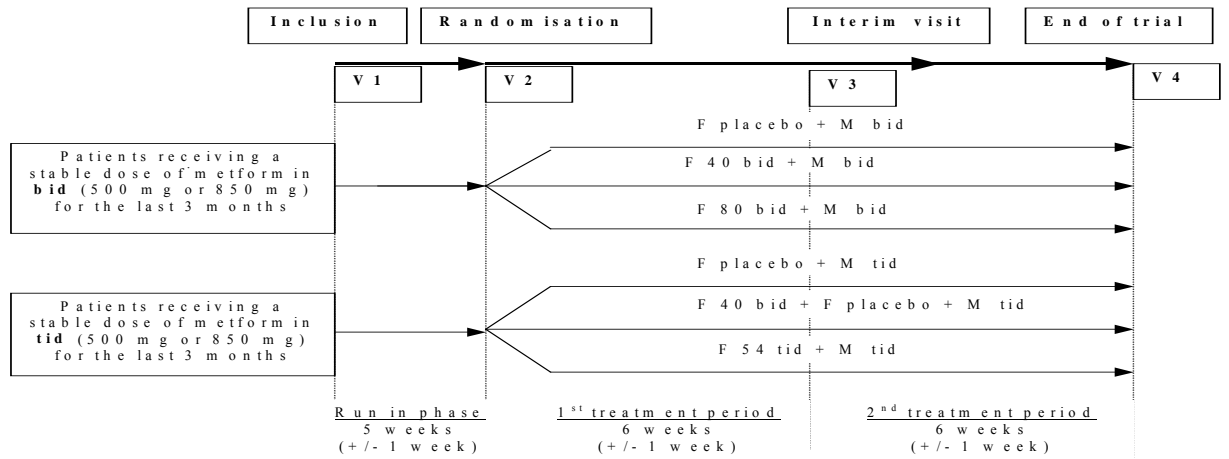


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Proprietary Drug Name: [Product Name/Trade Name may vary by country or area (e.g. Tricor [®] in the U.S., Lipanthyl [®] in the EU)]	Generic Drug Name: Fenofibrate	Condition: Dyslipidemia / Glucose Metabolism Disorder
Name of Sponsor/Company: Fournier Laboratories Ireland Ltd.		
Title of Study: A randomized, double-blind trial assessing the efficacy and safety of low and standard doses of fenofibrate in combination with metformin on the lipid profile in patients with type 2 diabetes and dyslipidemia. Protocol No.: CLF23-0121 03 01		
Investigators: Coordinating investigators: M. D. Feher, MD FRCP for the UK, B. N. Mankovsky, MD for Ukraine, B. Okopien, MD for Poland.		
Study Centers: The study was conducted at 50 investigational centers across 3 countries: UK (34 centers), Poland (4 centers) and Ukraine (12 centers).		
Publication (Reference): Not applicable.		
Study Period: 23 JAN 2004 (First Subject First Visit) – 04 OCT 2005 (Last Subject Last Visit)	Phase of development: II	
Objectives: The <u>primary objective</u> was to assess the effect of 3-month treatment of low (80 mg/day) and standard dose (160 mg/day) of fenofibrate in co-administration with stable dose of metformin on fasting serum triglycerides (TG) in patients with type 2 diabetes (T2DM) and dyslipidemia. The <u>secondary objectives</u> were to assess the effect of treatments on other lipid parameters and glycemic control, to compare the efficacy of fenofibrate 80 mg to fenofibrate 160 mg daily in co-administration with metformin, to assess the safety of both doses, to measure plasma fenofibric acid and metformin levels at steady-state, and to determine correlations with efficacy parameters.		
Methodology: Parallel-arm, randomized, double-blind, controlled, multicenter, dose-ranging study.		

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Number of Subjects: Planned: 385 patients treated: 55 in the placebo group (F0 + M*), 165 in the 80 mg fenofibrate group (F80 + M*) and 165 in the 160 mg fenofibrate group (F160 + M*).

*: metformin at 500 mg or 850 mg bid, at 500 mg or 850 mg tid.

