

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: Metabolic Syndrome
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Name of Sponsor/Company:
Fournier Pharma

Title of Study:
A randomized, double-blind trial comparing the efficacy and safety of fenofibrate, metformin, their combination and placebo in patients with metabolic syndrome.
Protocol No.: C FEN 0203

Principal Coordinating Investigator:
Professor John JP Kastelein – Academic Medical Center - Department of Vascular Medicine - Meibergdreef 9, room G1-146 - 1105 AZ Amsterdam – The Netherlands.
Country coordinating investigators: 1 in each of the 9 following countries: Canada, Finland, Hungary, Italy, the Netherlands, Norway, Poland, Romania and Sweden.

Study Centers:
Patients were randomized across 96 investigational centers: 19 in Canada, 6 in Finland, 15 in Hungary, 7 in Italy, 18 in the Netherlands, 8 in Norway, 8 in Poland, 11 in Romania and 4 in Sweden.

Publication (reference):
Not applicable

Study Period: 27 MAR 2003 (First Subject First Visit) – 21 JUN 2004 (Last Subject Last Visit)	Phase of development: II
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Objectives:
The primary objective was to study the effect of different combinations of fenofibrate and metformin on the cluster of metabolic syndrome (MetS) biochemical abnormalities, and for this purpose, to determine the dose combination allowing normalization of MetS patients.
The secondary objectives were to compare the treatments on different subgroups of patients and to assess the efficacy of each dose combination and monotherapy with regard to each MetS criterion, and with regard to the processes of lipids, lipoproteins and carbohydrate metabolism in MetS.

Methodology:
This study was an incomplete 3 x 3 factorial design (7 arms), randomized, double-blind, placebo-controlled multicenter study.

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Number of Subjects Planned:
533 patients, including 10% of drop-outs.

Number of Subjects Analyzed:
Out of 683 randomized patients (excess compared to planned number was due to high accrual rate in the last days of the study), 681 in the Full Analysis Set (FAS) and 523 in the Per Protocol Set (PPS). The placebo group was half in size compared with the active treatment groups.

Diagnosis and Main Criteria for Inclusion:

- Male or female patients aged from 18 to 75 years old (at inclusion V1).
- With 3 of the following 5 criteria, including at least 2 biochemical abnormalities (glucose and one lipid abnormality) according to the MetS definition provided in NCEP – ATP III guidelines:
 - waist circumference > 102 cm for males and > 88 cm for females;
 - fasting glucose \geq 110 mg/dL (\geq 6.1 mmol/L);
 - triglycerides (TG) \geq 150 mg/dL (\geq 1.69 mmol/L);
 - high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL (< 1.03 mmol/L) for male patients or HDL-C < 50 mg/dL (< 1.29 mmol/L) for female patients;
 - blood pressure \geq 130 and 85 mmHg.
- And having signed a written informed consent (at inclusion V1).

Test Product, Dose and Mode of Administration:

Formulation, mode of administration: fenofibrate: tablets containing 40 mg micronized fenofibrate; metformin: commercial product, tablets containing 500 mg or 850 mg metformin chlorhydrate.

Oral route: 8 tablets daily, 4 with breakfast and 4 with the evening meal.

Treatment groups:

fenofibrate 2 x 40 mg bid + metformin 850 mg bid (F160-M1700)

fenofibrate 2 x 40 mg bid + metformin 500 mg bid (F160-M1000)

fenofibrate 40 mg bid + metformin 850 mg bid (F80-M1700)

fenofibrate 40 mg bid + metformin 500 mg bid (F80-M1000)

fenofibrate 2 x 40 mg bid + metformin placebo (F160-M0)

fenofibrate placebo + metformin 850 mg bid (F0-M1700)

fenofibrate placebo + metformin placebo (F0-M0)

Duration of Treatment: 3 months.

Reference Therapy, Dose and Mode of Administration:

Matched placebo.

