses (mean levels or number of patients) are provided for the following baseline characteristics (age, gender, glucose control and lipids levels). Numbers of abnormally high biological values are also reported by study visits and are detailed by treatment groups.

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Summary:

Out of the 30 screened patients, 8 were randomized to either placebo treatment (2 patients, 1 in Finland and 1 in Ireland), or fenofibrate treatment (2 patients in Finland), or metformin (2 patients, 1 in Finland and 1 patient in Ireland), or fenofibrate and metformin co-administration (2 patients in Finland). One patient from Finland in the metformin group was randomized but not treated. The reason for non randomization was mainly related to non compliance to the inclusion criteria (n=20). Frequently patients had cholesterol levels and /or glucose levels within normal range after the wash-out period. Two patients withdrew consent.

Out of the 8 randomized patients, 4 were men and 4 were women, all white, with a mean age of 60.1 (Standard deviation [SD] 9.7) years (58.6 years for men and 61.5 years for women). The mean glucose and HbA1c levels at inclusion (V1) were 7.3 (SD: 1.4) mmol/L and 7.0 (SD: 1.1) % (N=7), respectively. With regards to lipid levels at inclusion, mean TG level was 2.35 (SD: 0.96) mmol/L, mean HDL-C was 1.24 (SD: 0.19) mmol/L and mean measured LDL-C was 2.60 (SD: 0.75) mmol/L (N=7).

Among the eight randomized T2DM patients, four have completed the study. The efficacy parameters, i.e. changes in insulin sensitivity, including skeletal muscle and liver fat content measured by magnetic resonance spectroscopy (MRS), abdominal fat content measured by magnetic resonance imaging (MRI), body energy expenditure and respiratory quotient measured by indirect calorimetry were measured but not analyzed for any of these patients.

Efficacy results:

Due to premature termination of the study, none of the efficacy parameters were analyzed including assays for hyperinsulinemic euglycemic clamp and quantification of magnetic resonance spectroscopy and imaging.

Safety results:

Four adverse events were reported by three patients. Patient IE3010003, a woman of 61-year-old, randomized to placebo experienced one non-serious adverse event (conjunctival hemorrhage of the right eye). This event was not related to any study procedures or underlying disease or concomitant medication. The event resolved after one day. Patient IE3010002, a woman of 63-years old, randomized to metformin, experienced one non-serious adverse event (left sided abdominal pain, unknown causal relationship to study drug) and one serious adverse event (breast cancer [suspicious right breast mass, suggestive of underlying malignancy], not related to study treatment). The abdominal pain occurred 72 days after her first study visit. The duration of such event was 11 days, with a mild severity. This event was not related to any study procedures or

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underlying disease or concomitant medication. The serious adverse event occurred 109 days after her first study visit with a severe severity. This serious event was not related to any study procedures or underlying disease or concomitant medication, but led to permanent discontinuation of the study treatment and premature withdrawal from the study. The outcome of the event was recovering / resolving at the time of the study termination. Patient FI2010011, a man of 67 year-old randomized to fenofibrate + metformin experienced one non-serious adverse event (vertigo paroxysmalis benigna). This event occurred 94 days after his first study visit with a mild severity. The duration of this event was 1 day and was not related to any study procedures or underlying disease or concomitant medication. However, a reasonable Suspect Causal Relationship to Study Drug was considered. The number of abnormally high values reported during the study was low. Only 6 abnormally high values of AST and ALT were reported during the study for 2 patients: 1 in the fenofibrate group and 1 in the fenofibrate + metformin group (2 of 6 values on treatment). All AST /ALT abnormalities are > UNL and < 3 x UNL. No abnormally high values of creatinine or CK were reported. Only 3 abnormally high values of uric acid were reported for 2 patients before treatment, 1 in the placebo and 1 in the fenofibrate groups. All abnormal values were considered as non clinically significant by the Investigator, except one glucose level of 11.7 mmol/L (1.95 x UNL) and HbA1c at 8.8% (1.5 x UNL) at V4 in the fenofibrate + metformin group for the same patient.

Date of report: 27JUN2008