Analyzed: Included: 1084. Randomized: 382, Treated (Full Analysis Set [FAS]): 381: 54 in the F0 + M* group, 165 in the F80 + M* group, 162 in the F160 + M* group.

Per Protocol Set (PPS): 320: 50 in the F0 + M* group, 137 in the F80 + M* group, 133 in the F160 + M* group.

Pharmacokinetic Set (PKS) = PPS.

Diagnosis and Main Criteria for Inclusion: T2DM treated with stable dose of metformin for a minimum of 3 months, either alone or in combination with another oral hypoglycemic agent (sulfonylurea including extended release formulations, meglitinide analogue, or α -glucosidase inhibitor); HbA1c between 6.0% and 10.0%, fasting serum TG level greater than 150 mg/dL (1.69 mmol/L).

Test Product, Dose and Mode of Administration:

Fenofibrate tablets: 40, 54 and 80 mg, oral route.

The dose of 80 mg was administered as 40 mg bid, the dose of 160 mg as 80 mg bid or 54 mg tid, depending on the metformin regimens.

Metformin tablets: 500 and 850 mg.

Duration of Treatment: 3 months.

Reference Therapy, Dose and Mode of Administration:

Placebo tablets, oral route.

Criteria for Evaluation:

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Efficacy:

Primary evaluation criterion: % change in fasting TG between baseline and end of treatment.

Secondary evaluation criteria: % change in fasting total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, TC/HDL-C ratio, very-low density lipoprotein cholesterol (VLDL-C), fasting free fatty acids (FFAs), number of responders defined as patients whose TG were < 150 mg/dL (1.69 mmol/L) after treatment, absolute change in fasting plasma glucose, HbA1c and fasting plasma insulin.

Safety: Adverse events (AEs), biochemistry: creatine kinase (CK), aspartate aminotransferase (AST), alanine amino transferase (ALT), gamma-glutamyl transferase (Gamma-GT), alkaline phosphatase, serum creatinine, total bilirubin, blood urea nitrogen (BUN), uric acid, albumin, total homocysteine, folic acid and vitamin B12, hematology: white blood (WBC) and differential count, red blood cells (RBC), hemoglobin, hematocrit and platelets.

Statistical Methods:

For the efficacy parameters, summary statistics for raw values are provided by treatment group, for FAS and PPS at baseline and end of treatment, as well as absolute and % changes at end of treatment.

The main efficacy analysis, conducted on FAS, consisted in testing the effect of the active doses together versus placebo using the following analysis of covariance (ANCOVA) model: $\text{Log}(\text{TG at end of treatment}) - \text{Log}(\text{Baseline TG}) = \text{intercept} + \text{Log}(\text{Baseline TG}) + \text{Metformin regimen} + \text{Treatment group} + \text{Error}$. This model was required due to the non normality of the % change in TG. This analysis proceeded first with an exploration of the homogeneity of treatment effects across metformin doses.

Complementary analysis on the primary efficacy criterion included (1): same analysis as the main efficacy analysis on PPS, (2): pairwise comparisons on FAS using a step-down procedure, if the global treatment effect was statistically significant, (3): robustness analyses.

The secondary efficacy analyses, conducted on FAS and PPS, included the ANCOVA model on the % change in lipids, except for FFAs for which the model was applied to absolute changes. The ANCOVA model was applied on absolute change in HbA1c and fasting glucose, and on Log-transformed end-of-treatment insulin values, with determination of the 95% confidence intervals (CIs) of the differences $(F_{160} + M^*) - (F_0 + M^*)$ and $(F_{80} + M^*) - (F_0 + M^*)$. The % of responders defined as the number of patients reaching the target of TG < 150 mg/dL (1.69 mmol/L) after 3 months of treatment was also determined.

The pharmacokinetic evaluation included: (1): descriptive statistics of plasma concentrations of fenofibric acid and metformin after 6 ± 1 weeks (V3) and 12 ± 1 weeks (V4) of treatment (2): correlations between all the plasma fenofibric acid values and relevant efficacy parameters (3): correlations between metformin concentrations and relevant efficacy parameters.