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Criteria for Evaluation:

Primary Criterion:

Number of “normalized patients” defined as patients with no biochemical abnormalities after 3 months of treatment:

- TG < 150 mg/dL (< 1.69 mmol/L);
- HDL-C \geq 40 mg/dL (\geq 1.03 mmol/L) for males or \geq 50 mg/dL (\geq 1.29 mmol/L) for females;
- fasting glucose < 110 mg/dL (< 6.1 mmol/L).

Main Secondary Criteria:

- Efficacy variables:
 - Fasting blood insulin and fasting blood glucose, HbA1c.
 - Area under the curve from 0 to 2h (AUC_{0-2h}) of glucose, insulin, C-peptide and free fatty acids (FFA) during Oral Glucose Tolerance Test (OGTT).
 - Insulin sensitivity assessed by the OGTT-derived composite whole-body Insulin Sensitivity Index (ISI), as published by De Fronzo and Matsuda [29].
 - Fasting lipid parameters: FFA, TG, total cholesterol (TC), HDL-C, measured low-density lipoprotein cholesterol (LDL-C), very-low density lipoprotein cholesterol (VLDL-C), LDL subfractions, apolipoprotein (Apo) A1, Apo A2, Apo CIII, LDL and HDL sizes, remnant-like particle cholesterol (RLP-C).
 - At 0, 4, 5 and 6 hours post-fat load: AUC_{0-6h}, Cmax, Tmax for TG.
 - Plasminogen -1 Activation Inhibitor (PAI-1) activity, PAI-1 antigen, tissue-type Plasminogen Activator antigen (t-PA-ag), high sensitivity C-reactive protein (hsCRP), fibrinogen, tumor necrosing factor (TNF) alpha, interleukin (IL)1 and IL6.
 - Body mass index (BMI), waist circumference, hip circumference, waist to hip ratio, and blood pressure.

Percentage of patients who presented 0, 1, 2, 3, 4 or 5 MetS criteria.

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- Safety variables:
 - Adverse events (AEs).
 - Biochemistry: creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, serum creatinine, total bilirubin, blood urea nitrogen (BUN), uric acid, albumin and total homocysteine.
 - Hematology: white blood cells (WBC) and differential count, red blood cells (RBC), hemoglobin, hematocrit and platelets.
 - Blood pressure.

Statistical Methods:

- Descriptive analysis: mean, SD, median, Q1, Q3, min, max for quantitative variables and n, % by category for qualitative variables.
- Statistical analysis of the primary endpoint: proportions of “normalized” patients by treatment group.

Inferential analyses were performed on differences between proportions in order to test the superiority of each fixed combination over each of the monotherapies (fenofibrate 160 mg per day and metformin 1700 mg per day).

The procedure consisted in:

- At the combination level: applying the conventional Min test, as defined by Laska and Meisner, which rejects the inferiority of the combination with regard to the monotherapies at level α , using the Pearson X^2 test.
- At the clinical trial level: managing the multiplicity aspect (four combinations were assessed) and identifying the minimum effective combination using a step-down procedure.

A complementary analysis was performed in order to identify the most efficient combination using the multiple comparison to the best. Furthermore, the presence of interaction was tested between the 4 groups receiving F160-M1700, F160-M0, F0-M1700 and placebo.

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Summary

Study Population:

2288 patients were included, 683 patients, across 96 centers, were randomized and 681 patients were treated (FAS): 109 in the F160-M1700 group, 104 in the F160-M1000 group, 106 in the F80-M1700 group, 104 in the F80-M1000 group, 103 in the F160-M0 group, 100 in the F0-M1700 group and 55 in F0-M0 group.

In FAS, the mean age was 56 ± 9 years, 99% of the patients were Caucasian, and males accounted for 59%. Mean weight was 98 ± 15 kg in males and 88 ± 15 kg in females, mean waist circumference was 110 ± 10 cm in males and 106 ± 11 cm in females, mean BMI was 31.6 ± 4.1 kg/m² in males and 33.3 ± 5.1 kg/m² in females, and the mean waist-to-hip ratio was 1.01 ± 0.07 in males and 0.91 ± 0.06 in females.

Ninety-six percent (96%) of FAS patients had MetS according to NCEP/ATP III, 99.6% had fasting glucose ≥ 6.1 mmol/L, 52% had type 2 diabetes mellitus (T2DM⁺) according to the American Diabetes Association criteria, 25% had impaired fasting glucose (IFG), 21% had impaired glucose tolerance (IGT) (15% having both IFG and IGT).

99.4% of FAS patients had abnormal TG or HDL-C (90% for TG and 52% for HDL-C, 88% had abnormal waist circumference, and 46% had high blood pressure (Systolic BP ≥ 130 mmHg and Diastolic BP ≥ 85 mmHg).

The concomitant illnesses ongoing at V1 mainly concerned metabolism and nutrition disorders (81%) and vascular disorders (65%). The last lipid-lowering drugs stopped at V1 (at least one in 28% of patients) were HMG CoA reductase inhibitors (22%) and fibrates (7%). The most frequently concomitant treatments used during the study were agents acting on the renin-angiotensin system (45%), beta-blocking agents (34%), antithrombotic agents (26%), diuretics (21%), and calcium channel blockers (18%).

The 7 treatment groups were well balanced with respect to MetS presence according to the study protocol definition: from 93% to 98%. However, the percentage of patients with 5 MetS criteria was higher in the F160-M1700 group (19.3%) than in the F80-M1000 group (9.6%).

Compliance to study treatment ranged between 70 and 120% for most patients, means across treatment groups were between 97.1% and 100%. Out of the 681 treated patients, 51 patients were prematurely withdrawn from the study, 31 for clinical or biological AEs (including 3 for SAEs), 1 for non compliance with inclusion/exclusion criteria, 8 for consent withdrawal, 4 for non compliance with study procedures, 3 for wrong allocation, and 2 for unspecified reasons. Two patients were lost to follow up. 651 patients attended V4 as planned or a visit after premature withdrawal. 137 patients performed the fat load test (FLT). After exclusion of patients with major deviations, 523 patients were included in the PPS.

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Efficacy Results:

– Primary efficacy criterion: normalized patients at V4 in the FAS

Normalized patients		F160-M1700 (N = 109)	F160-M1000 (N = 104)	F80-M1700 (N = 106)	F80-M1000 (N = 104)	F160-M 0 (N = 103)	F0-M1700 (N = 100)	F0-M0 (N = 55)
All	n and %	19 (17.4)	9 (8.7)	8 (7.6)	12 (11.5)	6 (5.8)	5 (5.0)	2 (3.6)
	[95% CI]	[10.8 ; 25.9]	[4.0 ; 15.8]	[3.3 ; 14.3]	[6.1 ; 19.3]	[2.2 ; 12.38]	[1.6 ; 11.3]	[0.4 ; 12.5]
MetS ⁺ T2DM ⁺	N	60	57	63	48	46	55	28
	n and %	6 (10.0)	4 (7.0)	5 (7.9)	1 (2.1)	2 (4.4)	1 (1.8)	1 (3.6)
	[95% CI]	[3.8 ; 0.581]	[2.0 ; 17.0]	[2.6 ; 17.6]	[0.1 ; 11.1]	[0.5 ; 14.8]	[0.1 ; 9.7]	[0.1 ; 18.4]
MetS ⁺ T2DM ⁻	N	49	46	42	54	51	44	27
	n and %	13 (26.5)	5 (10.6)	3 (7.1)	11 (20.4)	3 (6.0)	4 (9.1)	1 (3.7)
	[95% CI]	[15.0 ; 41.1]	[3.6 ; 23.6]	[1.5 ; 19.5]	[10.6 ; 33.5]	[1.3 ; 16.2]	[2.5 ; 21.7]	[0.1 ; 19.0]