Exploratory/Complementary analyses included descriptive statistics of TG and HDL-C raw values, as well as absolute and % change from baseline on the following subgroups: male /

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female patients, < 60 years / ≥ 60 years, BMI < 30 kg/m² / BMI ≥ 30 kg/m², statin / no statin, TG at baseline < 2.3 mmol/L / ≥ 2.3 mmol/L; HbA1c at baseline: < 7.5 % / ≥ 7.5 % and < 8 % / ≥ 8 %.

Safety analysis included summary statistics of blood chemistry and hematology parameters, incidence of abnormal values, number of AEs, number and % of patients who experienced AEs.

Post-hoc analyses included (1): analyses by country: TG, HDL-C, LDL-C, lifestyle and risk factors, demographics, anthropometric and vital sign measurements, history of study disease including the cardiovascular prevention status, efficacy variables at baseline, (2): TC/HDL-C ratio on FAS and PPS (3): pairwise comparisons for the % change in TG on PPS, (4): LDL-C in patients treated with statins or not, (5): AST, ALT, CK, creatinine by country and in patients treated with statins or not, (6): abnormal changes in homocysteine.

Summary

Demographic and Other Baseline Characteristics

In FAS, male and female patients were in equal proportion. 99% of the patients were Caucasian. The mean (± SD) age was 60.4 ± 9.2 years. 70.3% had BMI ≥ 30 kg/m², 39.1% were on statins, 61.2% had fasting serum TG ≥ 2.3 mmol/L, 47.2% HbA1c ≥ 7.5 % and 32.0 HbA1c ≥ 8 %.

Regarding the metformin regimen, 150 FAS patients (39.4%) were on 500 mg bid, 89 (23.4%) on 500 mg tid, 81 (21.3%) on 850 mg bid, and 61 (16.0%) on 850 mg tid.

Mean (SD) and median values (mmol/L) of lipids at baseline in FAS are presented below:

TG	TC	LDL-C	HDL-C	Non LDL-C	TC/HDL-C	VLDL-C	FFAs
2.73 (0.84)	5.09 (1.11)	3.16 (1.05)	1.17 (0.26)	3.92 (1.03)	4.48 (1.06)	1.19 (0.30)	0.63 (0.27)
2.49	5.00	3.03	1.17	3.86	4.38	1.13	0.60

The 3 treatment groups had similar baseline values for fasting serum TG. There were borderline differences in mean and median TC, LDL-C, non HDL-C, and HDL-C in the 2 fenofibrate groups compared to the placebo group. There were also borderline differences for LDL-C and HDL-C in the 160 mg fenofibrate group compared to the placebo group. The borderline differences between the 3 groups were taken into account in the ANCOVA model used to compare the group responses.

Looking at metformin subgroups separately, no differences were observed for mean TG, HDL-C and TC/HDL-C ratio values, while mean TC, LDL-C and non HDL-C values were lower in the 850 mg tid subgroup than in the other subgroups. TG did not differ between sexes, while TC, LDL-C, HDL-C, non HDL-C and FFAs were lower in males than in females. TG and HDL-C did not differ between patients on statins and those not on statins, while TC, LDL-C, non-HDL-C and TC/HDL-C ratio were lower in the patients on statins. There were no differences between TG subgroups (< 2.3 mmol/L and ≥ 2.3 mmol/L) for LDL-C and HDL-C.

For any of the lipid parameters, there was no difference between the patients with BMI

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≥ 30 kg/m² or BMI < 30 kg/m², between those with HbA1c ≥ 7.5 % or < 7.5%, and between those with HbA1c ≥ 8.0 % or < 8.0%.

Mean (SD) and median values of fasting glucose control parameters at baseline in FAS patients were: fasting plasma glucose: 8.60 (2.30) 8.30 mmol/L, fasting plasma insulin: 143.0 (99.5) 122.4 pmol/L, HbA1c: 7.55 (1.07) 7.40%. Fasting plasma glucose and HbA1c levels tended to be lower in patients on metformin tid regimens than in those on metformin bid regimens.