The best treatment was the F160-M1700 combination with 17.4% of normalized patients. The F160-M1700 combination was statistically different from the monotherapies F160-M0 ($p = 0.009$) and F0-M1700 ($p = 0.005$). Odd ratios indicated that the probability of normalization with the F160-M1700 combination was 4 times higher as compared with the metformin monotherapy and 3.4 times higher as compared with the fenofibrate monotherapy. The F160-M1700 combination was not statistically different (multiple comparison to the best [MCB] test) from each of the other 3 combinations. F160-M1700 was also the best treatment in T2DM⁺ patients (10%) and in T2DM⁻ patients (26.5%). The results of the PPS analysis confirmed those of the FAS analysis.

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– Secondary Efficacy Criteria

- Normalized patients for biochemistry MetS criteria at V4 in the FAS

Normalized patients		F160-M1700 (N= 109)	F160-M1000 (N= 104)	F80-M1700 (N= 106)	F80-M1000 (N= 104)	F160-M 0 (N= 103)	F0-M1700 (N= 100)	F0-M0 (N= 55)
Fasting glucose	n and %	43 (39.4)	36 (35.0)	35 (33.3)	37 (35.6)	20 (19.6)	30 (30.0)	11 (20.0)
	[CI 95%]	[30.2 ; 49.3]	[25.8 ; 45.0]	[24.4 ; 43.2]	[26.4 ; 45.6]	[12.4 ; 28.6]	[21.2 ; 40.0]	[10.4 ; 33.0]
TG	n and %	55 (55.0)	42 (47.7)	45 (45.5)	35 (39.8)	47 (50.0)	17 (18.5)	8 (15.4)
	[CI 95%]	[44.7 ; 65.0]	[37.0 ; 58.6]	[35.4 ; 55.8]	[29.5 ; 50.8]	[39.5 ; 60.5]	[11.1 ; 27.9]	[6.9 ; 28.1]
HDL-C	n and %	21 (35.0)	20 (31.7)	16 (31.4)	15 (31.3)	17 (28.8)	9 (18.8)	4 (16.7)
	[CI 95%]	[23.1 ; 48.4]	[20.6 ; 44.7]	[19.1 ; 45.9]	[18.7 ; 46.3]	[17.8 ; 42.1]	[8.9 ; 32.6]	[4.7 ; 37.4]

The F160-M1700 combination was the best treatment with respect to normalization of each of the 3 MetS biochemical abnormalities: elevated glucose, elevated TG and low HDL-C.

The F160-M1700 combination was more effective in normalizing MetS patients than each of the 2 monotherapies in patients with family risk factors (22.5%) than in those without family risk factors (13.3%), in those with life style risk factors (24.6%) than in those without life style risk factors (9.6%). It was also more effective in females (21.7%) than in males (14.6%).

The percentage of patients with 3 MetS criteria decreased from 97% at baseline to 52% at end of study in the group treated with the F160-M1700 combination. In this group, 69.7% of the patients were responders (patients with a decrease in the number of biochemical MetS abnormalities).

- Fasting biological parameters: percent change from baseline in the FAS

% change from baseline		F160-M1700	F160-M1000	F80-M1700	F80-M1000	F160-M 0	F0-M1700	F0-M0
Glucose	M (SD)	-9.4 (13.0)	-5.7 (12.2)	-8.1 (12.2)	-5.1 (11.7)	1.9 (17.6)	-6.5 (14.4)	-0.0 (10.4)
	median	-10.1	-6.1	-7.7	-4.8	0.0	-7.3	-1.9
TG	M (SD)	-33.6 (26.9)	-27.2 (35.4)	-23.0 (37.3)	-23.7 (28.6)	-27.1 (39.5)	7.4 (51.2)	4.6 (45.8)
	median	-36.67	-32.39	-27.36	-29.46	-40.08	-2.87	0.00
HDL-C	M (SD)	7.4 (15.8)	8.0 (17.7)	5.5 (15.9)	5.7 (14.3)	6.5 (15.1)	0.9 (13.0)	-0.9 (11.0)
	median	5.6	6.5	5.3	3.9	4.7	-0.9	-1.6