Efficacy Results

Primary Analysis

Efficacy was assessed by intention to treat on the FAS population. The primary objective of the study was reached. The primary analysis showed that the response to fenofibrate treatment on TG, the 2 doses taken together, was statistically different from that to placebo ($p < 0.0001$), with an estimate of -26.6% (95%CI: -34.0 ; -18.3%). Descriptive statistics for fasting serum TG and LS-Means of % change at end of treatment from baseline are presented below:

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TG - FAS		F0 + M*	F80 + M*	F160 + M*
Laboratory reference range: 0 – 1.684 mmol/L		(N=54)	(N=165)	(N=162)
Baseline (V2)	Mean (SD)	2.51 (0.66)	2.80 (0.93)	2.73 (0.83)
	Median (Min ; Max)	2.36 (1.72 ; 4.97)	2.57 (1.71 ; 5.80)	2.48 (1.65 ; 5.38)
	Geometric Mean ^a	2.44	2.67	2.62
End-of-treatment	Mean (SD)	2.74 (2.00)	2.15 (0.91)	2.01 (1.04)
	Median (Min ; Max)	2.35 (0.76; 15.54)	1.94 (0.89 ; 5.22)	1.81 (0.76 ; 7.16)
	Geometric Mean ^a	2.43	1.99	1.81
Change at end of	Mean (SD)	0.23 (1.98)	-0.65 (0.91)	-0.72 (1.04)
	Median (Min ; Max)	-0.08 (-2.31 ; 13.46)	-0.60 (-3.87 ; 2.18)	-0.77 (-3.57 ; 4.69)
% change at end of	Mean (SD)	12.5 (93.5)	-21.0 (27.7)	-24.7 (36.6)
	Median (Min ; Max)	-3.0 (-75.3 ; 647.4)	-25.4 (-74.5 ; 90.2)	-31.6 (-72.9 ; 189.5)
	Back-T Mean ^b	-0.3	-25.5	-30.8
LS-Means and 95% CI of % change		0.3 [-9.2 ; 10.8]	-23.4 [-27.7 ; -18.9]	-29.2 [-33.2 ; -24.9]

: metformin at 500 mg bid, 850 mg bid, 500 mg tid or 850 mg tid. ^a Geometric mean = Exp(Mean in Log). ^b Back-transformed mean in %: 100(Exp(Mean in Log) - 1).

Fasting serum TG were Log-transformed at baseline and at end of treatment because of non normal distribution. The ANCOVA model on Log-transformed baseline and end-of-treatment values showed that there was no interaction between the study treatment effects and the metformin regimen. The difference between either dose of fenofibrate and placebo was statistically significant. The difference between the 2 fenofibrate doses almost reached statistical significance (p = 0.0585).

The PPS analysis confirmed the FAS analysis; the difference between the 2 fenofibrate doses was statistically significant (p = 0.0336) (post-hoc analysis). In PPS, the reduction in TG with the 850 mg tid regimen was greater than in FAS: -23.6%.

The results of the primary analysis were also confirmed by applying the ANCOVA model on ranks of % changes in TG and on % changes, but after excluding 3 outlier values.

Secondary Analyses

Mean (SD), median and LS-Means of % changes and 95% CI in main lipids in FAS patients are presented below:

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		F0 + M* (N=54)	F80 + M* (N=165)	F160 + M* (N=162)
TC	Mean (SD) median	2.2 (13.7), 0.0	-0.9 (18.2), -3.4	-1.5 (16.6), -3.4
	LS-Mean and CI	4.44 [0.23 ; 8.65]	-0.01 [-2.46 ; 2.45]	-2.06 [-4.59 ; 0.47]
LDL-C	Mean (SD) median	-2.7 (18.5), -1.1	5.4 (30.2), 0.0	4.1 (27.4), 0.6
	LS-Mean and CI	1.13 [-5.58 ; 7.85]	5.42 [1.52 ; 9.33]	2.13 [-1.88 ; 6.15]
HDL-C	Mean (SD) median	4.2 (13.0), 2.3	3.5 (13.0), 4.7	7.5 (13.4), 7.4
	LS-Mean and CI	4.71 [1.15 ; 8.27]	3.79 [1.71 ; 5.87]	7.25 [5.11 ; 9.39]
Non - HDL-C	Mean (SD) median	2.1 (17.8), 0.0	-1.7 (23.4), -5.0	-3.7 (21.9) -4.8
	LS-Mean and CI	4.79 [-0.73 ; 10.31]	-0.75 [-3.96 ; 2.47]	-4.07 [-7.37 ; -0.76]
VLDL- C	Mean (SD) median	0.2 (29.4), -3.4	-21.6 (23.7), -24.2	-29.7 (23.9), -33.3
	LS-Mean and CI	0.93 [-5.77 ; 7.62]	-20.38 [-24.39 ; -16.38]	-28.20 [-32.31 ; -24.08]
TC/ HDL-C	Mean (SD) median	-1.2 (12.9), -1.3	-3.4 (18.0), -5.8	-7.1 (18.3), -7.5
	LS-Mean and CI	-0.18 [-4.81 ; 4.45]	-2.96 [-5.66 ; -0.26]	-6.46 [-9.22 ; -3.70]
FFAs^a	Mean (SD) median	15.9 (51.4), 16.7	11.4 (55.2), 0.0	9.2 (51.9), 0.0
	LS-Mean and CI	0.05 [-0.02 ; 0.12]	0.00 [-0.04 ; 0.04]	0.00 [-0.04 ; 0.04]

*: metformin at 500 mg bid, 850 mg bid, 500 mg tid or 850 mg tid.

^aLS-Means on absolute changes.

The mean change in HDL-C was +7.3% in the patients treated with 160 mg fenofibrate, and +4.7% in those who received the placebo. The difference between fenofibrate treatment and placebo was not statistically significant.

The mean absolute changes in LDL-C were 0.02 mmol/L with 80 mg fenofibrate and -0.04 mmol/L with 160 mg fenofibrate, and the end-of-treatment values remained in the near optimal/above optimal NCEP-ATPIII range (2.58 - 3.35 mmol/L). The median % changes were -1.1% (placebo), 0.0% (80 mg fenofibrate), and 0.6% (160 mg fenofibrate). Differences in median LDL-C changes were observed depending on the use of statins: +13.4% with 160 mg fenofibrate and +4.9% with 80 mg fenofibrate in the patients on statins, and -8.7% with 160 mg fenofibrate and -3.8% with 80 mg fenofibrate in the patients not on statins. In the patients on statins, the baseline LDL-C values were lower than in patients not on statins. In the patients on statins and treated with 160 mg fenofibrate, the median end-of-treatment LDL-C value remained within the optimal target NCEP-ATPIII range (< 2.58 mmol/L). In the patients without statins and treated with 160 mg fenofibrate, it reached the near optimal/above optimal range, down from baseline values in the borderline-high range (3.36 mmol/L - 4.10 mmol/L).

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Reductions in TC and non-HDL-C were minor in both fenofibrate groups. However, the difference in LS-Means between 160 mg fenofibrate and placebo was -6.5% for TC and -8.9% for non-HDL-C. The TC/HDL-C ratio was reduced by 6.5% with 160 mg fenofibrate ($p = 0.0207$). As for TG, the difference between fenofibrate treatment and placebo was statistically significant ($p < 0.0001$) for VLDL-C. Fenofibrate had no effect on FFAs.

Fasting serum TG decreased below 1.69 mmol/L at end of treatment in 11.3% of the patients who received the placebo, in 35.2% of those who received 80 mg fenofibrate and in 44.7% of those who received 160 mg fenofibrate.

Exploratory analyses consisted in analyzing changes in TG and HDL-C in prespecified subgroups and by country. The 160 mg fenofibrate group had greater TG reduction in the following subgroups: male patients, age ≥ 60 years, BMI < 30 kg/m², no use of statins, TG ≥ 2.3 mmol/L, and low HbA1c levels. HDL-C analysis showed greater increases with 160 mg fenofibrate in female patients, in patients ≥ 60 years and in patients with BMI ≥ 30 kg/m². The reduction in TG with fenofibrate was the same in the 3 separate countries, while HDL-C changes differed between countries. The increase in HDL-C was greater in Ukraine than in the UK and in Poland.