The best treatment on the percent change from baseline of fasting glucose (F160-M1700) was significantly different ($p < 0.0001$) from the fenofibrate monotherapy but not significantly different from that observed after each of the other combination and the metformin monotherapy. There was a trend towards a synergy between the high doses of fenofibrate and metformin for the reduction of glucose. The F160-M1700 combination was slightly more effective in T2DM⁺ patients (median: -11.8%) than in T2DM⁻ patients (-9.6%).

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Changes in fasting insulin were highly variable. Decreasing trends could be observed. Decreases in insulin from ≥ 70 pmol/L to < 70 pmol/L were more frequent among the patients treated with the F160-M1700 combination (n = 25) than among those treated with the metformin monotherapy (n = 5). In FAS, median relative changes in HbA1c ranged from -3.4% to -5.8% across the groups who received metformin. In the same groups, median absolute changes ranged from -0.3 to -0.5 percent point in the T2DM⁺ patients and from -0.1 to -0.3 percent point in the T2DM⁻ patients.

For TG, there was a trend for a larger reduction with the high-dose combination as compared with fenofibrate 160 mg given alone when changes are expressed as adjusted means. However, this trend was not confirmed when changes were expressed as median % change. The F160-M1700 combination had the same effect in T2DM⁺ patients (median: -33.4%) and T2DM⁻ patients (median: -33.8%).

For HDL-C, the F160-M1700 combination was not statistically different from the other 3 combinations or the fenofibrate monotherapy. Metformin had no effect on HDL-C and no influence on fenofibrate effect. The F160-M1700 combination showed a trend to a better efficacy in T2DM⁻ patients (mean: +8.7%, median: +7.0%) than in T2DM⁺ patients (mean: +6.3%, median: +4.2%).

For TC, the best treatment was the F160-M1700 combination: median: -16.9% vs. -13.9% with the fenofibrate monotherapy and -8.0% with the metformin monotherapy. There was no interaction between fenofibrate and metformin. Fenofibrate and metformin monotherapies provided similar changes in measured LDL-C (median: -16.6% and -13.9%); the median change with the F160-M1700 combination was higher (-19.9%).

VLDL-C and RPL-C decreased in the groups who received fenofibrate, without meaningful differences between the high-dose combination and the monotherapy. Fenofibrate alone or in combination with metformin was associated with an increase in LDL size and no change in HDL size. Apo A2 increased with fenofibrate alone or combined with metformin (median: +11 to +19%) and Apo CIII decreased in these same groups (-25 to -36%). There was, however, no obvious differences between combinations and monotherapy.

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• Derived OGTT and fat load test parameters in the FAS

Absolute change (mmol/L.h) from baseline		F160-M1700	F160-M1000	F80-M1700	F80-M1000	F160-M 0	F 0-M1700	F0-M0
OGTT								
Glucose AUC _{0-2h}	n	100	91	96	94	88	88	52
	M (SD)	-1.1 (4.4)	-0.4 (3.1)	-0.9 (7.0)	-0.3 (3.6)	0.5 (4.1)	-0.5 (4.1)	0.1 (3.1)
	median	-1.4	-0.7	-0.9	-0.6	0.4	-0.4	-0.1
FLT								
TG AUC _{0-6h}	n	24	20	26	17	20	21	9
	M (SD)	-10.0 (7.4)	-9.0 (4.8)	-5.0 (5.3)	-7.5 (8.0)	-10.0 (7.8)	-2.4 (5.4)	-0.2 (6.9)
	median	-7.8	-7.9	-3.2	-6.7	-9.7	-0.8	-0.4

The AUC_{0-2h} of glucose determined during OGTT decreased in all groups who received metformin, and decreased more with the F160-M1700 combination than with the metformin monotherapy (more than twice based on means and more than 3 times based on medians). The differences between the F160-M1700 combination and the monotherapies were not statistically significant. The results of the interaction test (ANCOVA model) were compatible with potentiation between fenofibrate and metformin, which is, however, not to be taken as certain due to the great variability of data. Changes in AUC_{0-2h} of insulin displayed a great variability between patients; decreasing trends were observed in all treatment groups. AUC_{0-2h} of FFA decreased in all groups, without differences between combinations and monotherapies; AUC_{0-2h} of C peptide remained on average unchanged.

Regarding the results of the fat load test, the F160-M1700 combination was equivalent to the fenofibrate 160 mg monotherapy in reducing the AUC_{0-6h} of TG. There was no interaction between fenofibrate and metformin.

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Changes in inflammation and coagulation markers showed great variations between patients. There were no meaningful differences between combinations, monotherapies and placebo as far as PAI-1 activity, PAI-1 antigen and t-PA-ag were concerned. HsCRP decreased in all active treatment groups, without meaningful differences between monotherapies and combinations. Fibrinogen decreased in the groups who received fenofibrate, without differences between combinations and the monotherapy. Regarding TNF alpha, IL-6 and IL-1, changes did not provide evidence of active treatment effects.

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• Weight and waist circumference in the FAS

% change from baseline		F160-1700 (N= 109)	F160-M1000 (N= 104)	F80-M1700 (N= 106)	F80-M1000 (N= 104)	F160-M 0 (N= 103)	F 0-M1700 (N= 100)	F0-M0 (N= 55)
Weight	n	105	100	99	99	99	93	54
	M (SD)	-1.3 (3.2)	-1.4 (2.3)	-1.9 (2.7)	-1.2 (2.4)	-0.6 (2.8)	-1.2 (2.2)	-0.4 (2.3)
Waist cir.	n	103	100	99	99	99	93	54
	M (SD)	-1.2 (3.3)	-1.4 (3.1)	-1.8 (2.8)	-1.7 (3.1)	-1.2 (3.4)	-0.7 (3.6)	-0.7 (3.1)

Mean changes in body weight ranged between -1.2 and -1.9% in the groups who received metformin. Mean waist to hip ratio remained unchanged.

A slight and progressive decrease in blood pressure was observed in all treatment groups between baseline and end of treatment. There were no meaningful differences between the treatment groups.

Safety Results:

Deaths

There was no death during the study.

Other Serious Adverse Events (SAEs)

Nine SAEs were reported in 8 patients. Of the 8 patients, 3 patients were prematurely withdrawn (1 in the placebo group for stroke, 1 in the F80-M1000 group for abdominal pain and diarrhea that led to diagnosis of colon cancer, and 1 in the F0-M1700 group for lumbar pain that led to diagnosis of pulmonary cancer). The other 5 patients completed the study. One SAE, acute gastritis in a patient treated with the F160-M1000 combination, was considered as possibly related to study treatment.

Adverse Events (AEs)

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

	F160-1700 (N= 109)	F160-M1000 (N= 104)	F80-M1700 (N= 106)	F80-M1000 (N= 104)	F160-M 0 (N= 103)	F 0-M1700 (N= 100)	F0-M0 (N= 55)
All AEs	48 (44.0)	50 (48.1)	56 (52.8)	51 (49.0)	35 (34.0)	44 (44.0)	21 (38.2)
AEs related*	31 (28.4)	31 (29.8)	38 (35.8)	26 (25.0)	17 (16.5)	27 (27.0)	10 (18.2)

* possibly or probably related to study treatment according to the investigator.