Mean (SD), median and LS-Means of absolute changes in glucose and HbA1c, and mean (SD) median absolute changes in insulin, with LS-Means of end-of-treatment values in FAS patients are presented below:

		F0 + M* (N=54)	F80 + M* (N=165)	F160 + M* (N=162)
Glucose	Mean (SD), median	-0.16 (1.76), -0.30	-0.38 (2.27), -0.30	-0.31 (1.78), -0.40
	LS-Mean and CI	-0.10 [-0.59 ; 0.39]	-0.27 [-0.55 ; 0.02]	-0.27 [-0.57 ; 0.02]
Insulin	Mean (SD), median	-6.2 (47.0), -2.6	-20.5 (121.8), -3.6	-15.3 (77.3), -13.0
	LS-Mean and CI ^a	110.8 [95.8 ; 128.2]	109.7 [100.9 ; 119.4]	105.0 [96.2 ; 114.6]
HbA1c	Mean (SD)	0.00 (0.74), 0.00	0.11 (0.97), 0.00	0.01 (0.92), 0.00
	LS-Mean and CI	0.03 [-0.23 ; 0.29]	0.09 [-0.06 ; 0.23]	-0.01 [-0.16 ; 0.15]

* metformin at 500 mg bid, 850 mg bid, 500 mg tid or 850 mg tid. ^a: end-of-treatment values

In the 3 treatment groups, slight and clinically non-relevant decreasing trends were observed in fasting glucose between baseline and end of treatment. HbA1c remained unchanged. Insulin levels and changes at end of treatment from baseline were very variable, without statistically significant differences between the 3 groups. Fenofibrate had no effects on glucose control parameters. For all the secondary endpoints, the PPS analysis confirmed the FAS analysis.

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Pharmacokinetic Results

Analytical Results

The assay methods for the determination of fenofibric acid and metformin concentrations in plasma fully complied with FDA requirements. The determinations were performed in accordance with Good Laboratory Practices.

For fenofibric acid, accuracy and precision of the QCs were lower than 4% and 11%, respectively. For metformin, accuracy and precision of the QCs were lower than 5% and 4.5%, respectively. The calibration ranges, from 0.03 to 12.0 µmol/L for fenofibric acid, and 0.025 to 10.0 µmol/L for metformin, allowed to accurately assess plasma levels.

These data showed that the methods are reliable and robust, and provide a good level of confidence in the accuracy and precision of the plasma concentrations used for pharmacokinetic assessment.

Plasma Fenofibric and Metformin Concentrations

They were assessed at steady state, just to prior to morning dosing.

Mean (SD) of plasma fenofibric acid concentrations (µg/mL) by treatment group are given below:

		F0 + M* (N=46)	F80 + M* (N=130)	F160 + M* (N=128)
V3	n	45	129	127
	Mean (SD)	0.016 (0.007) ^a	4.16 (2.42)	8.11 (4.58)
	Median	0.015	3.73	7.41
V4	n	46	129	126
	Mean (SD)	0.015 (0.000)	4.18 (2.60)	8.05 (5.07)
	Median	0.015	3.63	7.38

*: metformin 500 mg bid, 850 mg bid, 500 mg tid or 850 mg tid. ^a Analytical interferences in 2 patients, corresponding to values of 0.053 and 0.040 µg/mL were taken into account.

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At V3 (6 ± 1 weeks) and at V4 (12 ± 1 weeks), plasma fenofibric acid concentrations were proportional to the dose of fenofibrate. Mean and median values were nearly similar at V3 and V4 .

Regarding the 4 metformin regimens separately, mean plasma fenofibric concentrations were slightly more elevated in the 500 mg metformin bid subgroup than in the other metformin subgroups, with both 80 mg fenofibrate and 160 mg fenofibrate.

Mean (SD) of plasma metformin concentrations (µg/mL) by treatment group are given below:

		F0 + M* (N=50)	F80 + M* (N=137)	F160 + M* (N=133)
V2	n	49	135	128
	Mean (SD)	0.662 (0.758)	0.648 (0.666)	0.710 (0.809)
	Median	0.376	0.440	0.414
V3	n	49	136	132
	Mean (SD)	0.694 (0.713)	0.657 (0.591)	0.658 (0.641)
	Median	0.439	0.455	0.408
V4	n	49	136	132
	Mean (SD)	0.636 (0.607)	0.580 (0.687)	0.594 (0.575)
	Median	0.446	0.391	0.402

*: metformin mg bid, 850 mg bid, 500 mg tid or 850 mg tid.

Mean plasma metformin concentrations in the 3 treatment groups remained globally unchanged throughout the study. Regarding the 4 metformin regimens separately, a great variability in metformin concentrations was observed between the treatment groups, but, globally there was no evidence of trends towards increase or decrease in concentrations in patients treated with fenofibrate.

Correlations Between Plasma Concentrations and Efficacy Parameters

Both end-of-treatment values and % changes in TG were correlated with steady-state plasma fenofibric acid concentrations, all treatment groups taken together and for each dose of fenofibrate. For HDL-C, the test on ranks showed a correlation between the % changes and the steady-state plasma fenofibric acid concentrations, all treatment groups taken together and for 160 mg fenofibrate (end-of-treatment values). For TG and HDL-C, the correlation coefficients were low.

There were no correlations between end-of-treatment glucose values or changes in glucose and steady-state plasma metformin concentrations. The correlation found for HbA1c was not relevant as HbA1c remained unchanged in all treatment groups during the study.

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Safety Results:

Deaths

One (1) patient in the F160 + M* group (500 mg metformin bid) died suddenly 7 days after completion of the study. According to the pathologist, death was due to cardiac arrest, ischemic heart disease, coronary atheroma, and old myocardial infarction. This death was considered to be independent of the study treatment. The patient had a history of cardiovascular risk factors including ischemic heart disease, coronary atheroma, old myocardial infarction and stroke.

Other Serious Adverse Events (SAEs)

Three (3) SAEs were reported during the treatment period, 2 patients in the F80 + M* group and 1 patient in the F0 + M* group. These 3 patients were hospitalized for conditions not related to study treatment: left heel abscess (1), acute bronchitis (1) and chronic hypertensive encephalopathy (1).

Adverse Events (AEs)

The number of treatment-emergent AEs and the number and % of FAS patients who reported at least 1 treatment-emergent AE are displayed below.

	F0 + M* (N = 54)		F80 + M* (N = 165)		F160 + M* (N = 162)	
	AEs	Patients	AEs	Patients	AEs	Patients
All AEs	36	19 (35.2%)	90	60 (36.4%)	131	68 (42.0%)
AEs related ^a	13	8 (14.8%)	33	21 (12.7%)	51	34 (21.0%)

*: metformin 500 mg bid, 850 mg bid, 500 mg tid or 850 mg tid. ^a: possibly or probably related to study treatment according to the investigator.

Twenty-two (22) patients were prematurely withdrawn from the study for AE: 1 patient in the F0 + M* group, 13 patients in the F80 + M* group, and 8 patients in the F160 + M* group. The most frequent AEs that led to premature withdrawal were gastrointestinal symptoms: 7 patients in the F80 + M* group and 2 patients in the F160 + M* group. Nausea was the reason for premature withdrawal in 6 patients.

These results are supplied for informational purposes only. Some clinical studies may include information not contained in the approved prescribing information. Please refer to the full prescribing information for additional information.

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: Dyslipidemia / Glucose Metabolism Disorder
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Gastrointestinal disorders were the most frequent AEs reported in the study, and were the main reason for premature withdrawal. They were reported by 13.0% of the patients in the F0 + M* group, 9.7% of those in the F80 + M* group and 13.6% of those in the F160 + M* group. The most frequent symptoms reported by the patients treated with fenofibrate were nausea, constipation and flatulence. Other symptoms were diarrhea, more frequent in the patients on placebo than in those on fenofibrate, and abdominal pain.