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The most frequent related AEs by MedDRA System Organ Class were gastrointestinal disorders: 32% in the F80-M1700, 23% in the F160-M1000, 22% in the F0-M1700, 21% in the F160-M1700, 16% in the F80-M1000, 11% in the F160-M0 and 9% in the placebo F0-M0 groups. The most frequent gastrointestinal symptoms, by MedDRA Preferred Term, considered as related AEs are reported below (number of patients)

	F160-M1700 (N= 109)	F160-M1000 (N= 104)	F80-M1700 (N= 106)	F80-M1000 (N= 104)	F160-M 0 (N= 103)	F 0-M1700 (N= 100)	F0-M0 (N= 55)
Diarrhea	7	6	6	9	4	12	2
Nausea	7	2	5	4	1	6	0
Flatulence	5	3	3	1	3	1	1
Abdominal pain	3	3	4	2	1	3	0
Abdominal pain	3	3	5	2	0	1	1
Loose stools	2	2	4	2	1	3	0

Thirty-one (31) patients were prematurely withdrawn from the study for AE, 3 for SAE and 28 for non-serious AE. The most frequent AEs that led to premature withdrawal were gastrointestinal symptoms. Three patients, 2 patients treated with the F80-M1000 combination and 1 patient treated with the fenofibrate monotherapy, were prematurely withdrawn because of skin allergic reactions. Three patients were prematurely withdrawn for abnormal laboratory investigations: 1 patient in the F80-M1000 group for increased ALT/AST, 1 patient in the same group for increased ALT/AST and creatinine, and 1 patient in the F160-M1700 group for increased creatinine.

Laboratory Evaluation

ALT or AST increased to values > 3 times the upper limit of normal (ULN) in 7 patients: 3 patients were treated with the F160-M1700 combination, 1 patient with F160-M1000, 1 patient with F80-M1700, and 2 patients with F80-M1000, who were withdrawn from the study. The highest increase was in a patient treated with the F80-M1000 combination whose ALT value was 7.7 times the ULN and AST value 5.4 times the ULN at V3. None of the patients who had increased ALT or AST had concomitant increased total bilirubin. On average, changes in transaminases were minor, the largest increase being 12% (median percent change) in AST in the F160-M1700 group.

CPK increased to values above 5 times the ULN in a patient treated with the F80-M1000 combination. This abnormal value (11.7 times the ULN) was attributed to physical exercise. No changes worth to be noted were observed in median CPK (to the exception of fenofibrate monotherapy: median: +17%).

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: Metabolic Syndrome
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Creatinine increased to values > 110 µmol/L in females and > 135 µmol/L in males in 4 patients in the F160-M1700 group and in the F80-M1700 group, in 3 patients in the F80-M1000 group, in 2 patients in the F160-M0 group and in 1 patient in each of the other 3 groups. Creatinine increased in the groups treated with fenofibrate, with a slight dose-effect: median: from +7 to +9% with 160 mg, vs. +4 and +5% with 80 mg at end of treatment. Besides increased ALT and AST, increased creatinine was the reason for premature withdrawal in one patient of the F80-M1000 group.

Homocysteine increased in all groups who received fenofibrate; the increase was greater with the high-dose fenofibrate combinations (median: +40 to +47%) than with the fenofibrate monotherapy (median: +36%).

Alkaline phosphatase decreased in all the groups who received fenofibrate (median: -19 to -27%). The same was true for uric acid, with a noticeable dose-effect (median: -13 to -16% with 80 mg and -19% to -22% with 160 mg).

Hemoglobin was reduced by 2.2 to 5.2% (median) across active treatment groups; decreases from normal range at baseline to values < the LLN at the end of treatment were observed in 1 to 3 patients by treatment group, except in the F160-M1000 group. Median changes in WBC ranged from -2.6 to -4.9% in the groups who received a combination and were +4.8% and 0.0% with the metformin monotherapy and the placebo, respectively. Increases in WBC to values > the ULN were observed in 1 to 5 patients by treatment group among those who received a combination and in 7 patients who received the metformin monotherapy. Platelets increased in all treatment groups, in a larger extent in those who received the combinations with fenofibrate 160 mg or metformin alone (median: +10 to +11%) than in the other groups (median: +5 to +7%).

Date of the report: 26 APR 2005