Abnormal laboratory investigations considered as related to treatment were reported in 1.9% of the patients in the F0 + M* group, 2.4% of those in the F80 + M* group, and 6.2% of those in the F160 + M* group. They were reasons for premature withdrawal in 1 patient in the F0 + M* group, 1 patient in the F80 + M* group and 2 patients in the F160 + M* group. Abnormalities leading to premature withdrawal were increased blood creatinine in 1 patient in each group, associated with increased AST in the patient of the F80 + M* group, and increased CK in 1 of the patients of the F160 + M* group.

The most frequent abnormalities considered as related to study treatment were: increased liver transaminases: 1 patient in the F0 + M* group, 2 patients in the F80 + M* group and 6 patients in the F160 + M* group, increased Gamma-GT: 2 patients in the F80 + M* group and 3 patients in the F160 + M* group, increased creatinine: 2 patients in the F80 + M* group and 2 patients in the F160 + M* group.

Two events related to glycemic control and considered as related to study treatment were reported in 2 patients in the F80 + M* group: inadequate glycemic control leading to study withdrawal and not requiring acute intervention (1) and minor hypoglycemia not requiring any intervention (1).

Arthralgia was considered as related to study treatment in 3 patients in the F80 + M* group, myalgia and muscle twitching in 1 patient each in the F160 + M* group.

Skin reactions considered as related to study treatment included urticaria in 1 patient in the F0 + M* group, hyperhidrosis in 1 patient in the F80 + M* group, and pruritus in 1 patient in the F160 + M* group. Three (3) patients in the F160 + M* group reported an episode of allergy considered as related to study treatment, however resolving without interruption of study treatment in 2 of them.

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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: Dyslipidemia / Glucose Metabolism Disorder
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Clinical Laboratory Evaluation

ALT increased from normal to values > 3 times the ULN in 3 patients in the F160 + M* group, and AST in 1 patient in the F80 + M* group. The greatest increase corresponded to an ALT value of 3.8 times the ULN at the interim visit, after 6 weeks of treatment. Increases in ALT or AST were not accompanied with increases in total bilirubin. Alkaline phosphatase decreased in the F80 + M* group and in the F160 + M* group: -14 and -20 IU/L for mean changes, respectively.

None of the patients were found to have an increase in CK to values > 5 times the ULN. The greatest increase was 3.5 times the ULN. There was no obvious effect of statins on changes in CK in the patients treated with fenofibrate; the median CK value increased at end of treatment by 2 IU/L in patients on statins treated with 160 mg fenofibrate.

BUN tended to increase in the F80 + M* group (+0.40 mmol/L) and in the F160 + M* group (+0.70 mmol/L). Creatinine increased above 110 µmol/L in females and 135 µmol/L in males in 2 patients treated with 80 mg fenofibrate and in 1 patient treated with 160 mg fenofibrate. The median change at end of treatment was nearly the same in the 2 groups: +8.0 µmol/L and +9 µmol/L in the F80 + M* group and the F160 + M* group, respectively. Four (4) patients in the F80 + M* group and 4 patients in the F160 + M* group were found to have an increase in creatinine of more than 30 µmol/L, with the maximal increase observed of 97 µmol/L in 1 single patient on fenofibrate 80 mg daily and metformin 500 mg tid. The other patients had minor increases between 35 and 44 µmol/L. The use of statins had no clear effect on creatinine.

In the 2 fenofibrate groups uric acid decreased: median change of -16.8% in the F80 + M* group and -22.3% in the F160 + M* group.

Total homocysteine increased in the F80 + M* group and the F160 + M* group: +22.5% and +42.8% (medians), respectively. However, the mean and median values at end of treatment remained within normal range.

Vitamin B12 mean and median values were lower at the end of treatment than at baseline in the 3 treatment groups. Based on the median values, the decrease was smaller in the F80 + M* group and the F160 + M* group than in the F0 + M* group. Mean and median values of serum albumin and folic acid remained globally unchanged in the 3 treatment groups.

There were minimal changes in hematological parameters, with a small increase in platelet numbers in the 2 fenofibrate groups: mean increase of +26 G/L in the F80 + M* group and +36 G/L in the F160 + M* group.

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